SYNTHETIC ROUTES TO 9-AZASTEROIDS

BY

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ABSTRACT

Syntheses of azasteroids both from natural steroids and from precursors bearing a nitrogen atom are reviewed.

The present research was directed towards the preparation of suitable tricyclic compounds possessing the future A-,B- and D-rings of a 9-azasteroid system which were suitably substituted for the construction of ring C of the azasteroid system with ring A-aromatic.

The first part of this work describes the synthesis of a tricyclic compound possessing a suitable side chain on the future D-ring for construction of the C-ring but the low yield of this compound proved prohibitive.

The second part concerns the attempted preparation of a tricyclic compound possessing an aromatic substituent on the future D-ring which was suitable for formation of the C-ring.

The last section describes the synthesis and stereochemistry of A-,B- and D-ring azasteroid precursors which possessed a substituent attached to the nitrogen atom of the future B-ring suitable for the formation of the C-ring and a leaving group attached to the future D-ring. Synthesis of the C-ring of these compounds all proved unsuccessful.

CONTENTS

I N T R O D U C T I O N

PHYSIOLOGICAL PROPERTIES

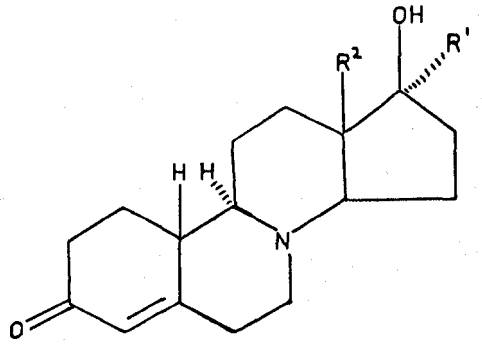
Because of the continued increase in demand for steroids in the medical world for use as oral contraceptives as well as highly specific therapeutic agents, the search for new derivatives has spread into the realm of azasteroids. Although large numbers of azasteroids have been prepared, relatively little work has been concerned with the biological properties.

Modification of naturally occurring steroids can cause suppression or enhancement of one or more of its range of activities. The activity of a steroid is in general related to its structure and only a limited number of structural variations are possible with retention of biological activity.[1]. The physiological properties of steroidal hormones depend on various factors. Among those of particular importance are the stereochemistry and the overall shape of the molecule. Thus any really fundamental change in the steroid nucleus should alter the stereochemistry as little as possible. A study of models has shown that expansion of the six membered C ring to a seven membered ring by insertion of a nitrogen atom has little effect on the molecules general shape and no change in configuration at any asymmetric centre need be made.[2]. The replacement of a trigonal sp^2-carbon atom by a trigonal nitrogen atom or of a tetrahedral sp^3-carbon by a tetrahedral positively charged nitrogen atom should produce little modification in the size or molecular geometry but could lead to marked alteration of chemical and physiological properties.[3]

Although an azasteroid might be related to a steroid hormone through replacement of $-CH_2-$ by -NH- or of -CH by -N= any protonation at physiological pH levels would prevent complying with the concept of bioisotrosism[4] and so considerably reduce the possibility of the azasteroid interacting in the same enzyme system as the natural steroid by way of mimicry or antagonism. Nevertheless, the fact that 6-aza-cholesterol is a potent cytotoxic agent[5] is not incompatible with it acting as an antimetabolite of cholesterol or as a biotransformation product. Also the claims of androgenic, anabolic or anti-oestrogenic activities in various azasteroids may be due to direct competition with natural steroid hormones for their target receptors, although several diazasteroids show no biological activity.[6]. However as the azasteroids become structurally more removed from the biologically active parent (which is particularly so with some synthetic

azasteroids) so the application of theoretical concepts becomes more difficult.

Clarkson and Doyle[7] reported that substitution of nitrogen for carbon at position eight of the steroid nucleus is one of the few changes that would not markedly alter the stereochemistry, nor add extra active hydrogen atoms nor modify the functional groups present. They were thus able to study the effect of a basic group on the biological properties of steroids. They prepared a number of 8-aza-19-nortestosterones and found that in general they were much less active than their steroid precursors. Thus 17α-ethynyl-3-methoxy-8-aza-oestra-1,3,5-triene-17β-ol had 1/20th of the oestrogenic activity of mestranol in inducing vaginal cornification when dosed orally to sprayed rats; 8-aza-19-nortestosterone(1)(R^1=H,R^2=CH_3) showed virtually no progestational activity at all while the



(1)

17α-ethynyl derivative (R^1=C≡CH,R^2=CH_3) has about 1/5th of the activity of its steroid precursor norethisterone when given orally. The derivative (R^1=Et,R^2=Et) is somewhat more active than norethisterone but is much less potent. As in naturally occurring steroids the 13β-ethyl group increases progestational activity and this roughly compensates for the contrary effect of the 8-aza-unit. The effect of the nitrogen on androgenic and anabolic activity was most marked. Most of the 8-azasteroids were completely inactive while some (in particular R^1=Et,R^2=Me) showed slight antiandrogenic activity. For the active compounds (R^1=R^2=Me and R^1=R^2=Et) the subcutaneous androgenic dose is 100 times that of testosterone propionate while the anabolic dose is even higher.

Several azasteroids have been reported as showing antimicrobial activity particularly the 17-azasteroids. Doorenbos and co-workers[8] have reported on the effects of azasteroids on gram + ve bacteria (i.e. those bacteria whose cell walls are made up of a protein complex of magnesium ribonucleate as well as lipids). They screened a number of azasteroids of closely related structure with Bacillus subtilis. The most active compounds were cholesterol derivatives containing a tertiary or quaternary nitrogen either attached to or incorporated in the A ring. A quoted example of inhibition was that of a 4-azacholestenone derivative (4-dimethylamino-ethyl-4-aza-5-cholesten-3-one). This caused extensive leakage in the cells of B. subtilis before loss of viability occurred, but at bacteriostatic azasteroid concentrations there was little leakage. The active azasteroids were found to be readily bound in large amounts to B. subtilis cells whereas inactive azasteroids were poorly bound. The degree of binding was ascertained by radioactive labelling and at least 50% of the binding was associated with the membrane fraction. It would seem therefore that the mode of attack is to cause loss of permeability of the plasma membrane.

Gaird and Mathur[9] tested several azasteroids for antifertility effects in rats. It was found that an oral dose rate of 20mg/kg body weight of rat from the first to the seventh day of pregnancy were up to 77% effective, and most significantly there were no toxic side effects.

Paroli and Piccinelli[10] found that 17-azaandrostenol caused a 3 fold increase in plasma corticosterone levels in rat. It increased the length of time of morphine induced thermoanalgesia and delayed recovery of righting reflexes following pentobarbitol. The decreased plasma corticosterone levels caused by dexamethazone morphine, pentobarbitol or cortisone treatment were bought back to normal levels by subsequent treatment with the azasterol.

Ranney and co-workers[11] have found that 17-azasterols and azacosterols as their hydrochlorides were non-specific inhibitors of at least 2 reductase systems involved in the synthesis of cholesterol. Lettre and Knof[12] reported that 6-azasteroids have a cytostatic effect and are useful in the therapy of malignant and non-malignant tumours. Meltzer and Brown[13] found that 8-azasteroids were useful in the treatment of shock and circulatory collapse in mammals. The 6-azaandrostane derivatives made by Cross and co-workers[14] were androgenic

hormones which stimulate the action of the pituitary gland and show anti-oestrogenic and anti-progestational activities. They were also found to inhibit luteinisation which is the formation of the yellow pigment in the yolk of eggs. Wildi[15] showed that 3-oxo-4-azasteroids showed masked anti-inflammatory activity with rats having inflamed ankles.

Other physiological properties associated with azasteroids are central nervous system stimulation[16] and depression,[17] and anti-fungal, anti-protazoal, anti-algal[18] activity and inhibition of the growth of dicotyledonous seeds. They have been shown to act as anabolic steroids,[20] androgenic agents[21] and show local anaesthetic,[22] catatoxic,[23] cardiovascular[24] and curare like[23] activities. They have been used in the treatment of arhythmia,[25] vascular ailments[26] and endocrine disorders[27] and are potential anti-carcinogens.[28] Naturally occurring azasteroids have been extracted from frogs and salamanders.[29] Peredes and Martinod[31] have shown the relations of esteroids, azasteroids and triterpenoids to the taxonomy of the flora of Equador. Positive alkaloid reactions were tabulated for 34 species of Solanum and for 7 other plants. Cevallos and Martinod[32] have found that the alkaloids (including azasteroids) of S. pseudoquina made up 2% of the dry weight of the fruit.

SYNTHESES OF AZASTEROIDS

The synthesis of azasteroids can be divided into two distinct approaches.

a) Partial Synthesis:- This involves modification of an existing steroid nucleus either by a process involving ring cleavage, nitrogen insertion and ring closure or else by application of the Schmidt reaction to an appropriate ketone or Beckmann rearrangement of an appropriate ketoxime formed from the ketone. Azasteroids made by partial syntheses can be further subdivided into:-

i) Azasteroids with an unexpanded ring system.
ii) Homoazasteroids - where one of the rings is larger than expected in normal steroids.
iii) Norazasteroids - where one of the rings is smaller than expected in normal steroids.
iv) Secoazasteroids - where one of the rings is open.

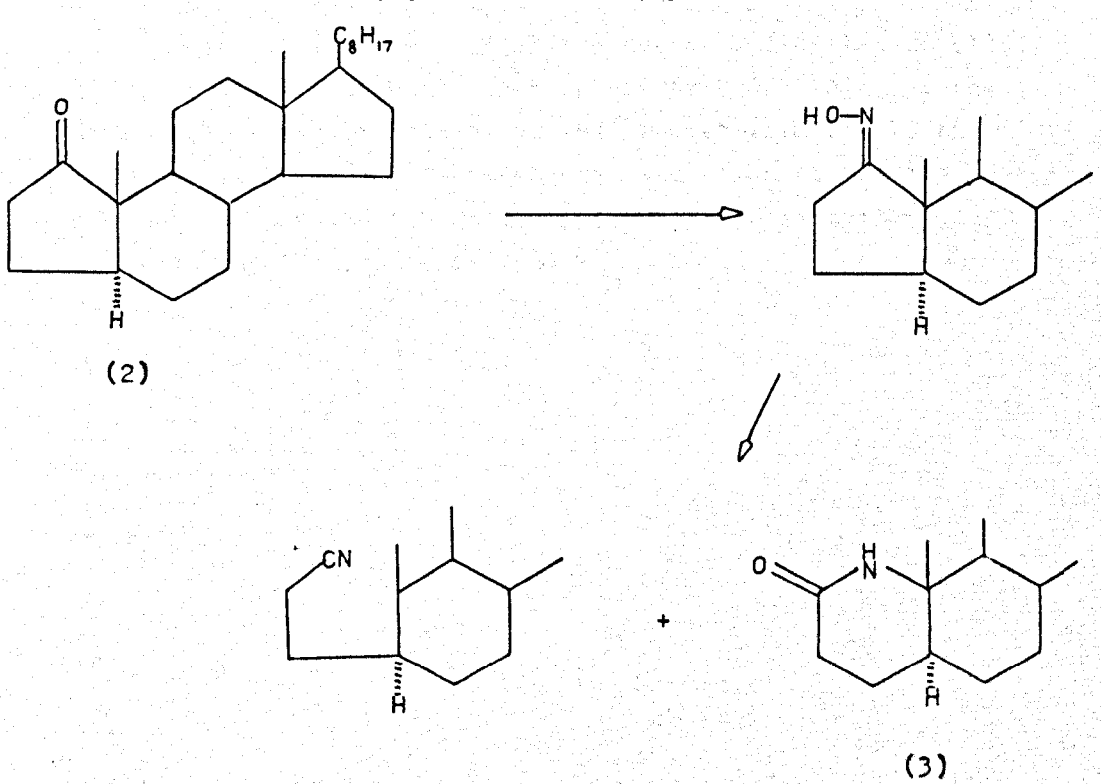
The scope of this literature review will only include azasteroids with an unexpanded ring system.

b) Total Syntheses:- This involves procedures which are concerned with building up the steroid model from precursors which already contain a nitrogen atom in the selected position.

In contrast to the synthetic work on partial syntheses of azasteroids and azahomosteroids very little work on the total syntheses of azasteroids was initially reported. Up until 1962 no total synthesis had been accomplished and no azasteroid with a bridgehead nitrogen was known. However since 1963 several total syntheses of azasteroids have been described including some where a nitrogen atom actually replaces one of the tertiary carbon atoms.

a) Partial Syntheses

The most commonly applied approaches to partial syntheses involve the Beckmann rearrangement and Schmidt reaction to give steroid lactams which give azasteroids on reduction with lithium aluminium hydride. Both of these methods have been applied more widely to syntheses of azahomosteroids. Using the Beckmann rearrangement Shoppee, Lack and Roy[33] prepared 1-aza-5a-cholestan-2-one(3) from A-nor-5α-cholestan-1-one(2). Also formed in 50% yield was the nitrile. Since only one oxime is formed, it is, judging from the lactam formed in the next stage, the sterically preferred oxime.

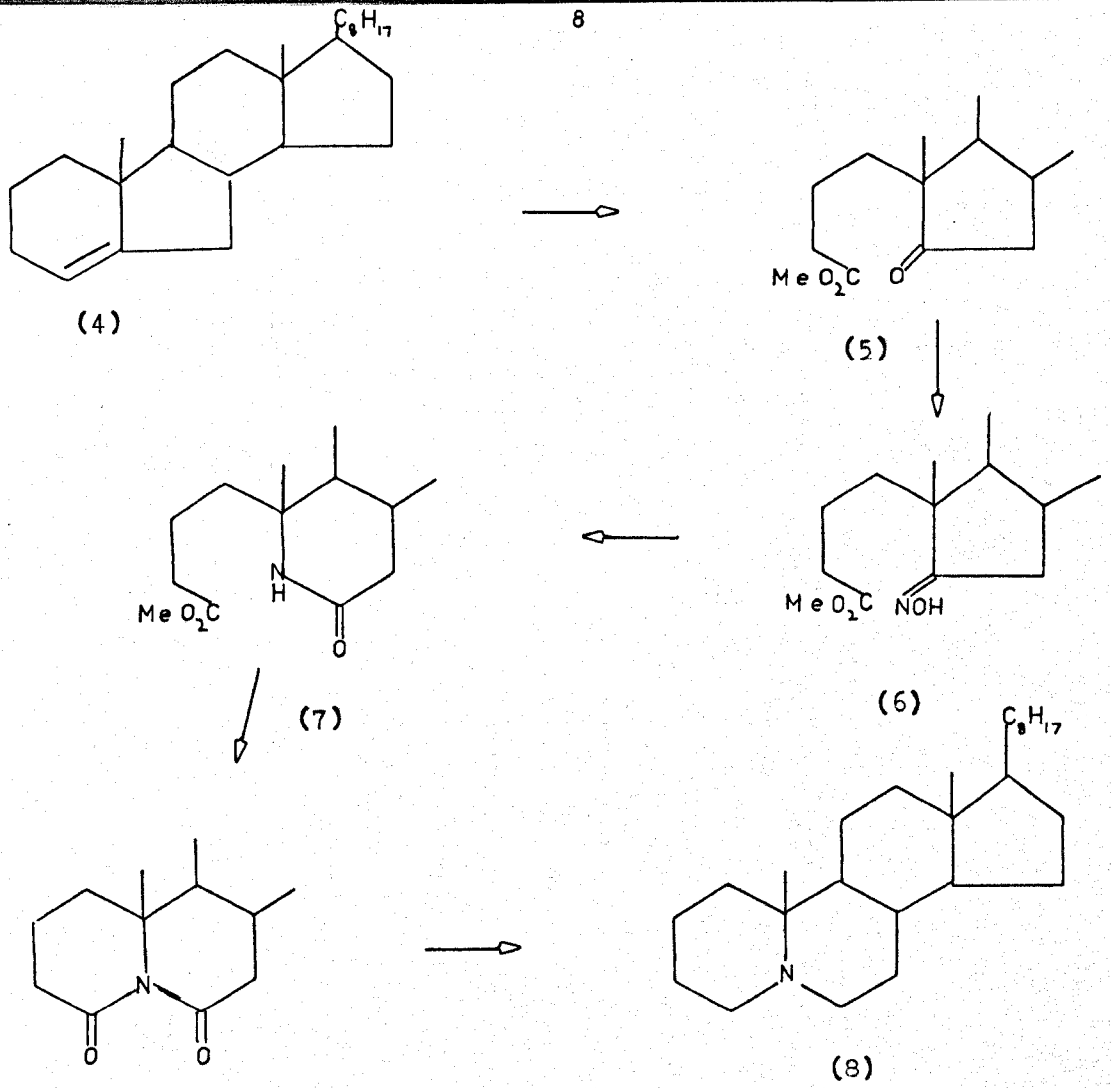


(2)

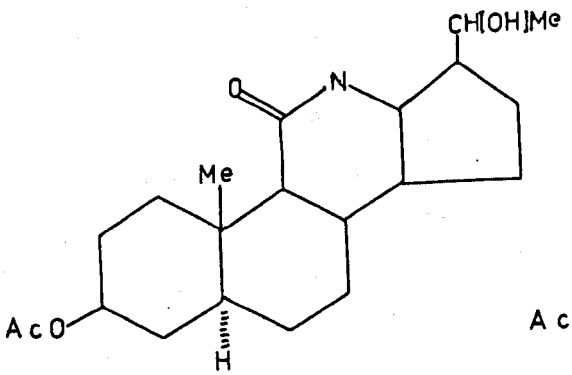
(3)

Beckmann rearrangement of a ring ketoxime can in theory give two isomeric lactams. The nature of the product of the rearrangement has been generally thought to depend on the configuration of the oxime, ie on the relative proportions of syn and anti forms assuming no change of configuration during the rearrangement. Certain steroid ketoximes give mixtures of lactams on rearrangement[34] while others are reported to give single products. This latter case could be due to the fact that only one particular oxime has been formed due to the steric requirements of the molecule or that only one isomer rearranges or that the rearrangement product is a molecular compound of the two lactams of sharp melting point.

3β-hydroxy-5-azacholestane was synthesised in a seven step synthesis utilising the Beckmann rearrangement by Rodewald and Achmatowicz[35]. Formation of β-norcholest-4-en-3-one(4) from cholesterol and then ozonolysis of the product followed by oxidative decomposition of the ozonides with 30% hydrogen peroxide and 98% formic acid and esterification of the resulting mixture with diazomethane gave the ester (5). Reaction of this ester with hydroxylamine hydrochloride in pyridine afforded the oxime (6) in the anti-configuration. Beckmann rearrangement of this oxime with thionyl chloride in ether at-10° gave 40% of the corresponding lactam (7). Cyclisation of the A ring was brought about by hydrolysis of the ester group followed by treatment of the product with acetic anhydride in pyridine at room temperature. Reduction of the two carbonyl groups was affected with lithium aluminium hydride in boiling dioxan to give the 5-azacholestane(8).



Mitsuhashi and Tomimoto[36] have reported a successful synthesis of 11-aza and 12-azasteroids starting from Hecogenin. This involved a seven step synthesis to give 3β,20-dihydroxy-5a-pregnan-12-one monoacetate. Oximation with hydroxylamine hydrochloride in pyridine gave the 3β-acetoxy-20-hydroxy-C-nor-5a-pregnan-11-one oxime. Beckmann rearrangement of this oxime with tosyl chloride in pyridine gave three products, two of which were identified as (9) and (10).



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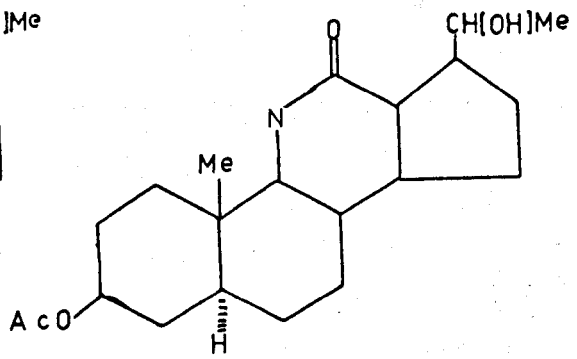

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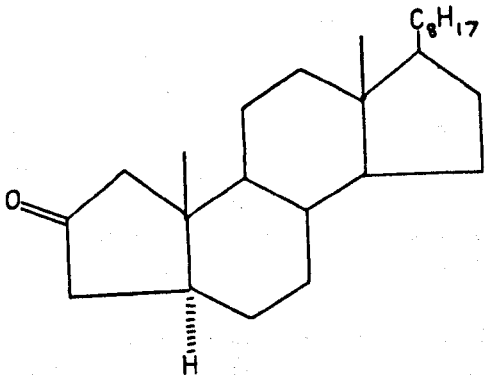

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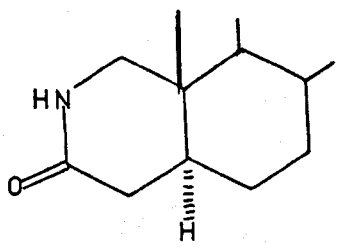

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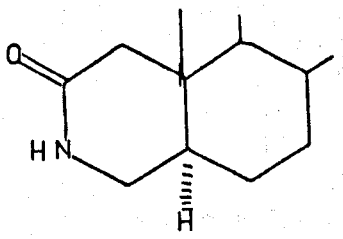

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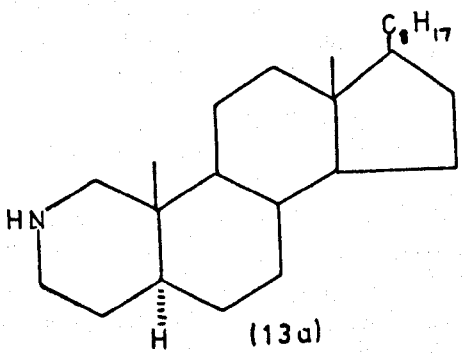

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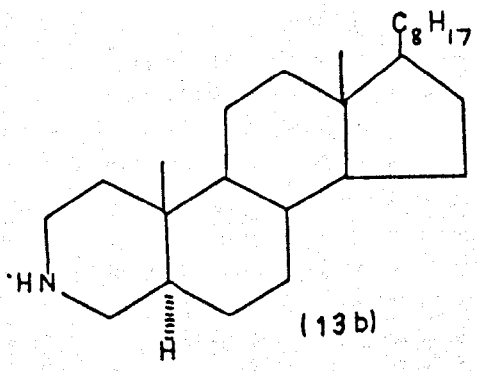
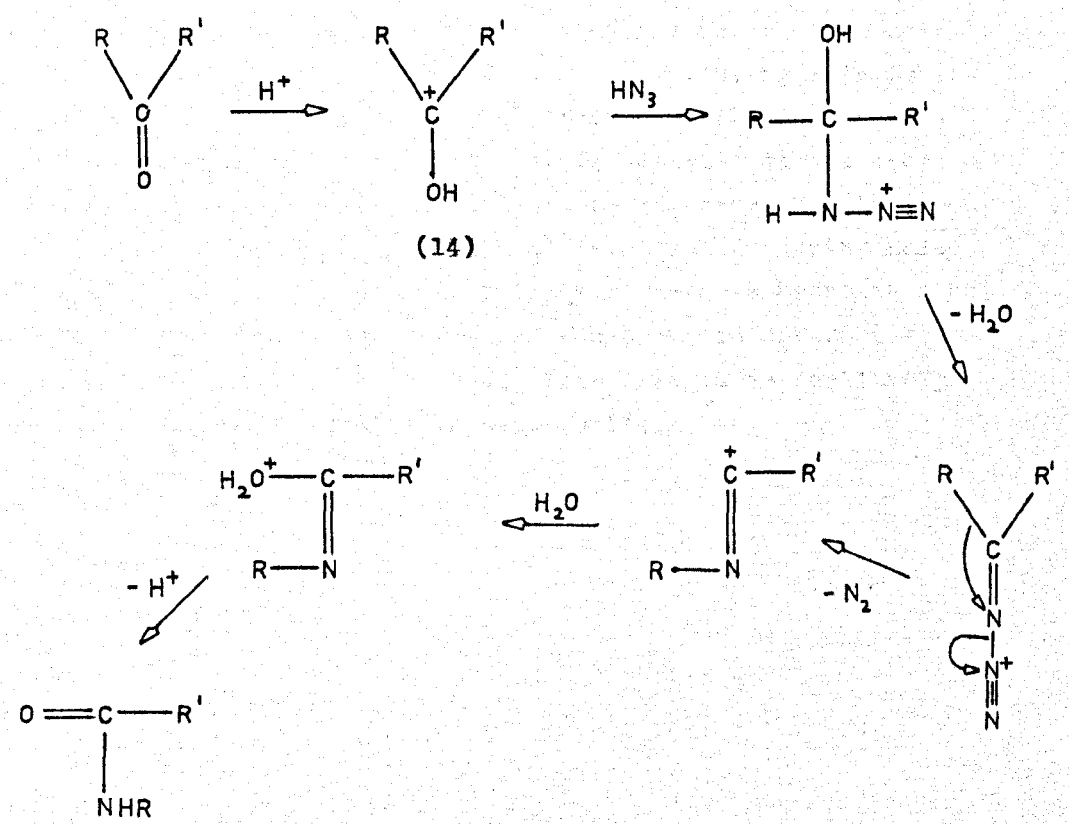


(13b)

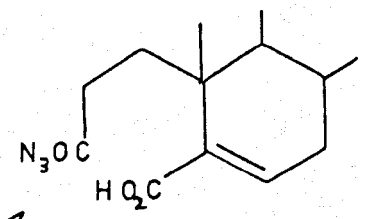
Havranek[37] has prepared 2-aza and 3-aza-5a-cholestanes from A-nor-5a-cholestan-2-one(11). Here Beckmann rearrangement of the oxime using polyphosphoric acid as solvent and catalyst gave equal amounts of a sharp melting mixture of lactams(12) which on reduction with lithium aluminium hydride gave an inseparable mixture of 2-aza(13a) and 3-aza-5a-cholestanes(13b).

The Schmidt reaction is capable of giving the same products as the Beckmann rearrangement. It involves the reaction between a carbonyl compound and hydrazoic acid in the presence of, for example, sulphuric acid, to give an amide. The mechanism has been shown to be intramolecular and Smith[38] has proposed the following mechanism which is an example of the 1,2 shift (from carbon to nitrogen).



If the two alkyl groups (R and R^1) are not identical then two geometrical isomers of (14) are possible. It is also reasonable to assume that the anti group (to the diazonium nitrogen) is the group that migrates. In this way it is possible to explain how steric factors may influence the isomer ratio of amides formed. Havranek and Doorenbos[39] treated A-nor-5a-cholestan-3-one with hydrazoic acid in polyphosphoric acid and obtained an inseparable mixture of lactams 2-aza-5a-cholestan-3-one and 3-aza-5a-cholestan-2-one in 77% yield. Separation was finally achieved by forming the N-methyl derivatives with methyl iodide followed by fractional crystallisation to give 38% N-methyl-3-aza-5a-cholestan-2-one and 44% N-methyl-2-aza-5a-cholestan-3-one. Reduction of the unsubstituted lactams with lithium aluminium hydride gave an oily isomeric mixture of 2-aza and 3-aza-5a-cholestanes.

Other methods of incorporating a nitrogen atom into a steroid are by the Curtius rearrangement and the Hofmann rearrangement. The Curtius rearrangement involves formation of the azide of an acid with sodium azide, decomposition to the isocyanate, hydrolysis to give the amine and then subsequent cyclisation. The Hofmann rearrangement entails formation of the amide or imide of the seco keto acid and then halogenation followed by rearrangement to the next lower homologous amine. Putokhin[40] claims that during halogenation of amides and imides the halogen replaces a hydrogen atom, attached not to the nitrogen but to an -OH group on carbon (tautomeric pseudoacid form of the amide). This halogen is positively charged and comparable to that in hypobromite.



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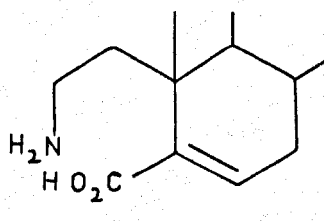

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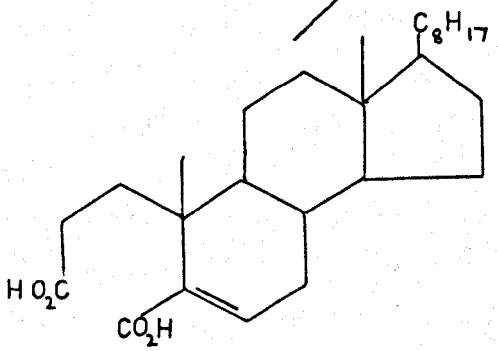

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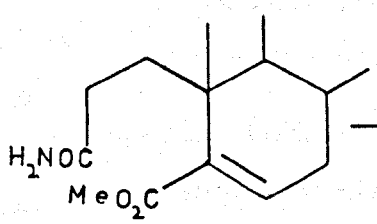

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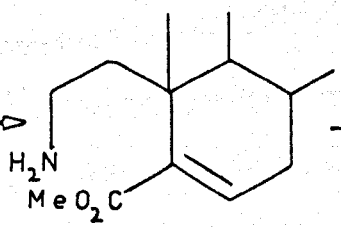

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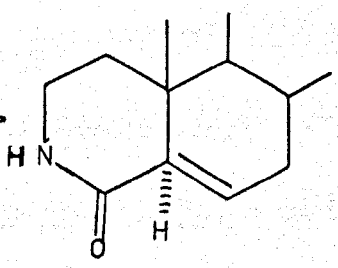

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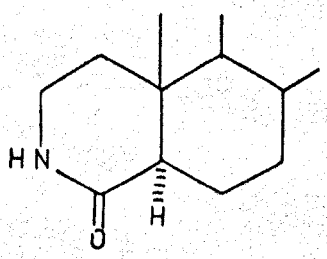

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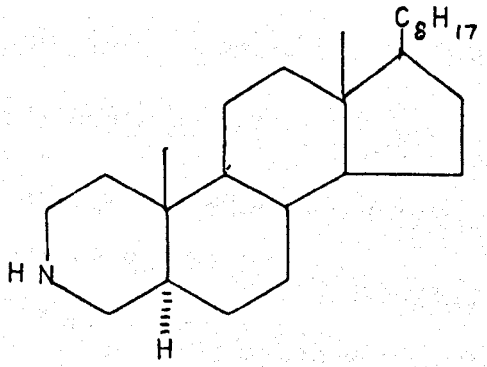


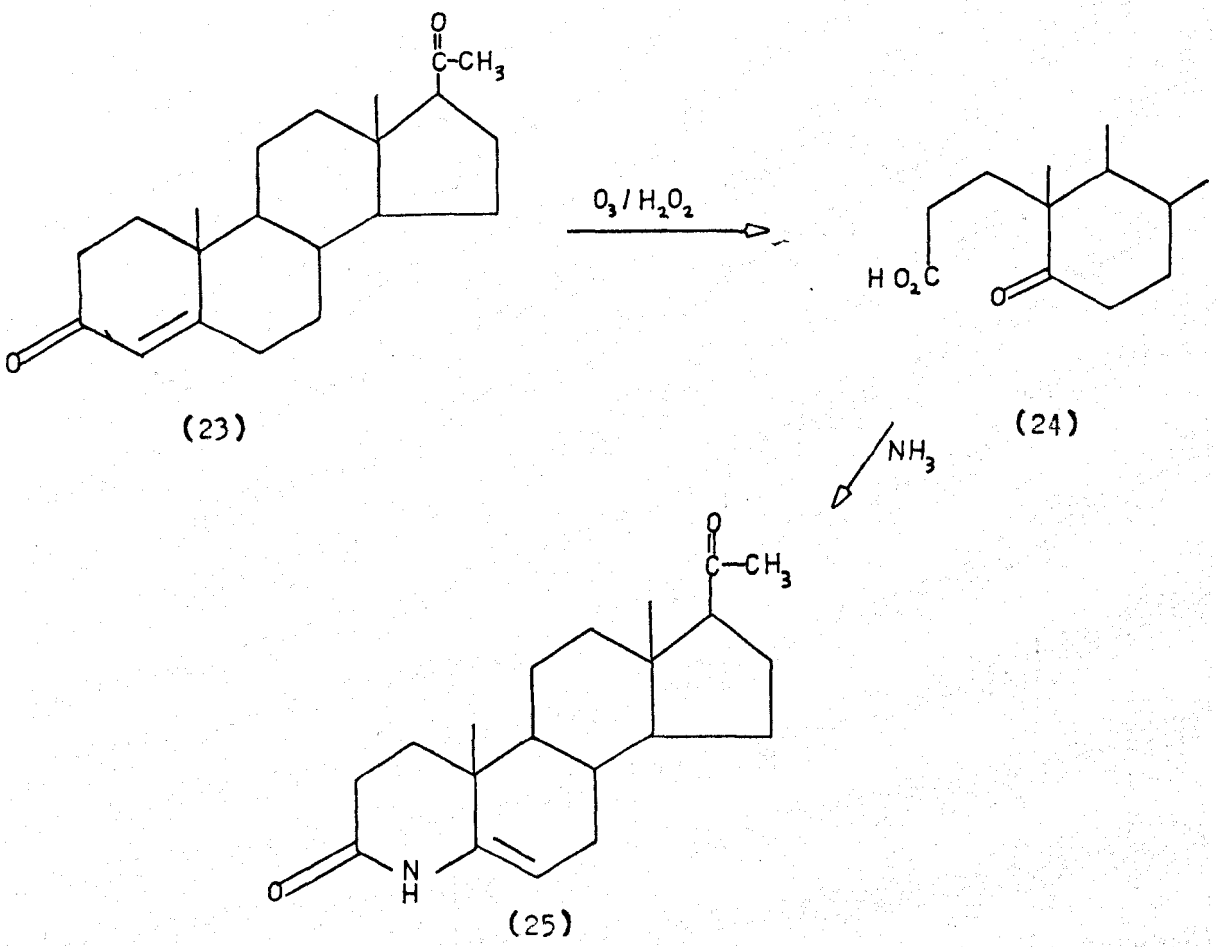
(22)

Shoppee and co-workers[3] have published an example of a synthesis of 3-aza-5a-cholestane(22) from 3,4-seco-cholest-5-en-3,4-dioic acid(15) by both the Hofmann and Curtius rearrangement methods. The seco-dicarboxylic acid(15) was converted into the 3-azido-4-acid(16) followed by Curtius rearrangement to the 3-isocyanate-4-acid. Acid hydrolysis of this yielded the amino acid(17) which cyclised spontaneously to give the lactam(18). Alternatively the seco-dicarboxylic acid was converted into the methyl ester of the 3-amide-4-acid(19). Hofmann rearrangement gave the amino acid ester (20) which cyclised spontaneously to give the lactam(18). Reduction of the lactam using Adam's catalyst gave the 5α-lactam(21) which was further reduced with lithium aluminium hydride to the 3-azasteroid(22).

Apart from the already cited examples, most partial syntheses of azasteroids, particularly the 4-aza and 6-aza steroids, have involved starting from the appropriate A,B or C-nor-seco-keto acid. The introduction of a nitrogen atom is achieved by the direct action of ammonia or an amine with simultaneous cyclisation or via the formation of some nitrogenous derivative of the carbonyl or carboxyl functions with subsequent reductive cyclisation. The necessary ring opening and loss of one carbon atom is in most examples effected during ozonisation of an α-,β-unsaturated keto-steroid to the A,B or C-nor-seco-ketoacid or by rearrangement of a nitrogenous derivative of the carboxyl group of a seco-keto-acid.

Doorenbos and co-workers[41] have prepared 4-azapregn-5-en-3-20-dione(25) from progesterone(23). Ring opening to form the seco-keto-acid (24) was achieved by treatment with ozone and hydrogen peroxide. Reaction of this acid with ammonia under pressure gave the azasteroid(25). Doorenbos amd Tamorria[42] have prepared several azapregnanes with a nitrogen incorporated in the A ring by using a variety of amines. By reacting 3,5-seco-4-norpregnane-5,20-dion-3-oic acid with methylamine they obtained both 4-methyl-4-aza-5-pregnen-3,20-dione and 4-methyl-20-methylimino-4-aza-5-pregnen-3-one.

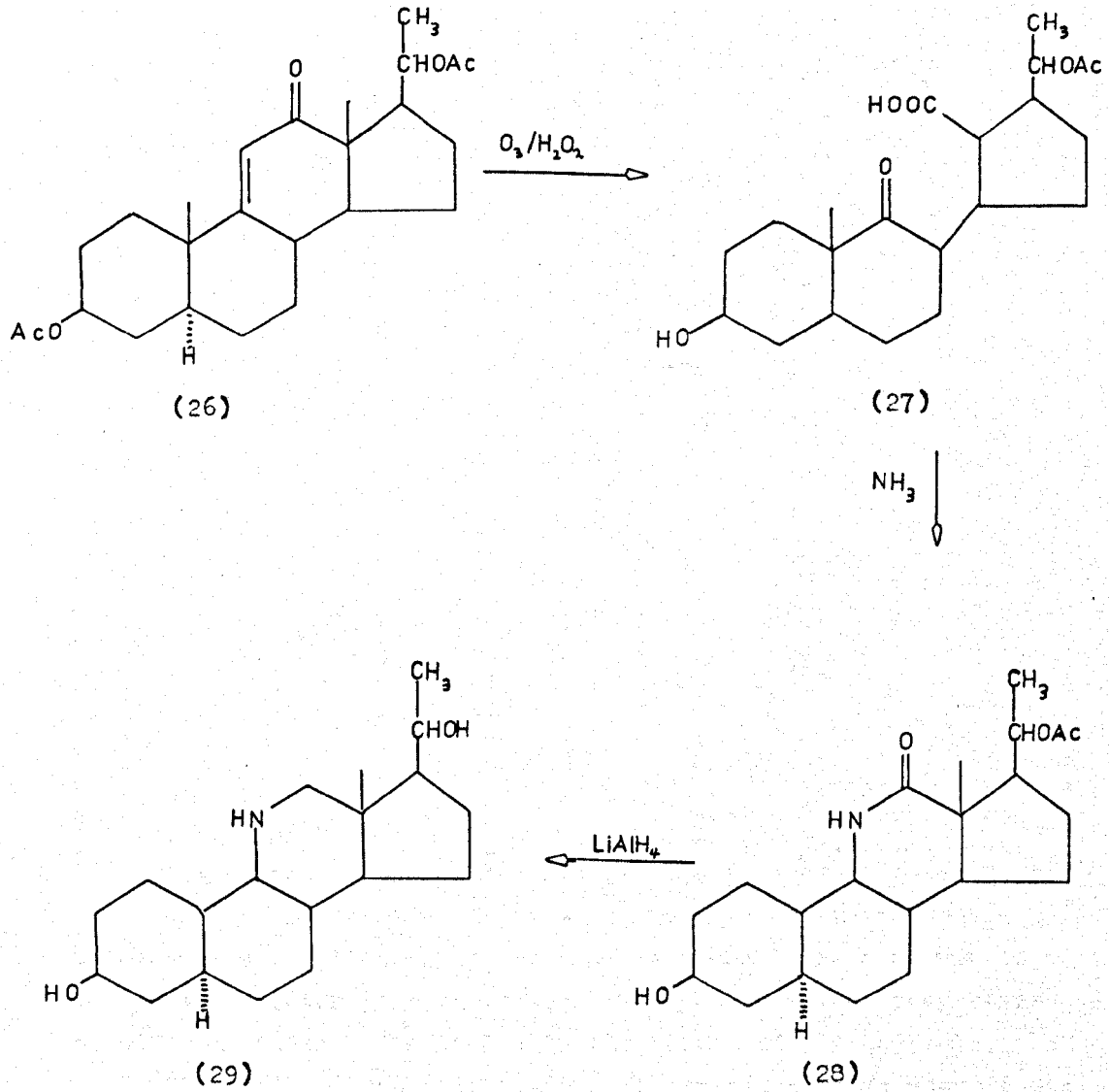
Jacobs and Brownfield[43] have successfully synthesised a 6-azasteroid by ozonolysis of 7-oxocholesteryl acetate to give 5-oxo-5,7-seco-6-nor-3-cholesten-7-oic acid, treatment of which with ammonia yielded 6-aza-2,4-cholestadiene-7-one. Other B ring



(23) (24) (25)

azasteroids have been prepared using amines instead of ammonia. Kutney and Johnson[44] using a similar procedure but involving benzylamine instead of ammonia, have synthesised N-benzyl-6-aza-5ξ-cholestane from 7-oxocholesteryl acetate. Likewise Kutney and coworkers[45] have prepared 17β-hydroxy-N-benzyl-6-aza-4-androsten-7-one which represented the first synthesis of a 6-aza derivative in the androstane series.

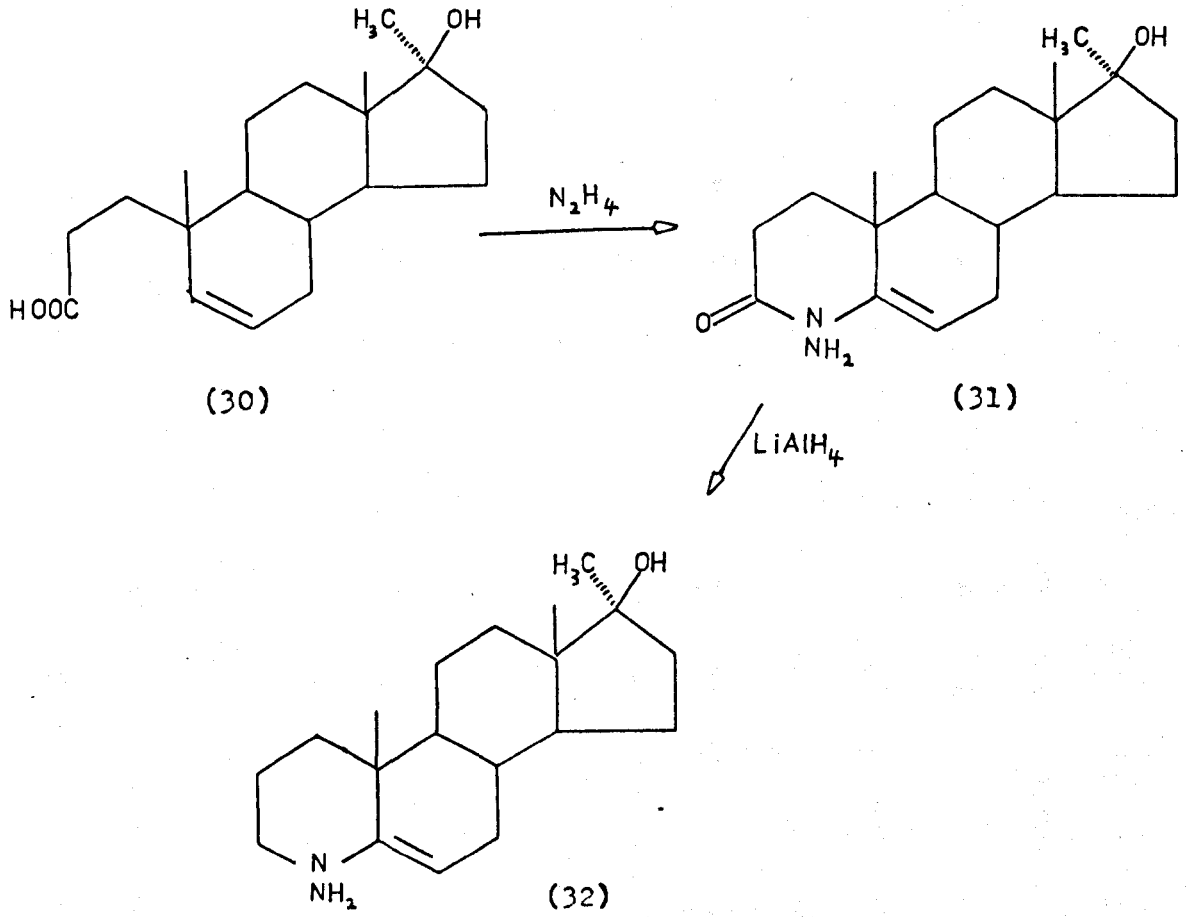
Reactions using ammonia have been successfully employed by Engel and Rakhit[46] to synthesise a C ring azasteroid. They ozonised 3β-20-diacetoxypregn-9(11)-en-12-one(26) which they previously prepared from hecogenin, to give the seco keto-acid(27). Treatment of this with ammonia under pressure gave the 11-aza-lactam(28) which was reduced to 11-aza-3β-20-dihydroxypregn-8(9)-ene(29).



(26) (27)

(29) (28)

Doorenbos and Mu Tsu Wu[47] have inserted nitrogen into a steroidal A ring using hydrazine. When 17a-methyl-3,5-seco-4-norandrostan-17β-ol-5-en-3-oic acid(30) was heated in an autoclave the tetracylic compound(31) was obtained. This, reduced with lithium aluminium hydride, gave 4-amino-17a-methyl-4-aza-5-androsten-17a-ol (32).

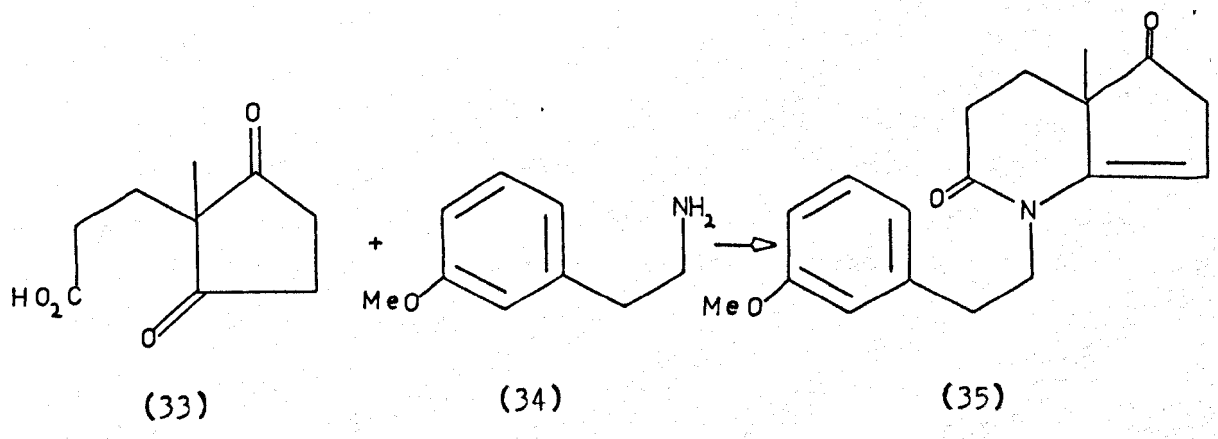


(30) (31) (32)

b) Total Syntheses

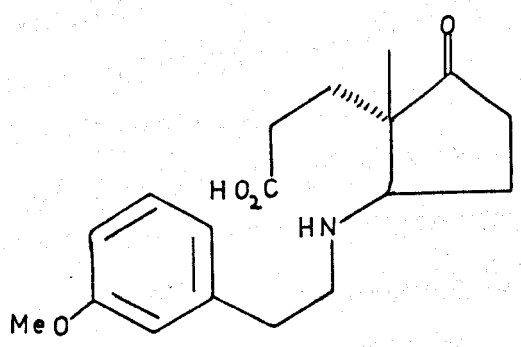
Of the total syntheses reported in the literature those that have attracted most interest are with the nitrogen incorporated in the 8 or 9 position. The interest is probably in part due to the possible alteration in chemical and physiological properties caused by a bridgehead nitrogen in the centre of the molecule.

8-AZASTEROID The first attempt to synthesise such an azasteroid was reported by Meltzer et al.[48]. The lactam(35) was prepared by condensation of 2-(β-carbethoxyethyl)-2-methyl-cyclopentane-1,3-dione(33) with meta-methoxyphenethylamine(34). This lactam(35) was then catalytically hydrogenated stereospecifically to give the saturated lactam(36) with C and D rings cis fused. The trans fused isomeric lactam(38) was formed by carrying out the condensation and the reduction simultaneously to give the trans amino acid(37) which cyclised to the lactam(38) on heating above its melting point. Treatment of these lactams with phosphorus oxychloride in benzene gave the cyclised products isolated as their perchlorates (39).

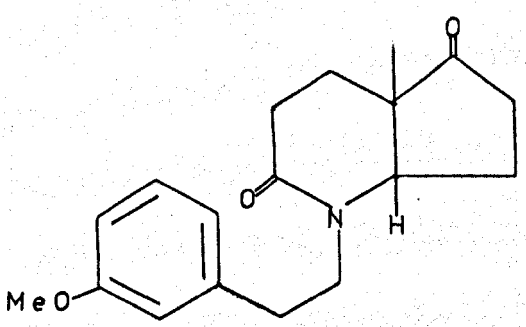


(33) (34) (35)

H_2/Pd



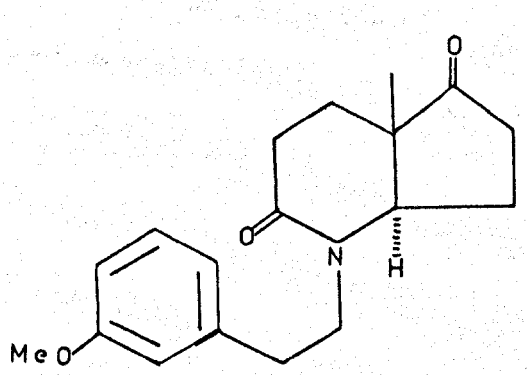
(37)



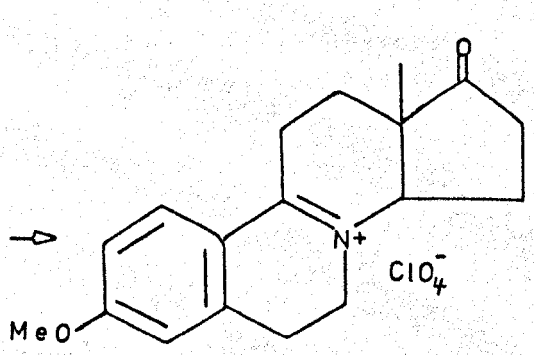
(36)

$POCl_3$

$\triangle$

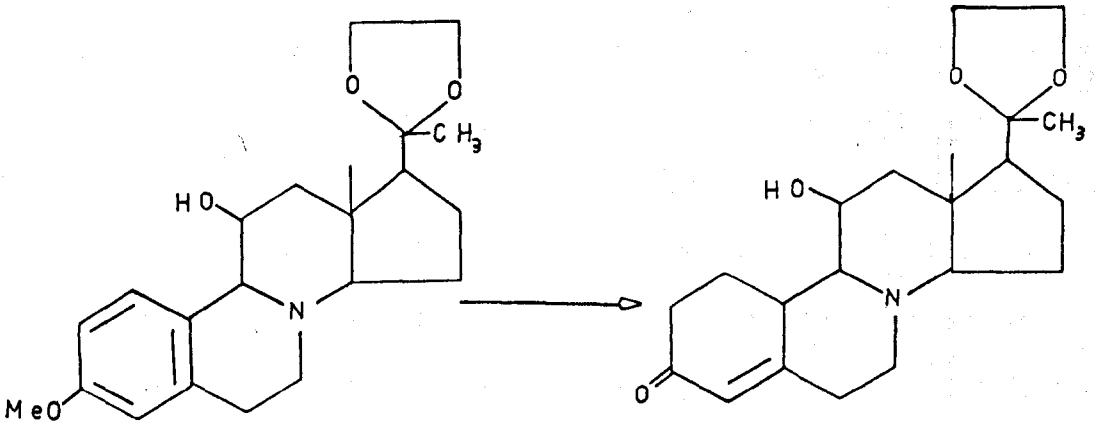


(38)



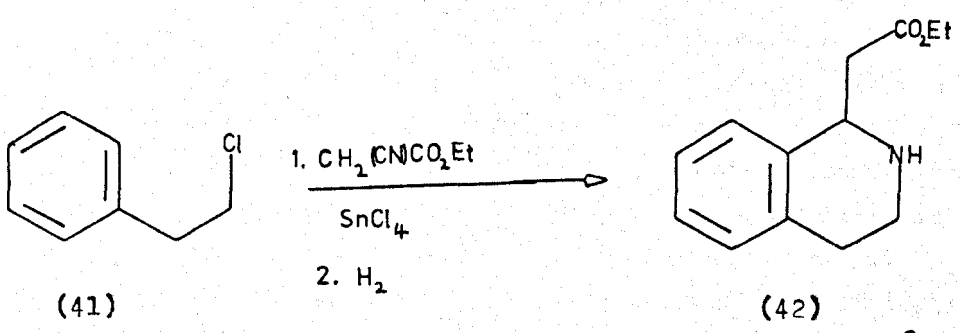
(39)

Meltzer and co-workers[49-51] have used similar methods to prepare other 8-azasteroids. Brown and Meltzer[52] have used a metal/amine reducing system to partly reduce the A ring of an 8-azasteroid(40) having prior to this ketalised the keto group to protect it from reduction.

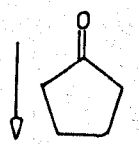


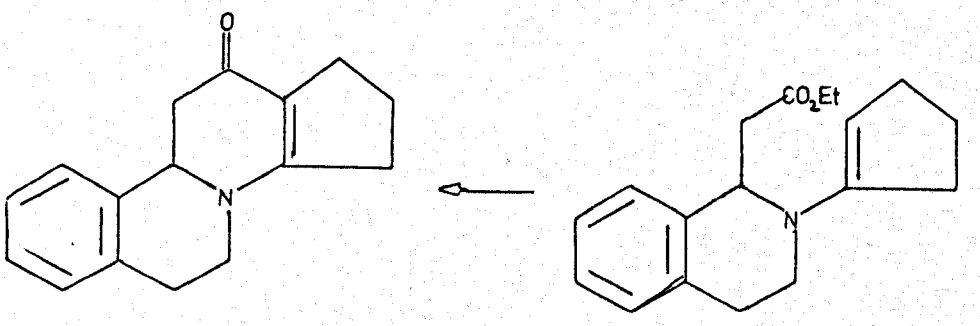
(40)

Meyers and co-workers[53,54] first synthesis of an 8-azasteroid involved using 1-carbethoxymethylene-3,4-dihydroisoquinoline prepared by condensing ethyl cyanoacetate with phenethyl chloride (41) in the presence of stannic chloride. The isoquinoline derivative was hydrogenated to give 1-carbethoxy-1,2,3,4-tetrahydroisoquinoline(42). Condensation of this with cyclopentanone gave the enamine(43) which was cyclised to give the enamino ketone(44). Angular methylation with methyl iodide gave the quaternary salt(45) which could be reduced catalytically to 8-aza-12-oxo-estratriene(46). The ring junctions were later shown[55] to be B/C cis and C/D trans instead of, as originally thought, B/C trans and C/D cis.

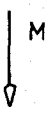


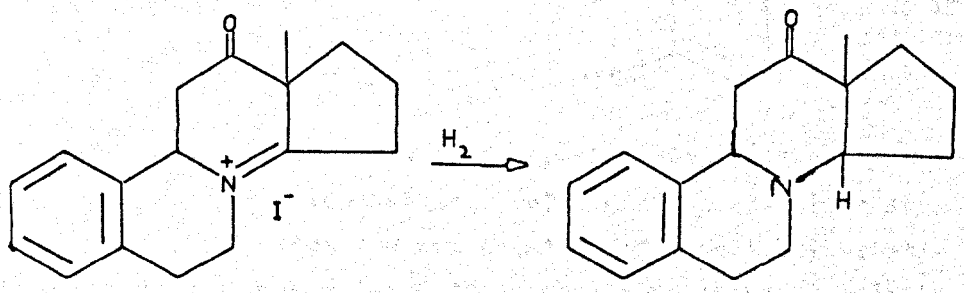
(41) (42)





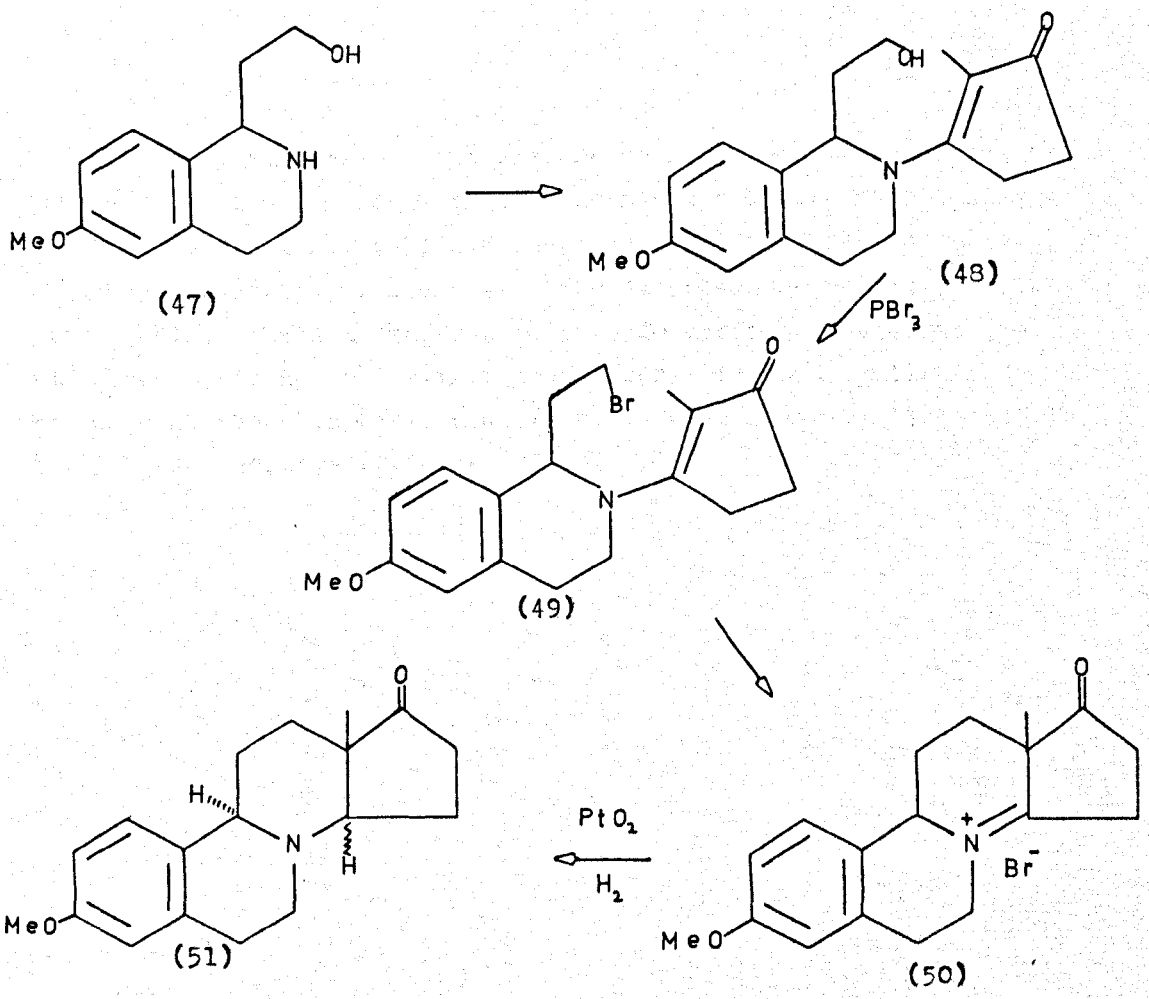
(44) (43)



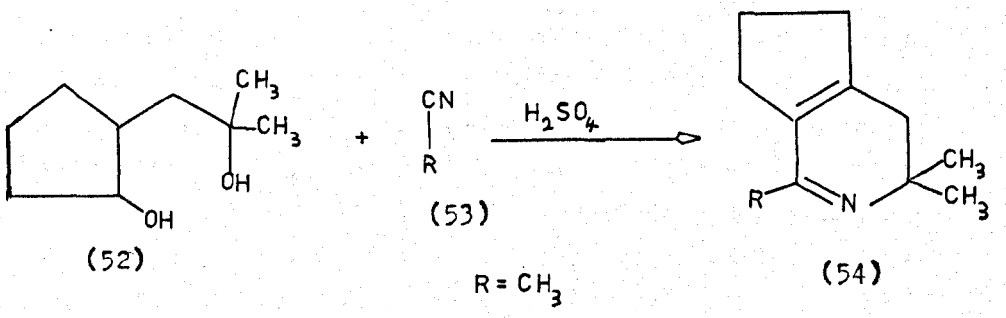


(45) (46)

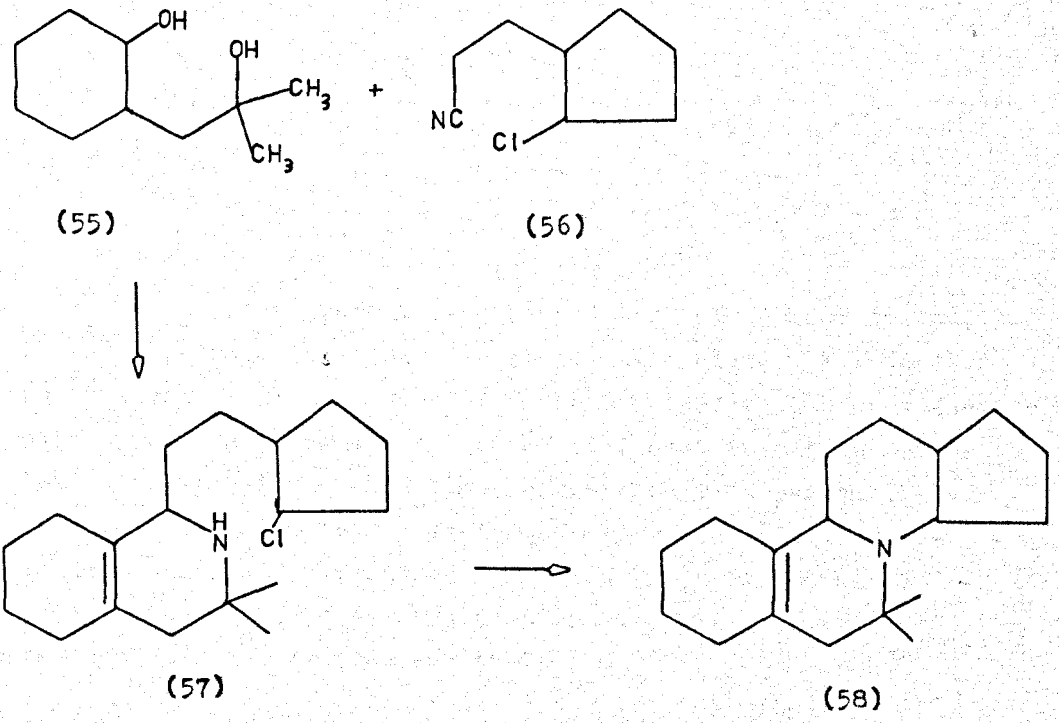
In later work Meyers et al[56] extended this synthesis, using diketones. They reported a three step synthesis of dl-8-azaestrone methyl ether in 43% yield. The tetrahydroisoquinoline alcohol (47) was condensed with 2-methyl-1,3-cyclopentanedione to give the enamino ketone (48) which was quantitatively transformed to the corresponding bromide (49). Cyclisation was achieved in acetonitrile to give the unstable iminium salt (50) which was reduced to almost equal amounts of dl-14a- and dl-14β-8-azaestrone methyl ether (51). Separation was successful by fractional crystallisation.



Meyers and co-workers extended their syntheses to include 13-azasteroid systems by a novel method involving few preparative stages[57]. The essential first stage was condensation of a suitably substituted nitrile (53) with a tertiary alcohol containing an additional nucleophilic substituent (52) in cold concentrated sulphuric acid which had a low water activity function. The 3,4-cyclopenteno-5,6-dihydropyridine (54) was thus prepared.

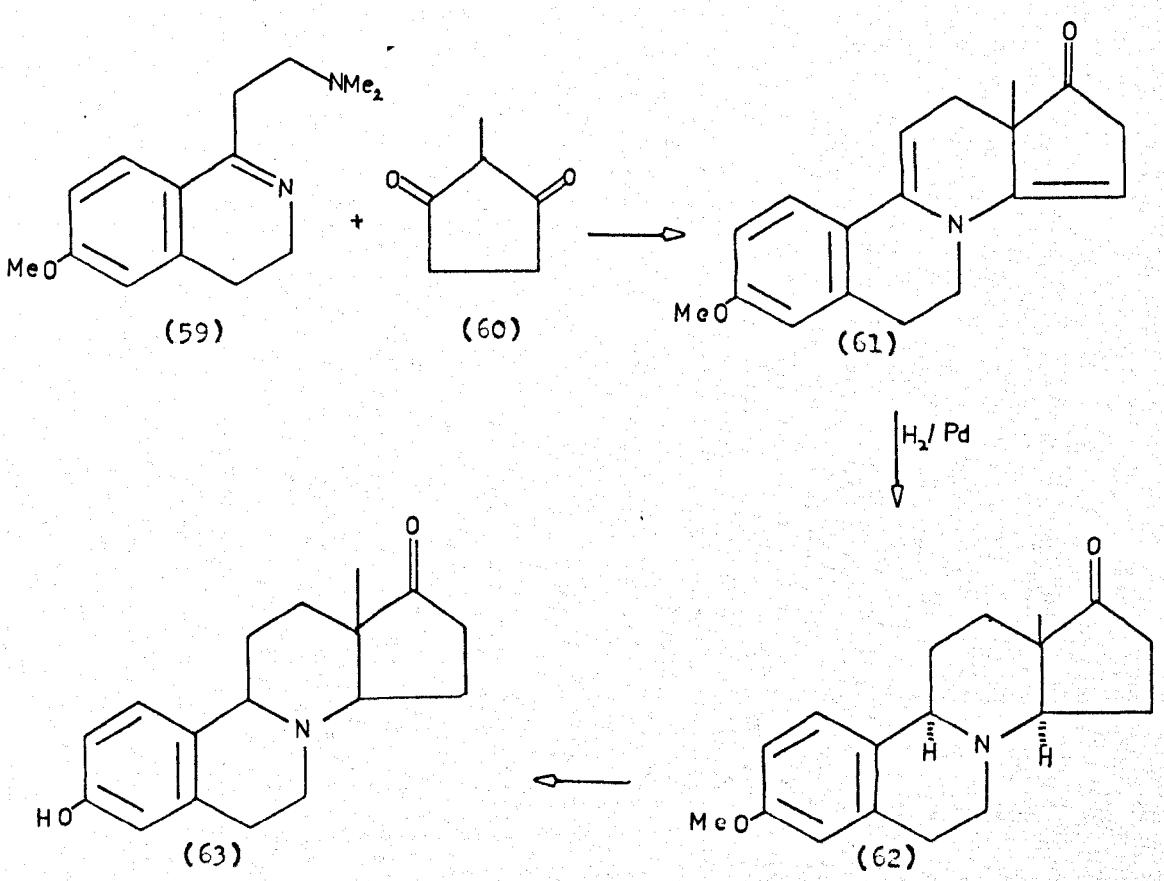


Other 2 and 3 ring azasteroid precursors have been prepared by this method. For the synthesis of an 8-azasteroid system α-(2-hydroxy-cyclohexyl)-t-butanol (55) was added to a cold solution of β-(2-chlorocyclopentyl)-propionitrile (56) in excess concentrated sulphuric acid. The dihydropyridine thus formed was reduced to the tetrahydropyridine (57) with sodium borohydride and cyclisation was brought about in basic conditions to give 8-aza-11,11-dimethyl-18,19-bisnorandrost-5(10)-ene (58).

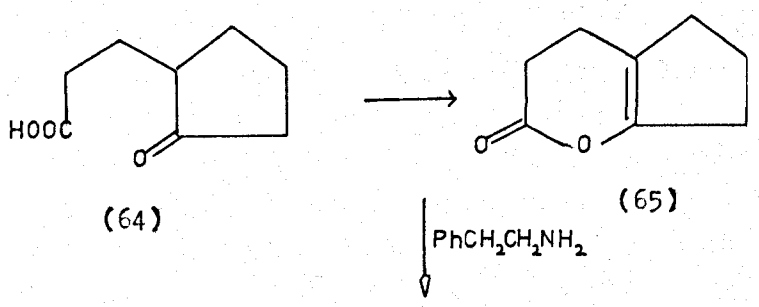


The reaction involves the formation of a tertiary carbonium ion.

Clarkson[58] has reported a convenient stereospecific synthesis of (±)-8-azaestrone (63) using as the key step a Michael reaction between 1-(β-dimethylaminoethyl)-3,4-dihydro-6-methoxyisoquinoline (59) and 2-methyl cyclopentane-1,3-dione (60) to give the tetracyclic system (61). Catalytic reduction of this dienamine gave the 3-methoxy azaestrone (62) which on reaction with pyridine hydrochloride gave the 8-azaestrone (63).

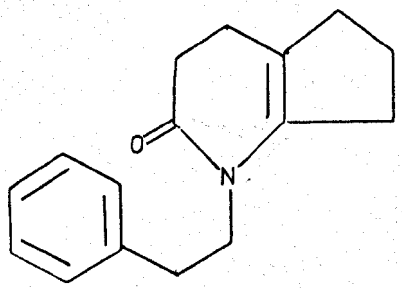


Kessar and co-workers have reported two methods for introducing nitrogen into the 8 position of a steroidal nucleus. The first method[59] involves the reaction of a lactone (65) with either gaseous ammonia or amines. Hence the lactone (65) (obtained from 2-oxocyclopentyl-3-propionic acid (64) on reaction with β-phenethylamine gave the lactam (66). Their second route[60] involved reaction of 2-methyl-cyclopentane-1,3-dione (67) with either β-phenethylamine or 1,2,3,4-tetrahydroisoquinoline to give the corresponding enamines (68) and (69).

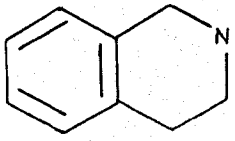


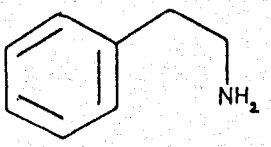
(64) (65)

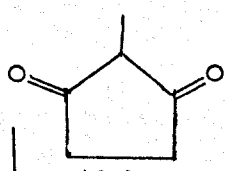
$PhCH_2CH_2NH_2$



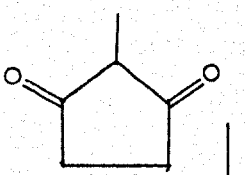
(66)



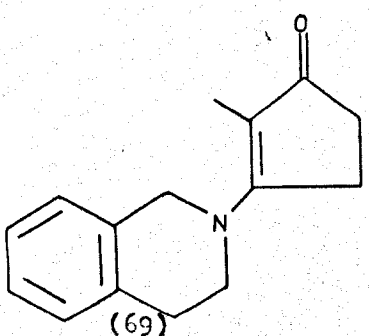




(60)



(60)



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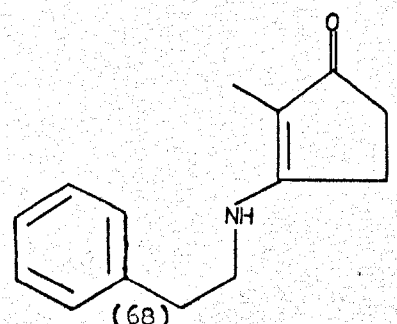
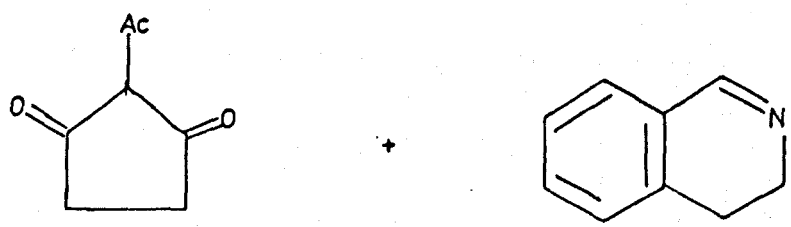


(68)

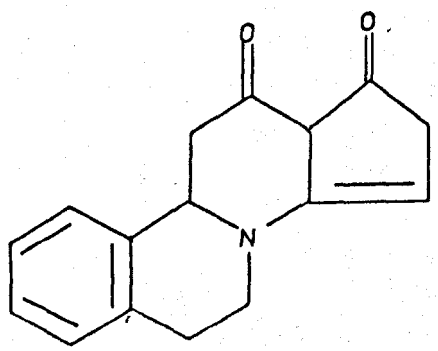
More recently Akhrem and co-workers[61,62] have synthesised analogues of 8-azaestrone (71) by reaction of 3,4-dihydroisoquinoline (70) with suitable triketones such as 2-acetyl-cyclopentane-1,3-dione.

Very recently Lyle and Heavner[63] have employed a modification of an initial route used by Meltzer et al[47] to synthesise several 8-azasteroids.

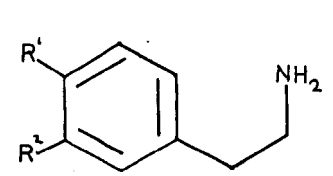
A high yield of the enamino ketone (74) was obtained by reaction of the methoxylated benzylethylamine (72) with 1,3-cyclopentanedione. Alkylation of compound (74) and subsequent cyclisation with β-propiolactone gave the tricyclic compound (75), cyclodehydration of which gave an equimolecular mixture of the A,C-bis-aromatic-8-azasteroid (76a) and its tetrahydropyridine analogue (77a). Compounds 76b [76a(R^1=H)] and 77b [77a(R^1=H)] were also prepared by a similar route. The C-13—C-14 double bond of compound (78) was reduced with lithium aluminium hydride to give compound (81). Several other azasteroids incorporating the basic structure of compound (78) were prepared. O-alkylation of compound (78) with methyl iodide gave the ether (79) separated as its salt which was reduced with sodium borohydride to give a mixture of compounds (82) and (83). Alkylation of compound (78) with allyl bromide gave the corresponding O-alkylated product (80).



(70)



(71)



(72)

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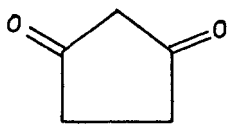
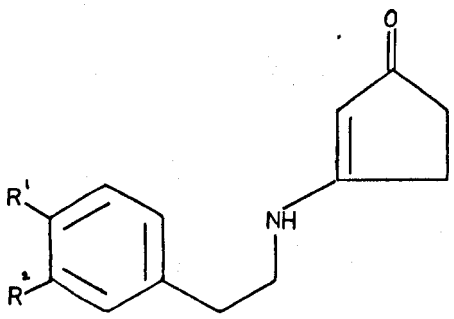
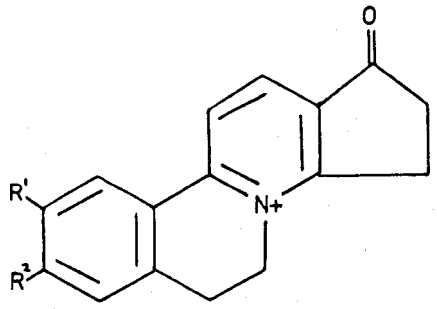


(73)

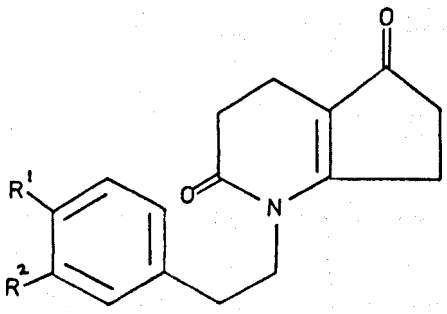


(74)



(76a)

P.P.A.



(75)

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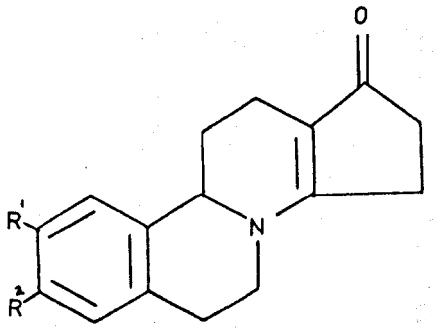
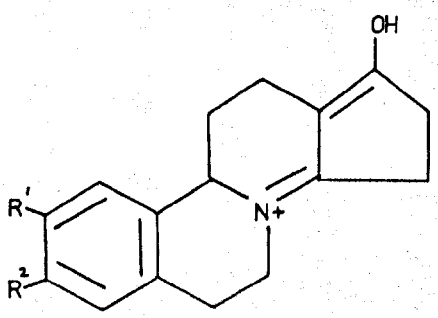


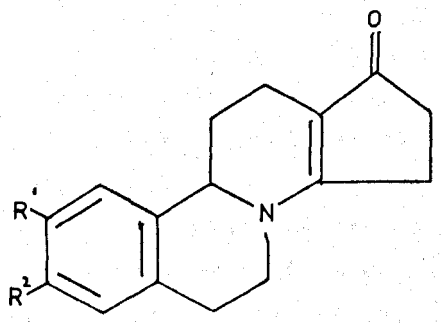
(77a)

$\rightleftharpoons$ (H^+ / OH^-)



(78)

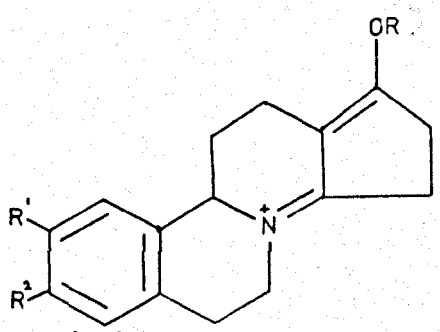
$R^1 = R^2 = CH_3O$



(77a)

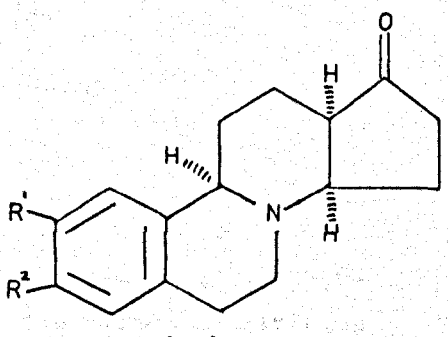
CH_3I / RI

$LiALH_4$



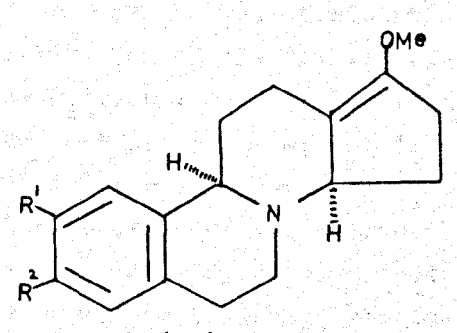
(79) $R=CH_3$

(80) $R=CH_2=CH-CH_2-$



(81)

$NaBH_4$



(82)

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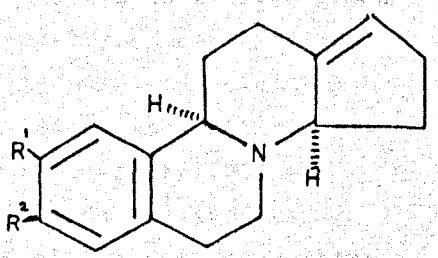
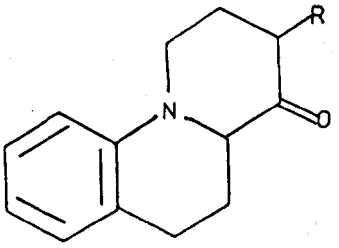


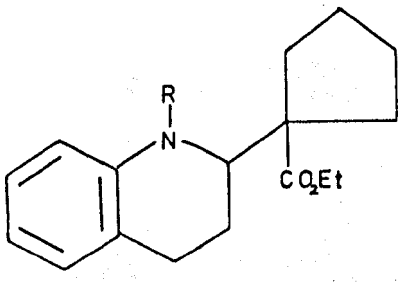
(83)

$R^1=R^2=CH_3O$

There are several ways of approaching the total syntheses of 9-azasteroids by synthesising different precursors. Jones and Wood[64,65] synthesised the A,B,C ring precursor suitably substituted for elaboration of the D ring (84) while Baty, Jones and Moore[66] tackled the problem by working from an A,B,D ring precursor which contained suitable substituents for cyclisation of the C ring (85).

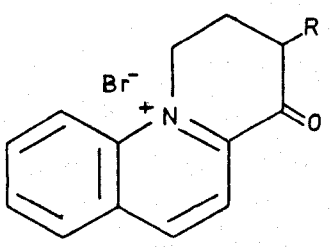


(84)

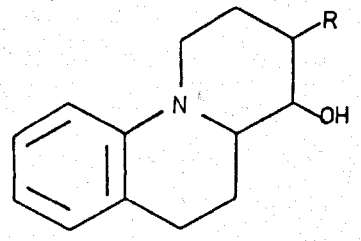


(85)

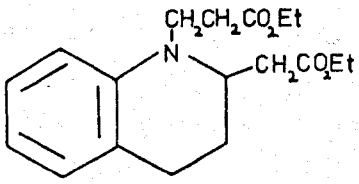
Several attempts were made to prepare the 4-oxo-1,2,3,4,5,6-hexahydrobenzo(C) quinolizine (84) (R=H). The benzoquinolizinium system (86) was easily prepared by refluxing 2-(3-ethoxybutyryl) quinoline in hydrobromic acid. However on reduction the ketone was reduced to the alcohol as well as the B ring being reduced (87). Attempts at reoxidation of the alcohol or protection of the ketone group prior to reduction all failed. The next attempt involved reducing the B ring before building the C ring. Dieckmann cyclisation of the diester (88) could give either of the β-ketoesters (89) and (90) since in theory both electron withdrawing groups have the same power. It was found that the product was (90) which was of no further use. Schleigh and Popp[67] however found that Dieckmann cyclisation of the diester (94) gave the required β-keto-ester (84). ($R=CO_2Et$) but attempts to form a D ring on model compounds failed. The next logical step was to use a compound in which one electron-withdrawing group was more powerful than the other and so influence the direction of the cyclisation. Thus the cyano-ester (91) was easily prepared and cyclised with sodium ethoxide to give the cyano-ketone (92). Alkylation with bromoacetone in dimethoxyethane



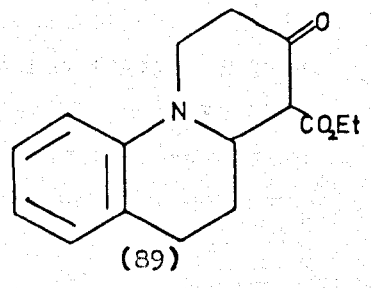
(86)



(87)

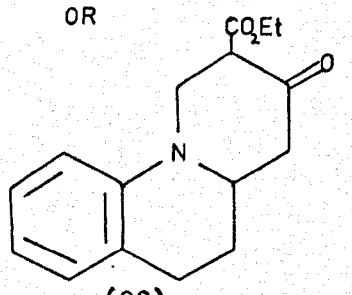


(88)

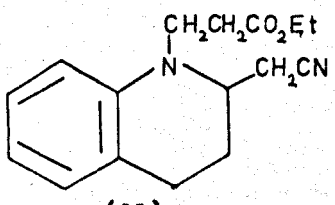


(89)

OR

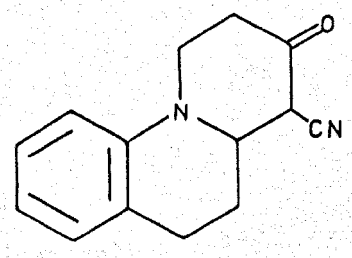


(90)

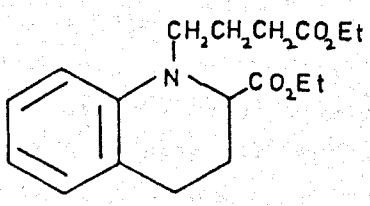


(91)

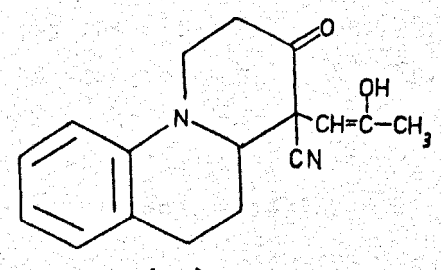
NaOEt



(92)



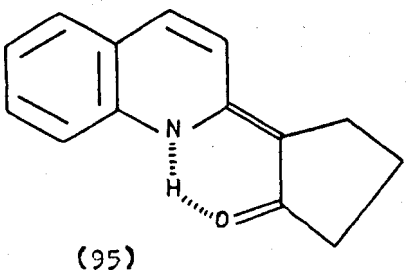
(94)



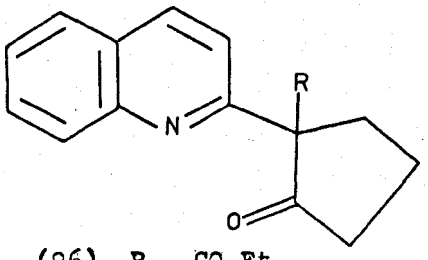
(93)

gave rise to C-alkylation and the product was fully enolised (93). Attempted cyclisation of (93) using potassium-t-butoxide in t-butanol failed and then heating for one hour gave a residue containing mainly starting material.

The approach to a 9-azasteroid via an A,B,D ring intermediate firstly involved formation of a series of 2-cyclopentyl quinolines. First 2-(2-quinolyl) cyclopentanone was prepared but failed to show any of the typical reactivity of a ketone. A major obstacle to the further elaboration of this cyclopentanone seemed to involve the potential conjugation between ketone and quinoline and the structure is better written as (95).



(95)



(96) R = CO_2Et

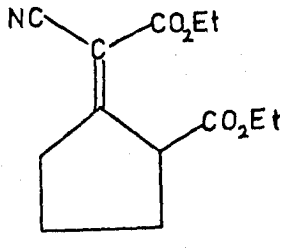
(97) R = CO_2tBu

(98) R = CN

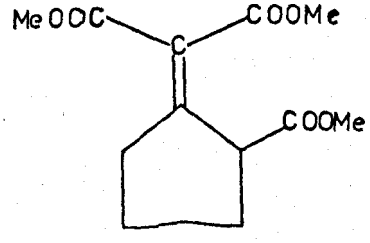
The next step was to prepare 2-(cyclopentyl)quinolines, (96), (97), (98), in which a second 2-substituent in the cyclopentane ring prevented the formation of the dihydroquinoline tautomer. In the compounds (96) and (97) the ester group could not be subsequently removed by any of the standard procedures. In compound (98) the cyano group could be removed but the product was unstable.

The next approach was to reduce the nitrogen ring of compound (96) and alkylate the nitrogen atom thereby inserting a 2 carbon fragment into the molecule, which could be used to form the C ring. By protecting the carbonyl group through forming its ketal, the quinoline (96) could be reduced to its corresponding amine using Adams' catalyst. All attempts at alkylation failed, possibly due to steric problems.

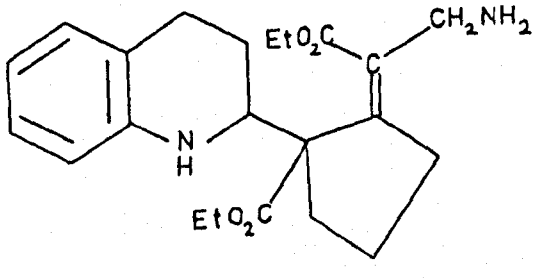
The next route involved reacting quinoline-1-oxide with cyclopentane derivatives already possessing a 2 carbon fragment and suitably activated with electron withdrawing groups (99a). Reduction of the cyano-diester (99b), subsequently prepared, not only caused reduction of the nitrogen ring but also reduction of the C≡N triple bond to give the amine (99c). Because this reduction of the cyanide group presented a serious problem the next cyclopentane derivative to be synthesised was the triester (100). However reaction of quinoline-1-oxide with this triester gave as the only product the dimer (101).



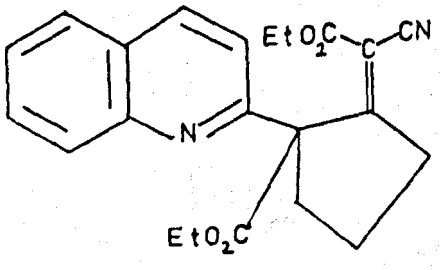
(99a)



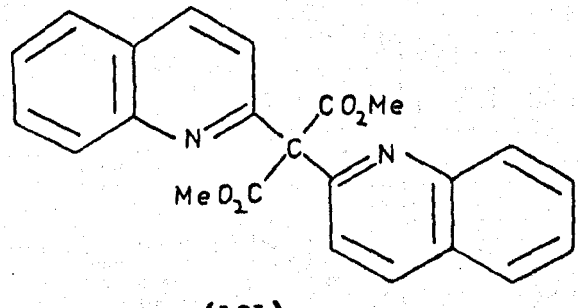
(100)



(99c)

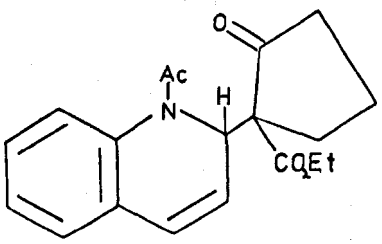


(99b)

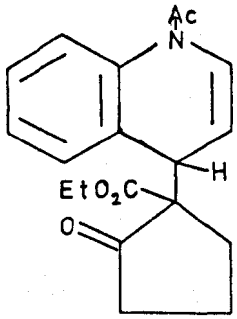


(101)

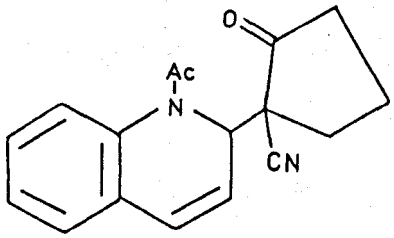
Von Dobeneck and Gotzsche[68] had reported the reaction of quinolines with active methylene derivatives in the presence of acyl halides to give N-acyl-1,2-dihydroquinolines. In a last attempt to synthesise a 2-cyclopentylquinoline, 2-carbethoxycyclopentanone was reacted with quinoline in the presence of acetyl chloride. Instead of the expected 1,2-dihydroquinoline (102), the product was the 1,4-dihydroquinoline (103). An analogous reaction using 2-cyanocyclopentanone gave the expected 1,2-dihydroquinoline (104) but intramolecular cyclisation using sodium hydride failed.



(102)

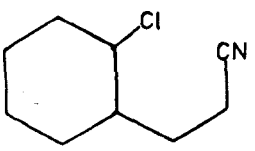


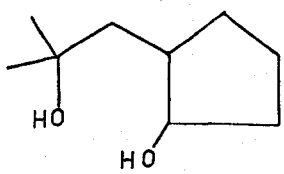
(103)

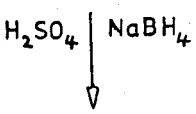


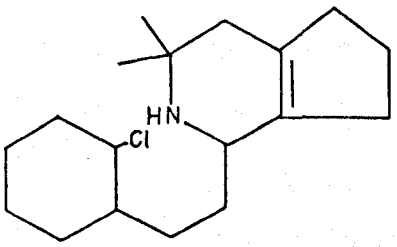
(104)

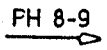
Meyers et al have applied their previously mentioned (p. 19) novel method for the preparation of 8-azasteroids[57] to those of 9- and 13-azasteroids by a suitable choice of starting materials. Hence for a 9-azasteroid system:-

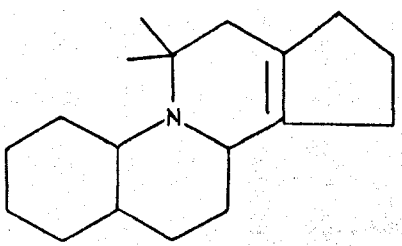




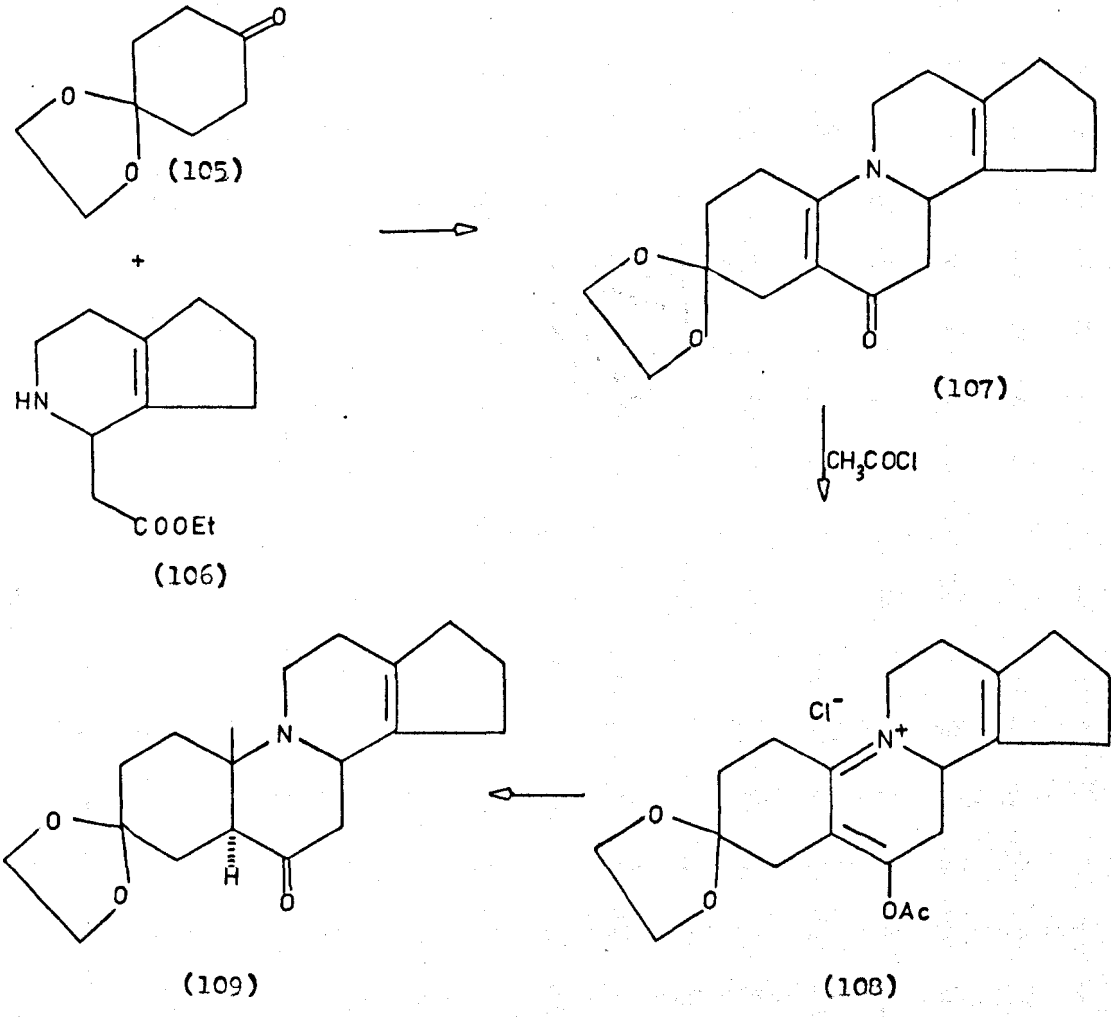






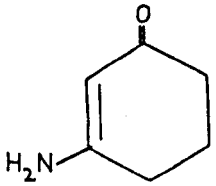


More recently Meyers and Beverung[69] have reported a three step approach to a 9-azasteroid system (109). The monoethylene ketal of 1,4-cyclohexanedione (105) and the piperidine ester (106) were refluxed in toluene to give the four ring system (107). Reduction of the 5,10 double bond was brought about by treatment with acetyl chloride to give the O-acetyl derivative (108) followed by treatment with methyl magnesium bromide to give 3,3-ethylenedioxy-18-nor-9-azaandrost-13(14)-ene-6-one (109).



Total syntheses of azasteroids with the nitrogen in other than the 8-or-9-position have also been performed.

4-AZASTEROID 4-aza-8,14-bisdihydro-estrone ethyl ether (116) has been prepared by Huisman.[70] The quinolinedione (112) was prepared by condensing methylpropiolate with 3-aminocyclohexen-2-one. On boiling

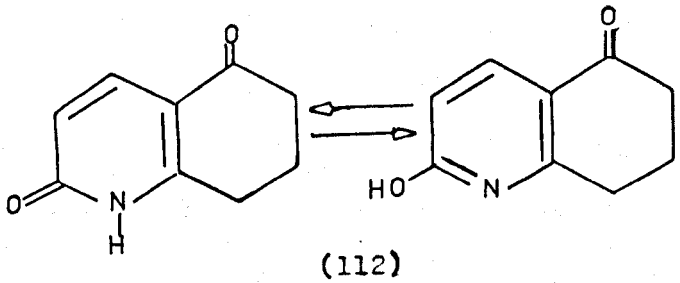


(110)

+

$HC{\equiv}CCO_2CH_3$

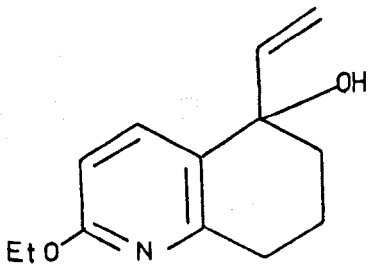
(111)



(112)

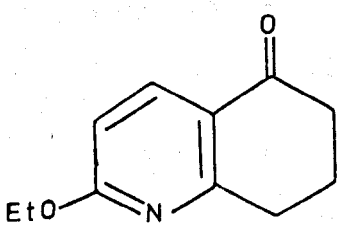
KOH $AgNO_3$

C_2H_5I



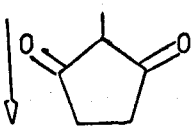
(114)

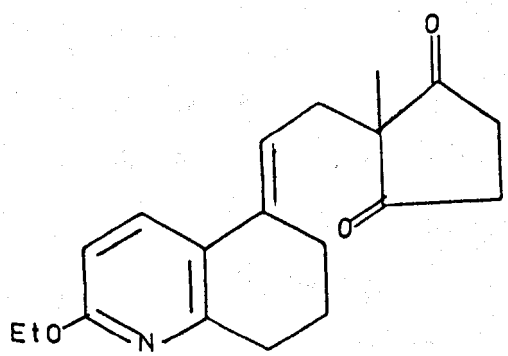
$CH_2{=}CHMgBr$



(113)

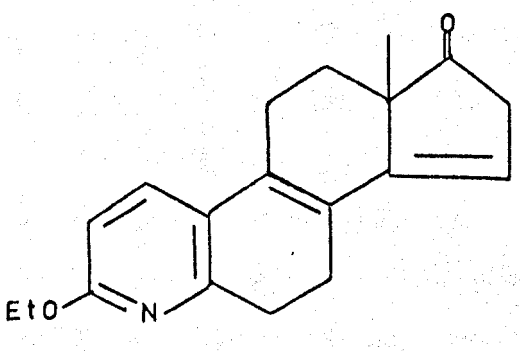
TRITON B





(115)

p-TsOH



(116)

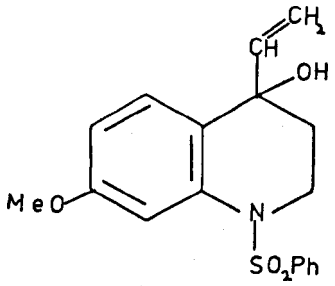
the silver salt of the quinolinedione with ethyl iodide the ethyl ether (113) was obtained, which, when treated with an excess of vinyl magnesium bromide gave the vinyl alcohol (114). The alcohol was condensed with 2-methylcyclopentane-1,3-dione in the presence of Triton B to give the diketone (115) which was cyclised to give the 4-azasteroid (116).

6-AZASTEROID 6-azaestranes have been prepared by Hughes and Smith[71] by condensing the previously prepared quinolol (117) with 2-methyl cyclopentane-1,3-dione (118) to give the diketone (119). Cyclisation to the tetracyclic compound (120) was achieved in methanol/tetrahydrofuran solution in the presence of concentrated hydrochloric acid. By two stages of reductions followed by an oxidative stage 3-methoxy-6-azaestra-1,3,5(10)-6,8-penten-17-ol (121) was obtained.

10-AZASTEROID Starting from the diseco-azasteroid precursor (125) Huisman[72] has prepared a 10-azasteroid. The diseco-azasteroid was prepared by Michael addition of 4-methoxy-2-vinylpyridine (122) to di-tert-butylmalonate (123) and condensation of the anion of the product (124) with 2,5-dioxo-1-methylcyclopentanepropionyl chloride. Decarboxylation and cyclisation of the C ring was brought about with tosyl chloride to give the diketone (126).

Having ketalised the 17-oxo group, the 9-oxo group was reduced with lithium aluminium hydride to the alcohol. Treatment of the alcohol with tosyl chloride and methyl cyanide in potassium carbonate gave a mixture of pyridinium salts (127) which on reduction with sodium borohydride and deketalisation gave 10-azaestr-8(14)-ene-3,17-dione (128).

11-AZASTEROID Clemo and Mishra[73] have prepared an 11-azasteroid which had the B ring aromatic. 2-carbethoxycyclopentanone (130) was condensed with α-napthylamine (129) at 180° to give the diketone (131) as well as a product with 2 napthylamine residues. Cyclisation of the C ring was achieved with concentrated sulphuric acid to the corresponding lactam (132) which on prolonged reduction with sodium in ethanol gave 11-aza-18,19-bisnorandrosta-5(10),6,8-triene (133).



(117)

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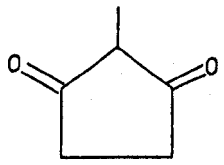
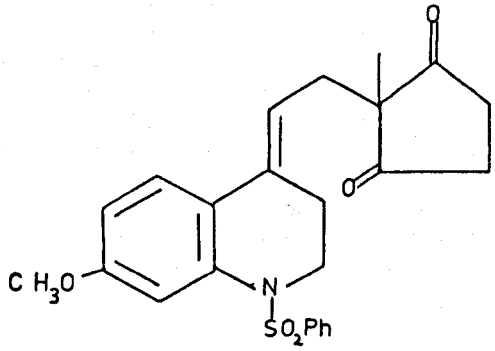
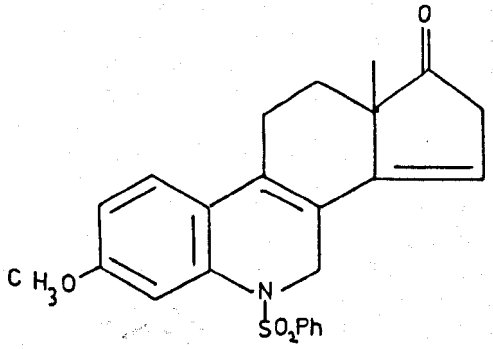


(118)



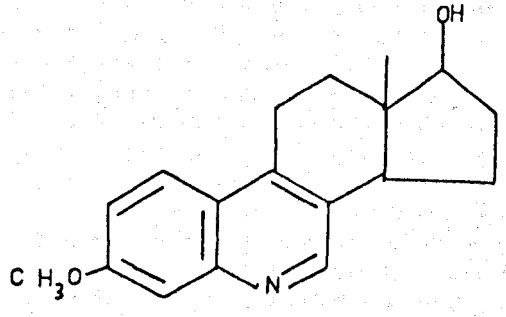
(119)

CONC. HCl

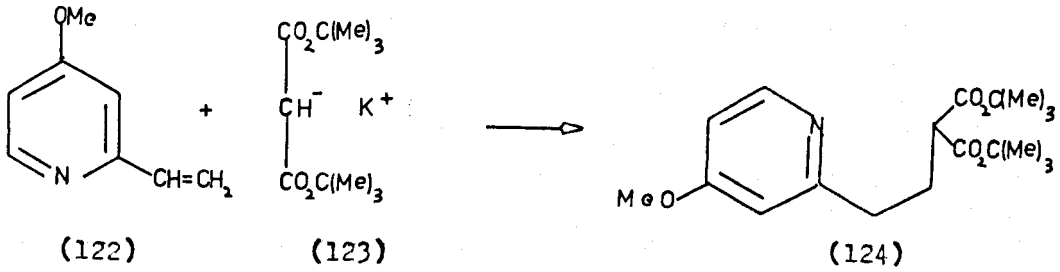


(120)

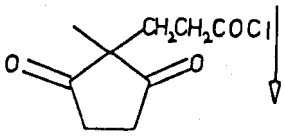
1. Pd/SrCO3
2. NaBH4
3. Li/NH3

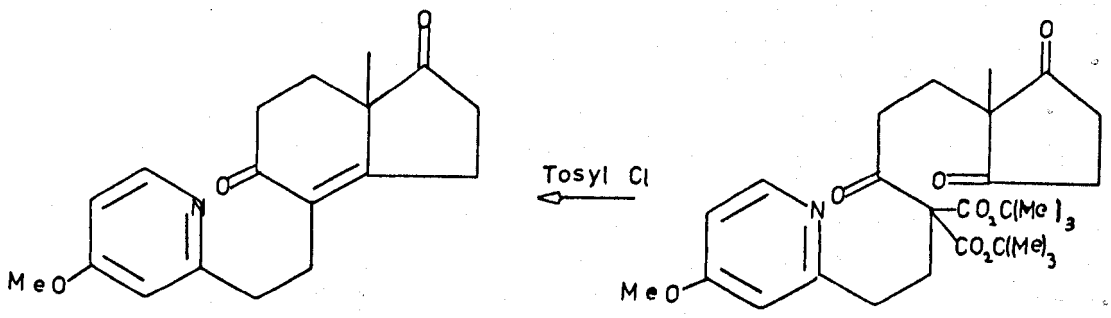


(121)



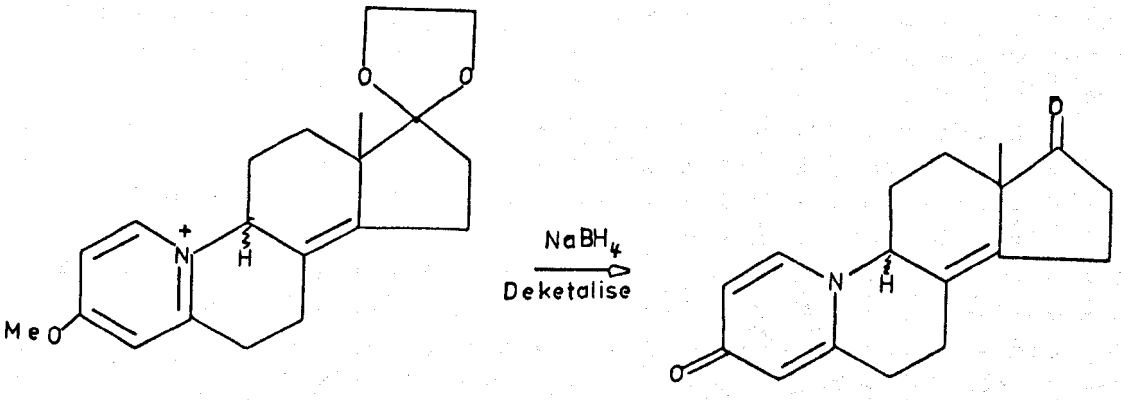
(122) (123) (124)



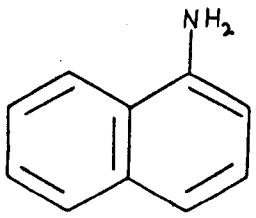


(126) (125)

1. Ketalise
2. $LiAlH_4$
3. Tosyl Cl



(127) (128)



(129)

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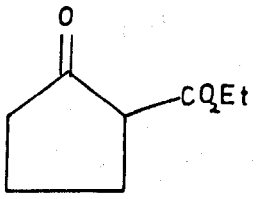
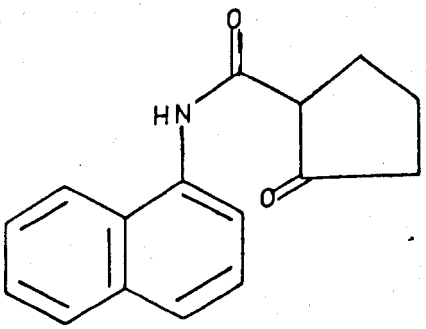


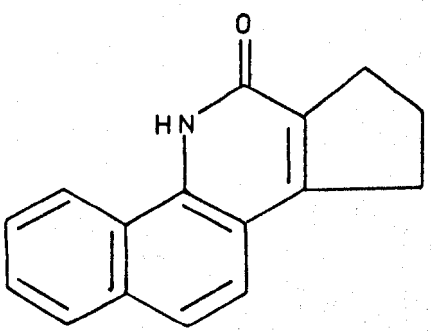
(130)

180° H_2SO_4



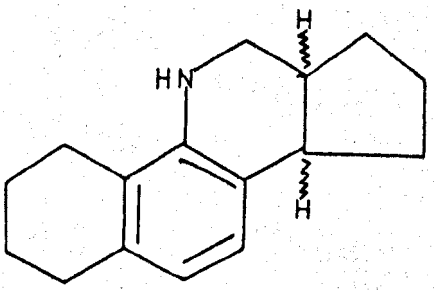
(131)

H_2SO_4



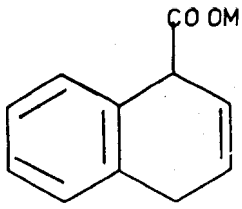
(132)

Na/EtOH



(133)

12-AZASTEROID Formation of the enamine ester (136) from 1-(1-pyrrolidin)yl-1-cyclopentene (135) and methyl-1,4-dihydro-1-naphthoate(134) was achieved by Pandit and Huisman[74] as the first step in the synthesis of a 12-azasteroid. Hydrolysis of the enamine ester gave the corresponding oxo-acid which on treatment with ammonia resulted in the 12-aza-11-oxosteroid (137). N.M.R. studies showed a trans B/C ring fusion.



(134)

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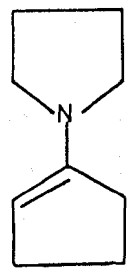
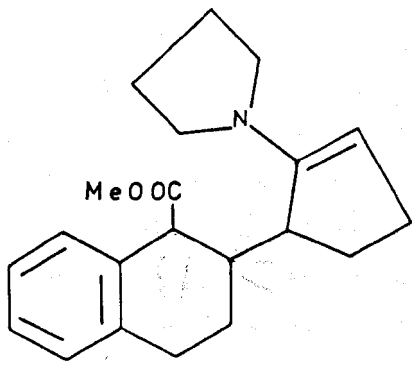
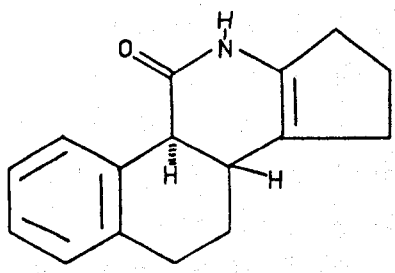


(135)



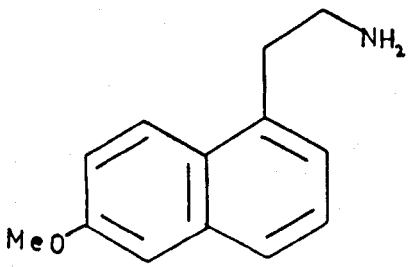
(136)

1. HYDROLYSIS
2. NH_3



(137)

13 and 14-AZASTEROIDS Kessar and co-workers[75] have reported a synthesis of (±)-13-aza-18-norequilenin methyl ether (141). Condensation of 2-(6-methoxy-1-naphthyl)-ethylamine (138) with β-(methoxycarbonyl) propionyl chloride (139) gave an amide (140), which on Bischler-Napieralski reaction followed by reductive cyclisation gave the azasteroid (141). The N.M.R. of the product indicated a semi-chair conformation for ring C.



(138)

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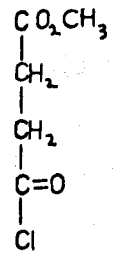

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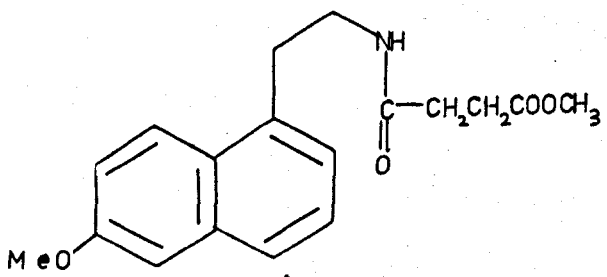

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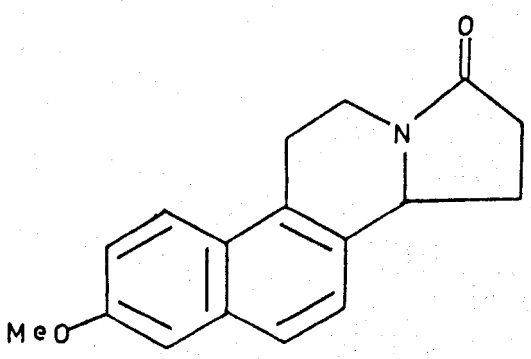

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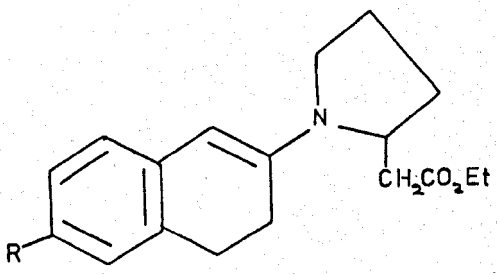

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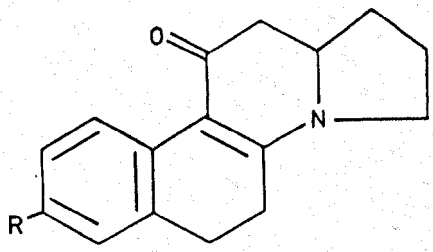

(143)

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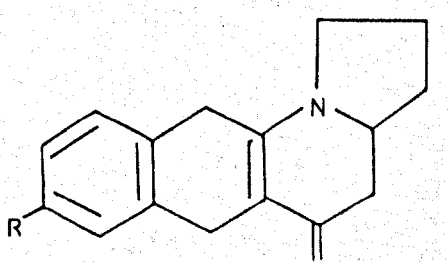
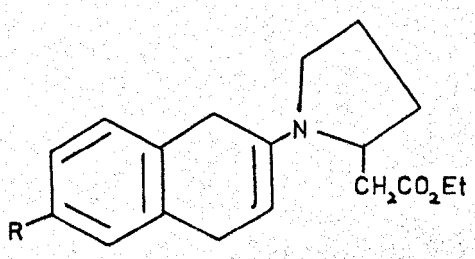


(144)

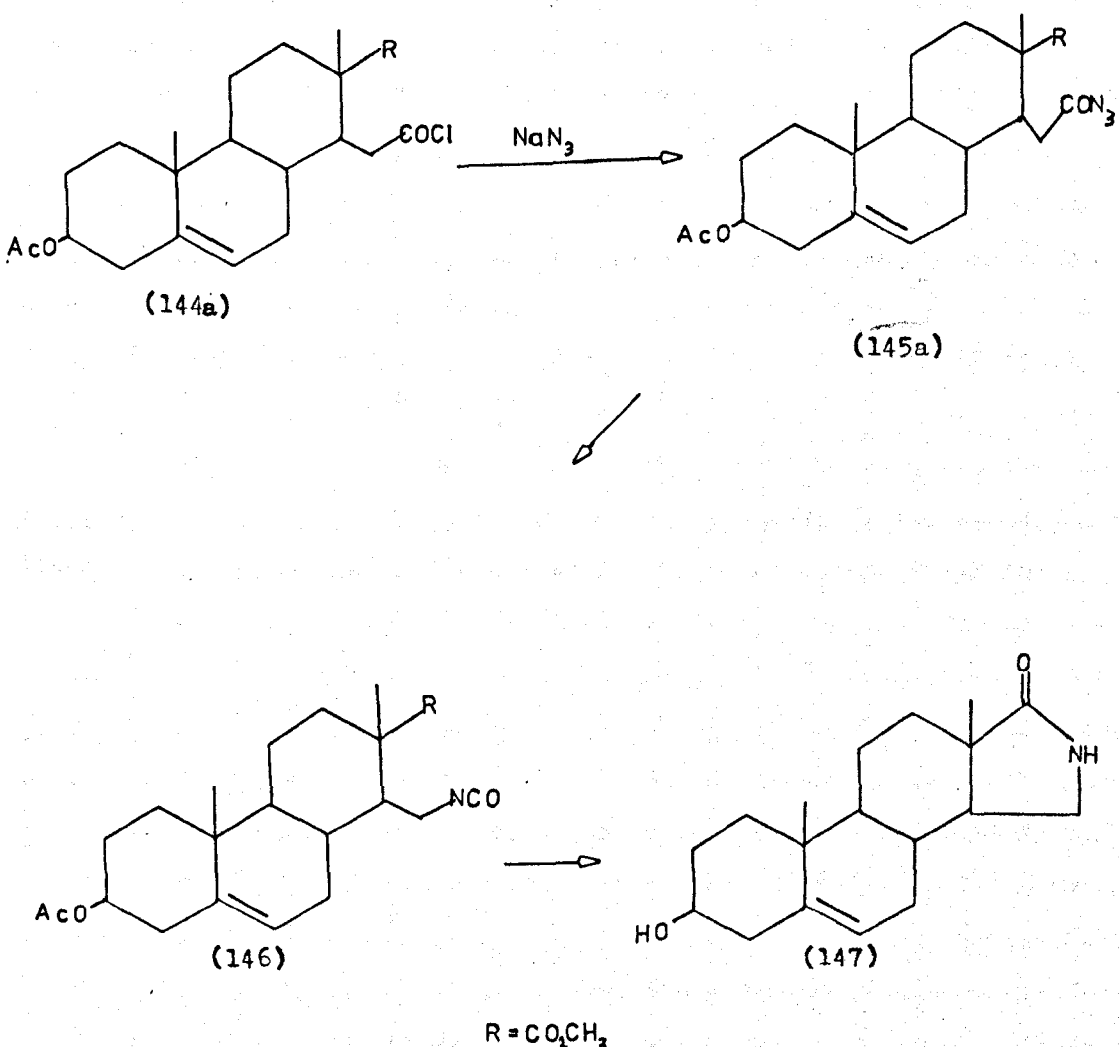
R = OMe



(145)

By a similar method to that used for preparation of a 12-aza-steroid Huisman and co-workers have synthesised a 14-azasteroid.[76] The pyrrolidine enamine (142) was formed from ethyl pyrrolidinyl-acetate and 6-methoxy-2-tetralone. The enamine was then boiled in ethylene glycol to give a mixture of the azasteroid (143) and the azaanthrosteroid (144). The appearance of the latter in the products was thought to be due to the cyclisation of the out of conjugation enamine (145) followed by oxidation.

16-AZASTEROID Kierstead[77] has reported the synthesis of a 16-azasteroid, incorporation of the nitrogen being achieved via formation of an azide. The azide (145a) was formed from the acid chloride (144a) with sodium azide in aqueous acetone. Refluxing the azide in benzene for 1½ hours gave the 1-isocyanato-methyl compound (146) which on being boiled with aqueous methanolic potassium hydroxide gave 3β-hydroxy-16-aza-androst-5-en-17-one (147).



PHYSICAL PROPERTIES OF AZASTEROIDS

Brown, Towns and Trefonas[78] have studied the crystal and molecular structure of 12-keto-17-deoxo-8-azaestrone methyl ether hydrobromide (148) which was prepared by Reine and Meyers.[79] From their results they concluded that the estrogen ring system remained relatively constant regardless of a) the insertion of a nitrogen at the 8-position and b) whether any of the rings had a hydroxyl, keto or methoxyl substituent.

There are a number of ways in which the rings can be fused to each other giving rise to a variety of possible conformations. The natural conformation of estrone has the hydrogens at C-9 and C-14 α-and the hydrogen at C-8β- with respect to the methyl. The azasteroid had the hydrogens at C-8 and C-14 in the natural configuration whereas the hydrogen at C-9 was in the unnatural β-configuration. This caused an unusual cis junction between the B and C rings. A second unusual feature was that both the B and C rings were in the boat rather than the natural chair configuration. The N^+-Br^- distance was found to be very small and the hydrogen of the hydrobromide was on a line between the two but much nearer the nitrogen so that one could envisage:

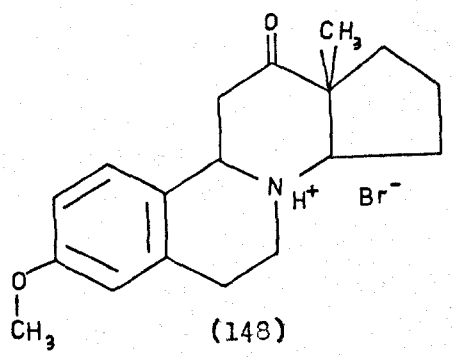
N—H·····Br

Thus this is strong evidence of hydrogen bonding through the bromide ion linking the molecules.

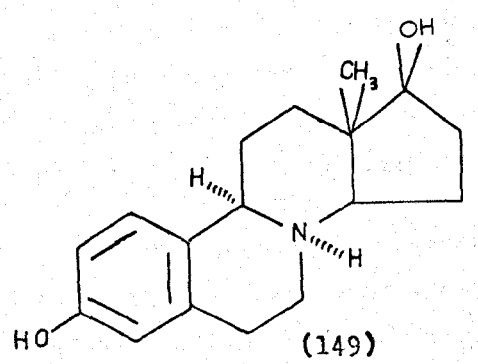
Brown and Trefonas[80] have also studied 8-azaestradiol (149). They preferred to study an azasteroid as a free base where the nitrogen is tertiary instead of quaternary, because the carbon-nitrogen distances in quaternary azasteroids showed no significant differences from natural estrones and in addition the bromide ion in the hydrobromide was found to disrupt the pattern of hydrogen bonding.[78]

The steroid studied was in its natural configuration with the hydrogens at position 9 and 14 in the α-position with respect to the methyl. Ring A was planar and rings B and C were in the chair configuration.

In ring A all the carbon-carbon bond lengths were as those in benzene apart from the C_2-C_3 distance which was shorter and was intermediate between that of benzene and the corresponding distance in estradiol.



(148)



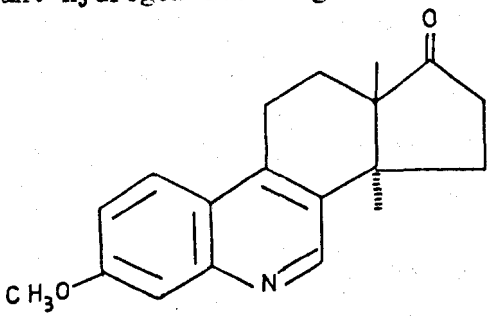
(149)

Rings B and C differ, from the other 8-azasteroids studied, at the 8 position. There is a shortening of the carbon-nitrogen distance about the tertiary nitrogen as opposed to those about the quarternary nitrogen in 8-azaestrone hydrobromide. The distances and angles in ring D are in agreement with those in estradiol. The carbon-oxygen distance at position 3 is consistent with that observed in phenolic groups although smaller than the estimated standard deviation. This suggests that the shortening of the carbon-oxygen bond is due to delocalisation into the aromatic system of the ring. The carbon-oxygen bond at position 17 is also smaller than the e.s.d. but equivalent to that in aliphatic alcohols. The oxygen-hydrogen distance is larger at position 3 than that at position 17 suggesting delocalising of the carbon-oxygen bond at position 3 has weakened the oxygen-hydrogen bond there making the hydroxyl hydrogen more labile.

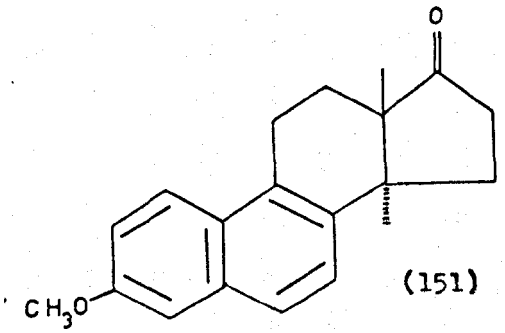
Thus 8-azaestradiol shows identical molecular parameters to estradiol but it has only weak estrogenic activity. It seems that this lack of activity must be caused by the competition between the admittedly weak protonation at the phenolic oxygen and the potential protonation of the nitrogen at the 8-position. Without this acid catalysed protonation at the normal 3-position, the chain of reactions necessary to stimulate estrogenic activity will be supressed.

Pandit and co-workers[81] have studied the mass spectral breakdown patterns of various 6-azasteroids and have compared them with their natural steroid analogues. The only difference in structure between 6-azaequilenin (150) and equilenin (151) is the replacement of a CH by a N atom. It was not surprising therefore to find that the breakdown pattern for equilenin corresponded to the pattern of azaequilenin but having undergone a regular shift of one mass unit.

Later Baranowska et al[82] found that a 9-azasteroid provided an opportunity to study the effect of the N atom on the decomposition routes in the mass spectra. For 9-aza-D-homogonane (152) the molecular breakdown occurred along three principal decomposition routes. The first involved loss of an H atom with subsequent fragmentation of the M-1 ion. The second involved loss of rings A and B while the third involved elimination of a $C_3H_7^{\bullet}$ radical from the molecular ion with concomitant hydrogen atom migration.



(150)



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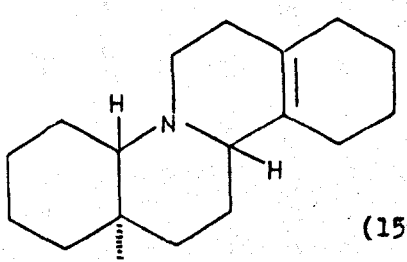
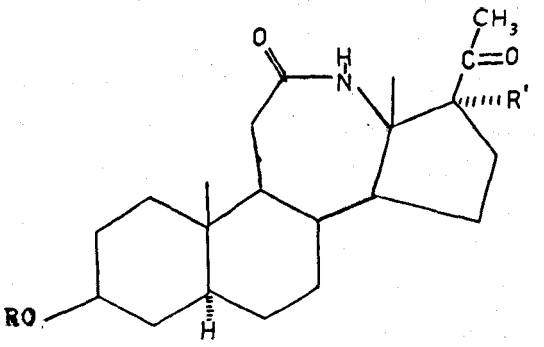


(152)

MICROBIAL OXIDATIONS

Mazor and Muir[83] have reported novel microbial dehydrogenation of C-ring azasteroids. 12a-aza-3β-hydroxy-C-homo-5a-pregnane-12,20-dione (153)(R=R^1=H) was converted by a fermenting culture of Nocardia to 12a-aza-C-homo-1,4-pregnadiene-3,12,20-trione (154)(R=H)



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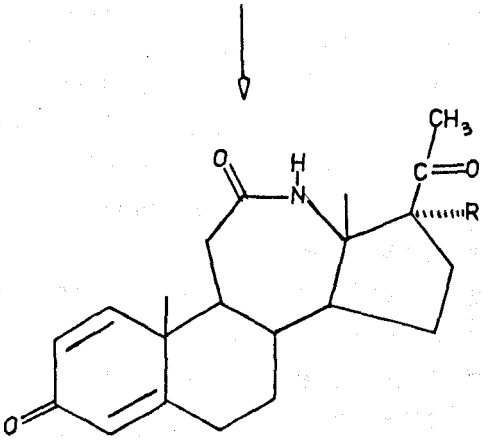
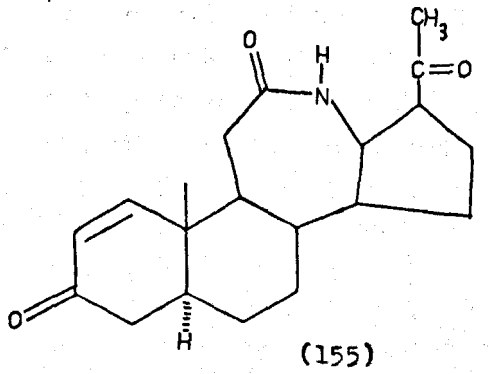


(154)

Also Arthrobacter converted (153) (R=Ac ,R^1=H) to the trione (155).



(155)

DISCUSSION

GENERAL SYNTHETIC APPROACH

It was decided that the initial work should centre on the synthesis of a 9-azaestra-1,3,5(10)-triene nucleus (156). This structure would be stereochemically less complex than the corresponding androstane derivative. Because a large number of naturally occurring steroids possess a methoxyl group in the 3-position, further work would be directed towards the syntheses of azasteroids possessing such a group.

Previous workers[64,65] had approached the synthesis of a 9-azasteroid (156) by preparation of an ABC ring precursor (84) and more recently by preparation of ABD ring precursors[66] (85). The main aim of the present work was to prepare further ABD ring precursors with the intention of cyclisation to form the C ring. These precursors would bear suitable substituents on the nitrogen and on the cyclopentane ring to enable formation of the C ring to take place.

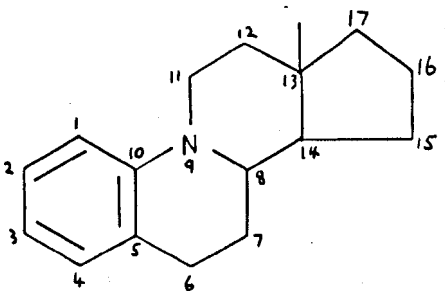
Initial experiments were conducted towards the synthesis of a 9-azaestrol (158) by formation of the tricyclic precursor (157).

The 9-azasteroid structure could be approached by two main synthetic routes. The first involves the formation of a suitably substituted cyclopentane derivative, for example 2-(2-ethoxyethyl) bromocyclopentane (159). Grignard reaction of this with quinoline or with quinoline-1-oxide could give the tricyclic system (160).

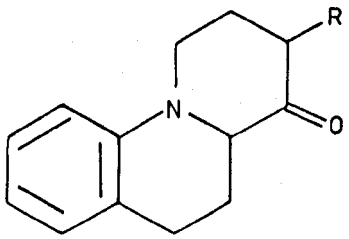
Reduction of the compound using Adams' catalyst to give the tetrahydroquinolyl derivative (161) followed by acid-catalysed cyclisation involving the side chain on the cyclopentane ring could give the tetracyclic azasteroid (162).

The second main approach would be to form the C ring by having a suitable substituent on the B ring of the A,B,D ring precursor instead of on the D ring. Such a synthetic route could be envisaged as starting from the 2-(2-quinolyl) cyclopentanone (163) prepared by the method of Baty, Jones and Moore[66].

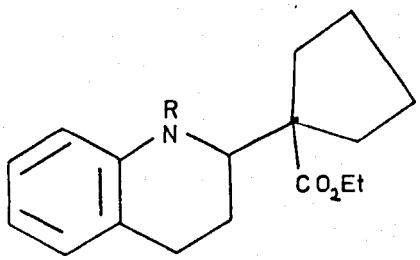
Catalytic reduction of this compound (163) could lead to the tetrahydroquinolyl cyclopentanol (164) which could have the necessary substituent incorporated in the B ring by alkylation with ethyl bromopropionate to give the amine (167). Oxidation of the hydroxyl group could give the ketone (166) which could be cyclised to give the



(156)



(84)



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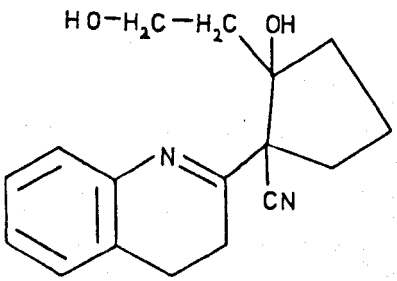

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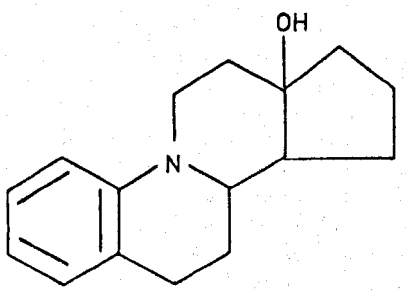

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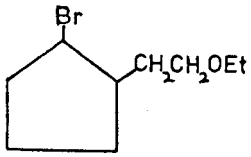

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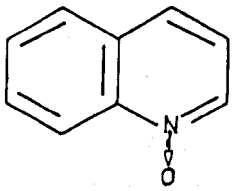
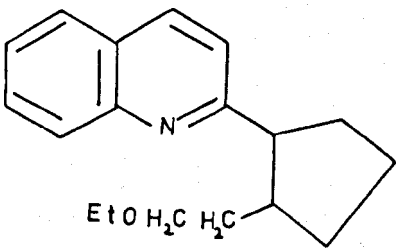
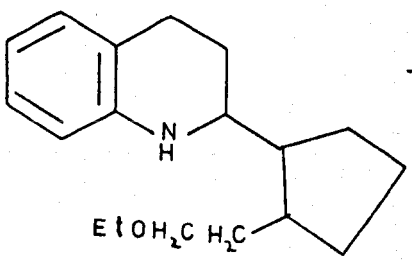


Mg



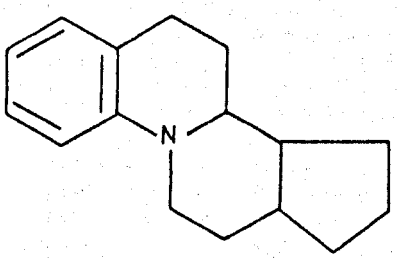
(160)

H_2/PtO_2



(161)

HBr
REFLUX



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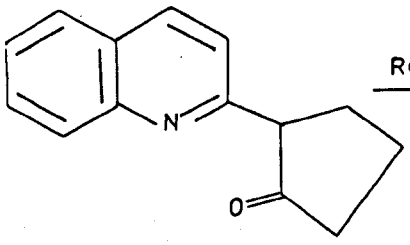
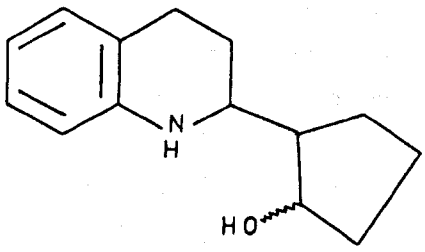


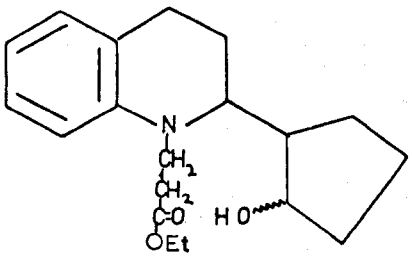
Redt.



(163)

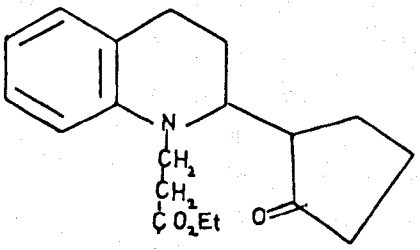
(164)

$BrCH_2CH_2CO_2Et$



(167)

OXID.



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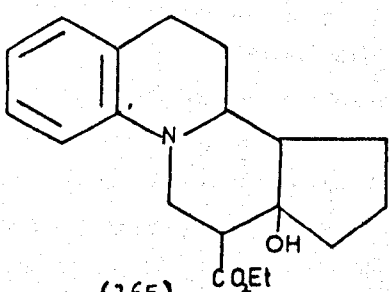
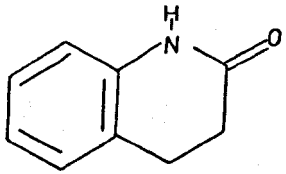
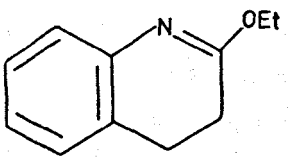


(165)



(168)

$(Et)_3\,O^+$ BF_4^-



(169)

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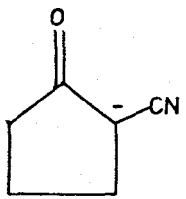

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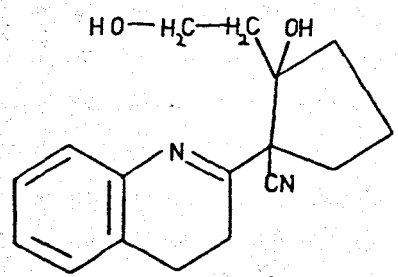
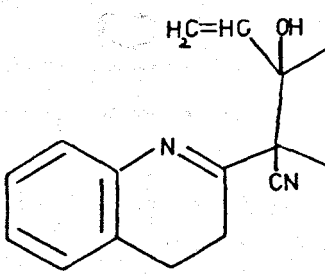


(157)

HBR_2

H_2O_2



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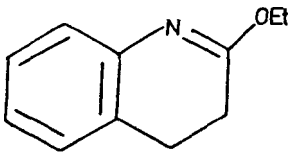

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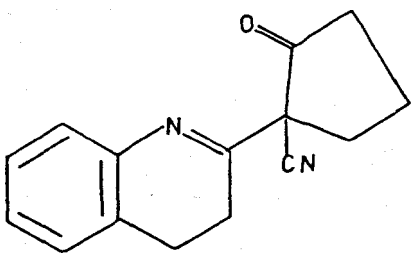
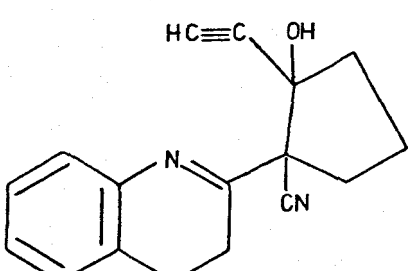


(171)

$CH{\equiv}C^-$



(173)

LINDLAR'S CATALYST / H_2

tetracyclic structure (165).

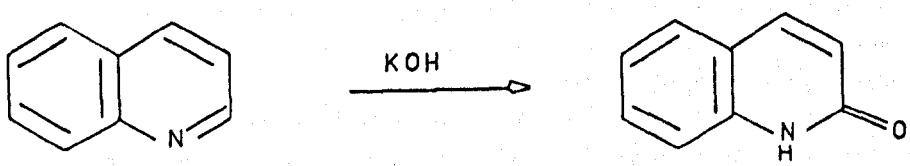
Syntheses based on these methods of approach will be discussed later.

ATTEMPTED SYNTHESIS OF 9-AZAESTROL

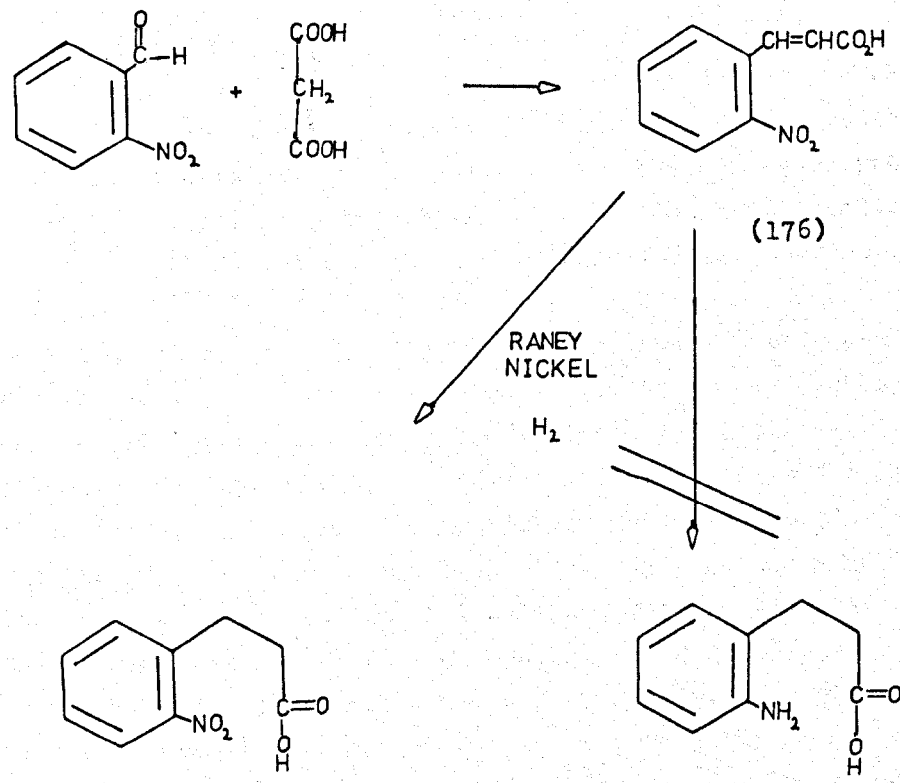
The first step in the intended route of this synthesis was ethylation of 1,4-dihydro-2-quinolone (168) to give the ether (169). Formation of the sodium salt of 2-cyanocyclopentanone (170) prepared by the method of Thompson[84] with sodium hydride in dimethoxy ethane could bring about condensation with the ether (169) to give the 2-substituted dihydroquinoline (171).

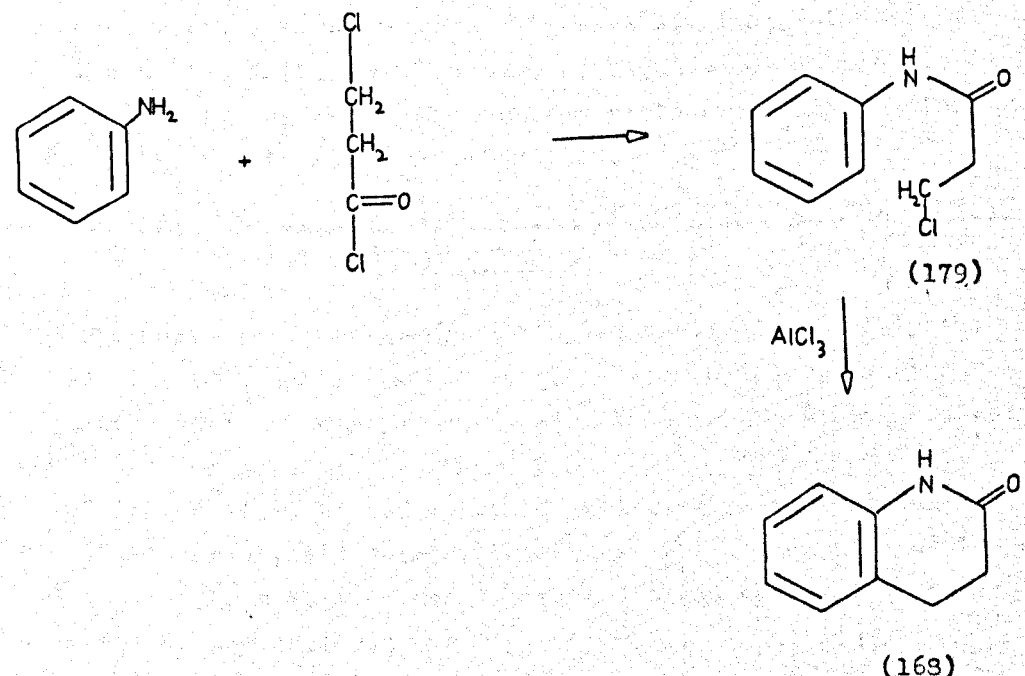
Acetylation of the tricyclic compound (171) with sodium acetylide could give the acetylenic carbinol (173) bearing a two carbon fragment necessary for the formation of a six membered C ring. Reduction of compound (173) catalytically with Lindlar's poisoned palladium charcoal catalyst in the presence of hydrogen could reduce the acetylenic triple bond in compound (173) only as far as the required double bond, hence giving the carbinol (172). Reaction with dialkyl borane followed by oxidation with hydrogen peroxide could give the diol (157) which is suitably substituted on the D ring for formation of the C ring of the azaestrol.

Attempts on the synthesis of 1,4-dihydro-2-quinolone proved initially unsuccessful. The first method was via 2-quinolone (175) and subsequent reduction of the nitrogen ring double bond. The method of Tchichibabin[85] was followed for the preparation of 2-quinolone by reaction of quinoline (174) with solid potassium hydroxide but this method failed.



(174) (175)


CH=CHCO2H
NO2
(176)
RANEY
NICKEL
H2
NO2
NH2
(177)
(178)


NH2
Cl
CH2
CH2
Cl
(179)
AlCl3
(168)

The second method for the preparation of 1,4-dihydro-2-quinolone was a Perkin condensation of 2-nitrobenzaldehyde with malonic acid to give 2-nitrocinnamic acid (176). Reduction of this acid with Raney Nickel catalyst in the presence of hydrogen under pressure gave 2-(2-nitrophenyl) propionic acid (177) instead of the anticipated amino acid (178) which could undergo cyclisation to form the hetero ring.

The third approach to 1,4-dihydro-2-quinolone was to react aniline with β-chloropropionyl chloride to give 2-chloro-N-phenylpropionamide (179) following the procedure of Mayer and co-workers[86].

Friedel-Crafts cyclisation of this gave the required 1,4-dihydro-2-quinolone (168). The next step in the synthesis was to alkylate the oxygen to give an ether. Ethylation with triethyloxonium fluoroborate or methylation using dimethyl sulphate both proved unsuccessful. Methylation using toluene instead of benzene so that a higher refluxing temperature could be attained was also unsuccessful. The reactions were followed on I.R. solution cells and in neither case was there a reduction in the carbonyl absorption at 1650 $cm.^{-1}$ after a reaction time of 72 hours.

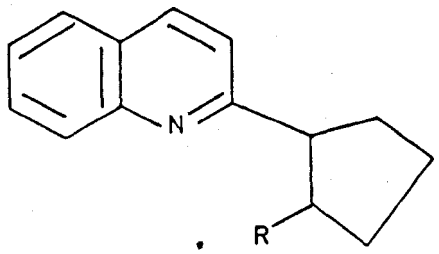
One possible explanation for the lack of success in the ethylation could be that ethylation had occurred to give the isomeric 2,4-dihydro-2-ethoxyquinoline which could be easily hydrolysed, perhaps during the work up procedure to give starting material again.

Due to the failure of 1,4-dihydro-2-quinolone to undergo O-alkylation and the greater attraction of more feasible alternative synthetic routes, this route was abandoned.

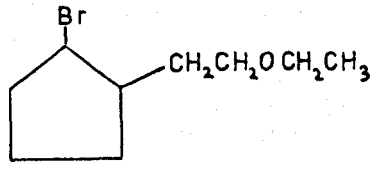
SYNTHESIS AND REACTIONS OF SOME SUITABLY SUBSTITUTED CYCLOPENTANE DERIVATIVES.

The next synthetic approach adopted involved initially the preparation of a tricyclic azasteroid precursor (180) bearing the A,B, and D rings of the future azasteroid with the D ring suitably elaborated for formation of the C ring.

It was decided that a suitable intermediate to synthesise would be 2-(2-ethoxyethyl)-1-bromocyclopentane (159). Reaction of the Grignard reagent from this compound with quinoline would give the required tricyclic compound (180).



(180)



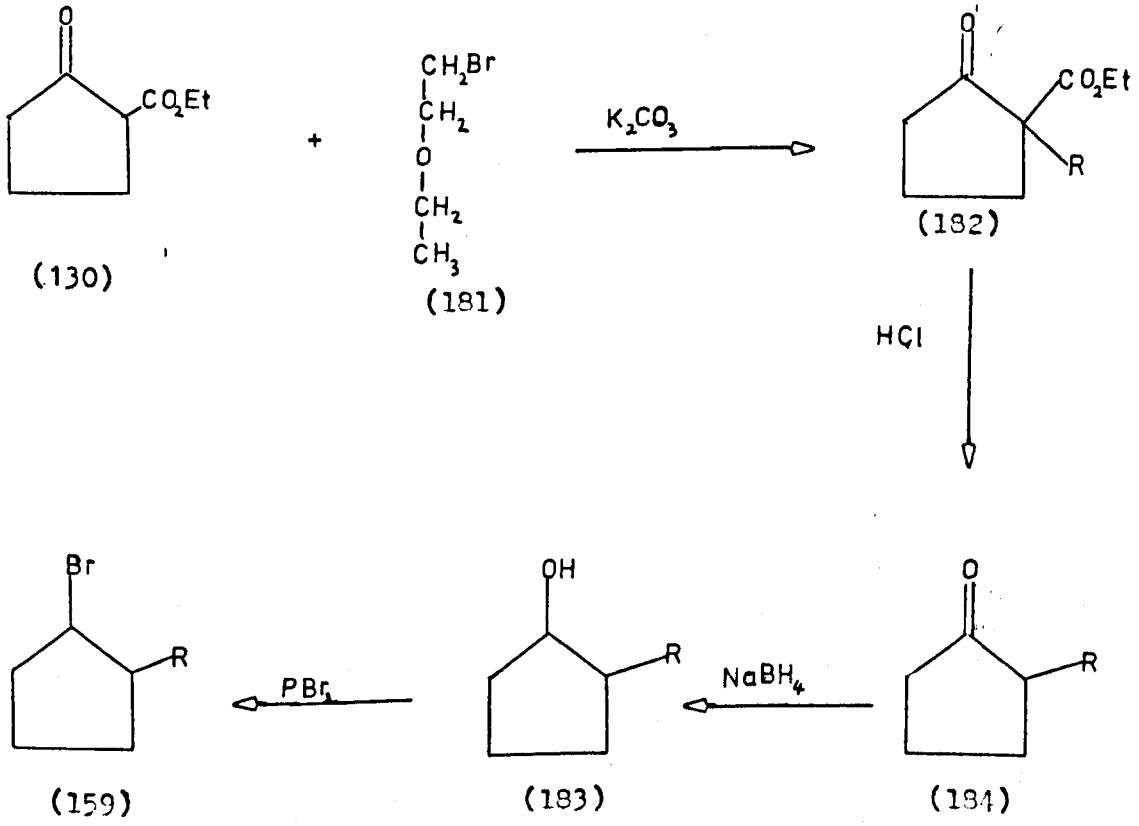
(159)

PREPARATION OF 2-(2-ETHOXYETHYL) BROMOCYCLOPENTANE (159).

Preparation of this compound involved a four step synthesis.

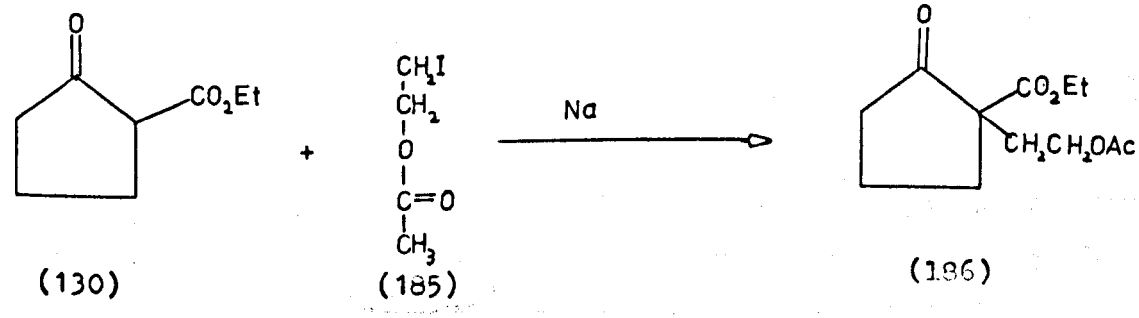
The β-keto-ester (130) was prepared in a straight forward procedure by a Dieckmann cyclisation of diethyl adipate. The preparation of 2-bromoethoxyethane was carried out as a modification of the procedure used by Wood[87]. Difficulty was initially encountered in the alkylation of the keto-ester (130). The carbanion of compound (130) can undergo either C-alkylation or O-alkylation. Factors favouring C-alkylation are solvents such as toluene, ethanol, tetrahydrofuran, and a small counter-ion used to form the carbanion. Factors affecting O-alkylation are solvents such as dimethylformamide, dimethoxyethane, dimethylsulphoxide or hexamethylphosphoric acid triamide as solvents and a large counter-ion[88].

Conducting the alkylation in ethanol with sodium ethoxide failed to give the expected product but gave only diethyl adipate again. King and co-workers[89] have reported that when 2-bromoethoxyethane was condensed with ethyl-sodio-2-ketocyclohexane carboxylate in ethanol they obtained only diethyl-α-2-ethoxyethyl pimelate (189). They overcame this difficulty by employing toluene as solvent but ketonic hydrolysis of the resulting ester by partial ring fission to substituted pimelic acid was found to cut the yield considerably. They found that it was better to recyclise the resulting pimelic ester to give the product (191) which could be hydrolysed to the ketone (190) using barium hydroxide.

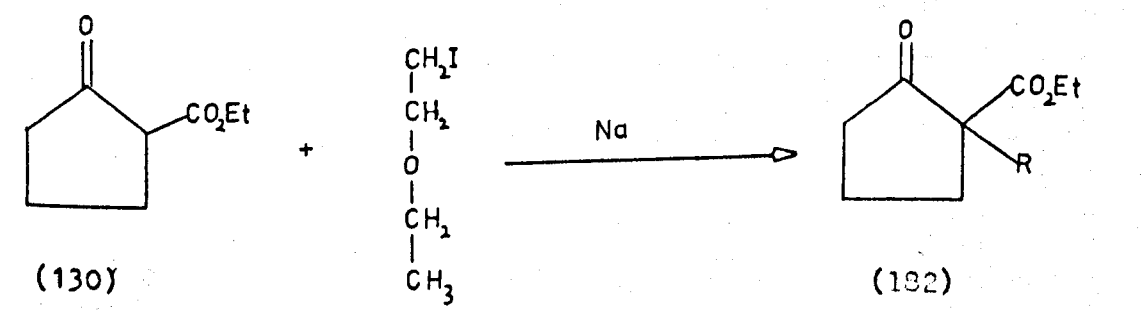


(130) (181) (182)

(159) (183) (184)

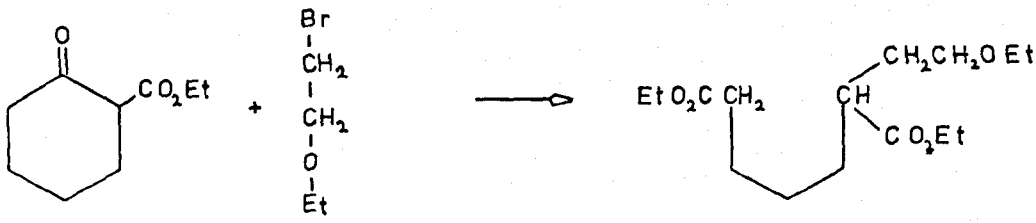


(130) (185) (186)

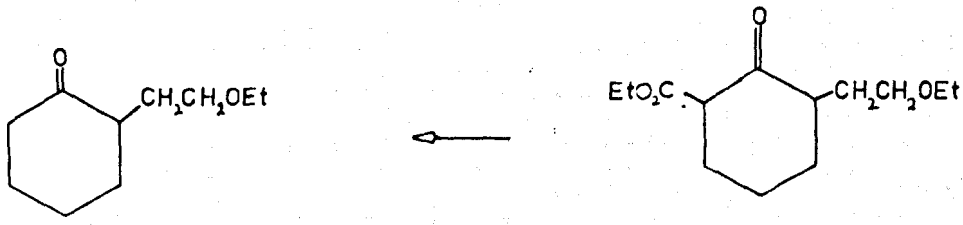


(130) (187) (182)

R = CH_2CH_2OEt



(188) (189)



(190) (191)

Attempts to apply King's work to the five membered ring system were not successful. Alkylation using toluene as the solvent and sodium hydride or sodium to form the carbanion gave a low yield of product (14%) and a large amount of higher boiling material boiling over a wide range.

Booth and co-workers[90] have reported that 2-carbethoxycyclopentanone (130) could be alkylated with 2-iodoethylacetate (185) without ring opening or ketonic hydrolysis taking place to give the required compound (186) by forming the carbanion with metallic sodium and refluxing in benzene for four days. However alkylation of the keto-ester (130) with 2-iodoethoxyethane (187) employing the conditions of Booth et al[90] again gave only a low yield of product and a large amount of higher boiling material. Similar results were obtained when attempting the alkylation in either dimethoxyethane or dimethylformamide using either sodium or sodium hydride to form the carbanion.

Very recently Barco and co-workers[91] have reported on facile

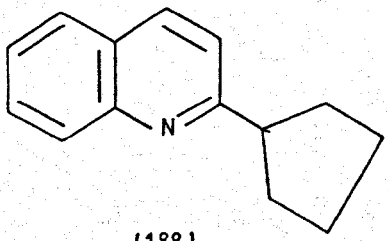
alkylations of the keto-ester (130). Their relatively simple method involves alkylation in the presence of potassium carbonate in acetone solution, without the isolation of the enolate. Using 1-bromoprop-2-ene and n-1-bromopentane as alkylating agents, C-alkylation occurred giving yields of 91% and 85% respectively. However when 1-chloro-2-phenyldimethyl ether was the alkylating agent, C-alkylation accounted for 70% of the yield and O-alkylation for 30%.

The procedure of Barco et al[91] was thus followed in a further alkylation attempt using their general method. This gave a product in high yield (82%) that was exclusively C-alkylated. Hydrolysis and decarboxylation of the keto-ester was brought about by boiling in alcoholic hydrochloric acid using the method employed by Prelog and Szpilfogel[92] for the hydrolysis and decarboxylation of a related compound. The ketone group of the product, 2-(2-ethoxyethyl) cyclopentanone (184) was reduced to the corresponding alcohol (183), by treatment with sodium borohydride in absolute ethanol. The 2-(2-ethoxyethyl)-1-bromocyclopentane (159) was prepared from the alcohol (183) by treatment with phosphorus tribromide in benzene. The more readily obtainable bromocyclopentane was synthesised by an analogous route and used as a model compound in reactions with quinoline and quinoline-1-oxide.

REACTIONS WITH QUINOLINE AND QUINOLINE-1-OXIDE

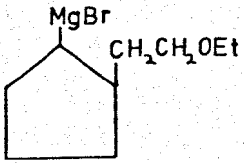
The first attempted reaction was between bromomagnesiumcyclopentane and quinoline in boiling benzene. After 24 hours and 48 hours extracts were worked up and subjected to G.L.C. analysis which showed only quinoline and cyclopentane peaks but no peaks with a greater retention time than these two which could correspond to the expected product, 2-quinolylcyclopentane (188).

In the second Grignard reaction involving bromomagnesiumcyclopentane, quinoline-1-oxide was used instead of quinoline since this is activated for substitution in the 2-position. After reaction in boiling ether for four hours a brown oil was obtained which was shown by T.L.C. to be composed of three compounds. These were separated by distillation at reduced pressure to give cyclopentane, quinoline and 2-quinolylcyclopentane (188). The N.M.R. spectrum of 2-quinolylcyclopentane showed six aromatic protons between 8.15 and 6.95 p.p.m., a single proton multiplet between 3.4-2.9 p.p.m. (the cyclopentane proton in the 1-position) and eight cyclopentane protons at 2.15-1.45

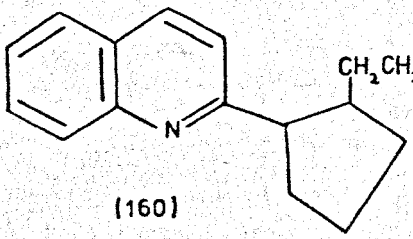


(188)

Quinoline



(189)

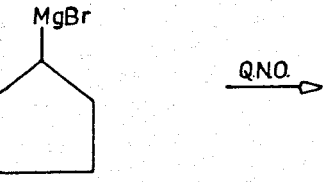


(160)

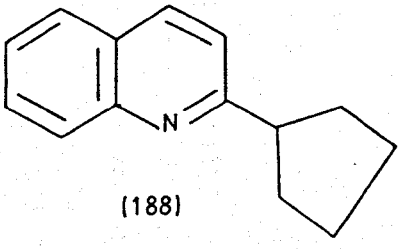
QNO

TMEDA

-78°

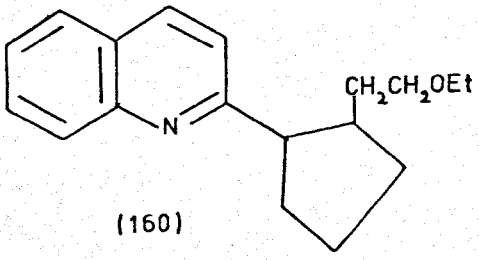


Q.NO.

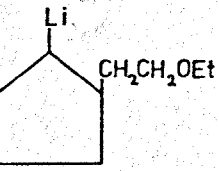


(188)

Q.NO.

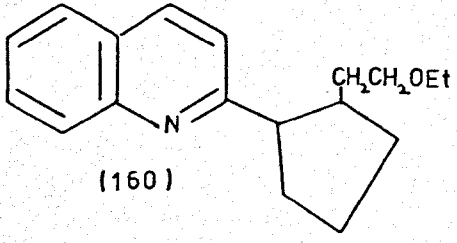


(160)



(190)

Quinoline



(160)

p.p.m. Because quinoline-1-oxide is only moderately soluble in ether the reaction was performed again using tetrahydrofuran as solvent in which the quinoline-1-oxide was more soluble. However the yield of product (26%) was significantly lower than that obtained using ether as solvent (43%).

Because of the success of the Grignard reaction between quinoline-1-oxide and bromocyclopentane the same reaction was performed on the ethoxyethyl analogue (189). A red oil was obtained, the T.L.C. of which showed it to be composed of three compounds. Distillation at reduced pressure gave 2-ethoxyethylcyclopentane, quinoline and quinoline-1-oxide but no 2-(2-quinolyl) ethoxyethyl cyclopentane (160).

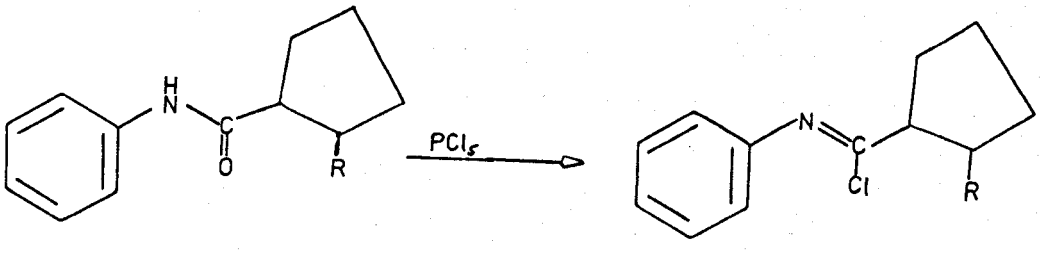
Due to the relative lack of reactivity of the bromomagnesium compounds, interest was diverted to the more reactive lithium compounds. Reaction of the lithium reagent of 2-(2-ethoxyethyl)-1-bromocyclopentane (190) with quinoline in boiling ether failed to give any product. The reaction was also tried again using a higher boiling solvent. The lithium reagent was formed in ether and the solvent changed to toluene for the reaction but no success was obtained with this method.

Frankel and co-workers[^] private communication have reported successes with Grignard reactions with quinoline using tetramethylethylenediamine (T.M.E.D.A.) as solvent at low temperatures. The reaction between the lithium reagent (190) and quinoline-1-oxide was performed in tetramethylethylenediamine at -78° in a dry ice/acetone bath. The temperature was then raised to 50° for cyclisation of the C ring to occur. G.L.C. analysis indicated that no product (199) nor any tetracyclic compound were present.

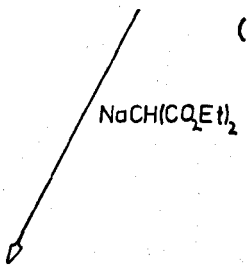
REACTIONS OF ANILINE AND PHENYL ISOCYANATE WITH CYCLOPENTANE DERIVATIVES

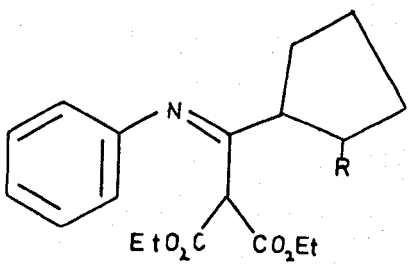
Because of the difficulties encountered in the reaction involving quinoline and quinoline-1-oxide a slightly different approach was adopted. This had the disadvantage that the intended azasteroid precursor only had the A and D rings complete but was suitably substituted for formation of the B and C rings. The next aim was thus to prepare the anilide (191).

The azasteroid could by synthesised in the following scheme. The anilide (191) could undergo nucleophilic substitution with phosphorus pentachloride to give the chloro compound (192). Condensation

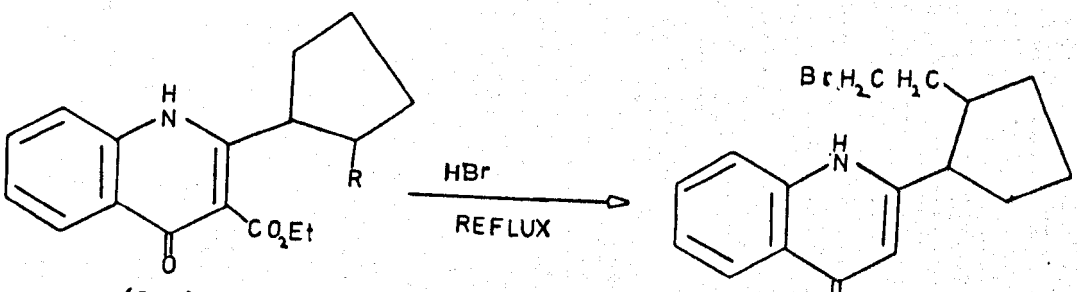


(191) (192)





(193)



(194) (195)

R = CH_2CH_2OEt

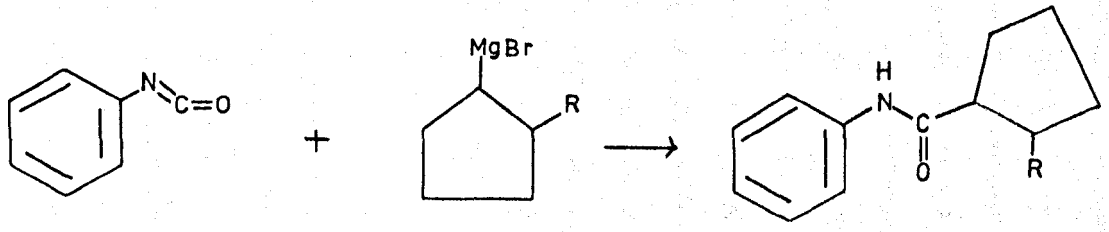
of the sodium salt of diethyl malonate could give the diester (193) which could undergo cyclisation of the B ring by heating alone. The ester group could be removed by acid hydrolysis and decarboxylation. Reduction of the 7,8 olefinic bond could be achieved with the use of palladium on charcoal catalyst.

The preparation of the anilide (191) could be achieved by reaction of aniline with the acid chloride (198) or the methyl ester (199). These compounds could be prepared from the bromo compound (159) via the corresponding cyanide (196) and carboxylic acid (197). Trial reactions using the acid chloride (200) and the methyl ester (202) of cyclopentane carboxylic acid as models were performed to see if either could react with aniline to give the anilide (201). The cyclopentane carboxylic acid chloride (200) reacted with aniline to give the anilide (201) but the methyl ester (202) failed to give the expected product. However attempts to prepare the cyano compound (196) failed.

An alternative method for the preparation of the anilide (191) is a Grignard reaction between phenyl isocyanate (203) and the previously prepared 2-(2-ethoxyethyl)-1-bromocyclopentane (159). The reaction was performed in the usual way to give a brown very viscous oil and a white solid. The solid proved to be diphenyl urea formed by the hydration of excess phenyl isocyanate in the work up procedure.

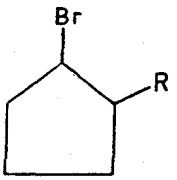
Chromatography on Woelm alumina (activity 4) separated the crude oil to give a small percentage (3%) of the desired anilide (191).

Because of the low yield obtained this approach was abandoned. The most likely reason for the lack of success in obtaining a good yield in the synthesis of the anilide (191) is thought to be the steric hindrance produced by the ether side chain of the cyclopentane ring.



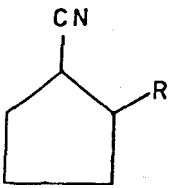
(203) (189) (191)

R= CH_2CH_2OEt

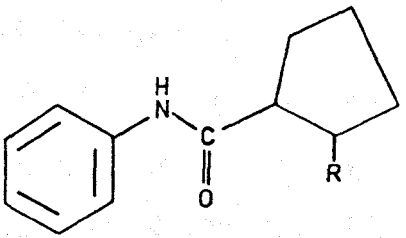


(159)

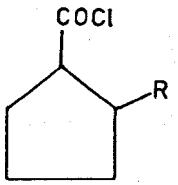
NaCN



(196)

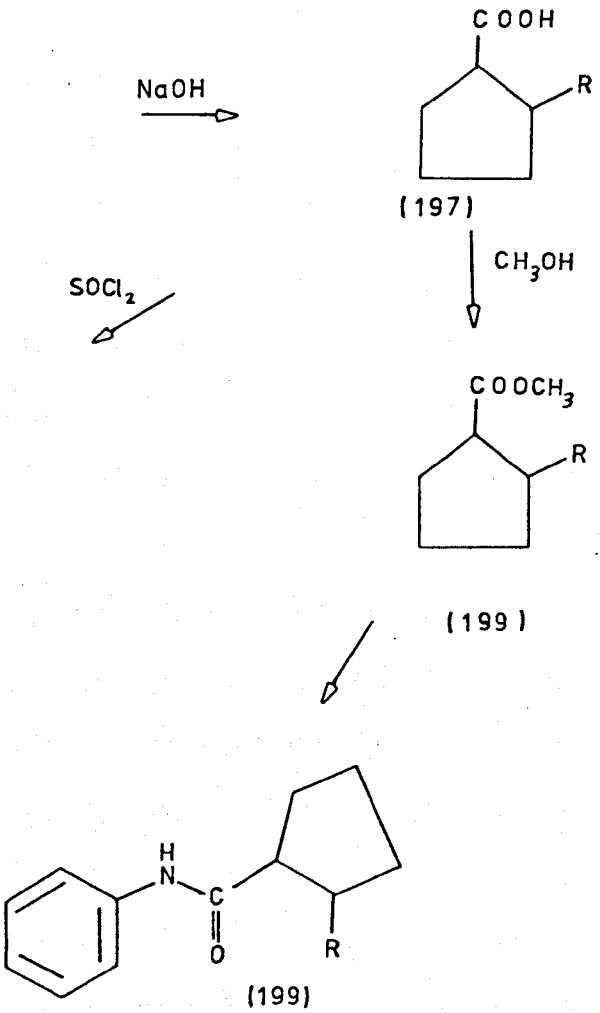


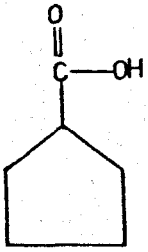
(191)

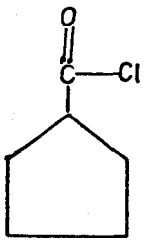


(198)

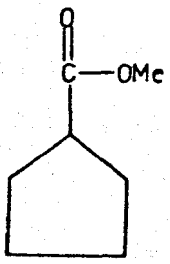
$R = CH_2CH_2OCH_2CH_3$


NaOH
COOH
R
(197)
CH_3OH
$SOCl_2$
$COOCH_3$
R
(199)
H
N
C
O
R
(199)

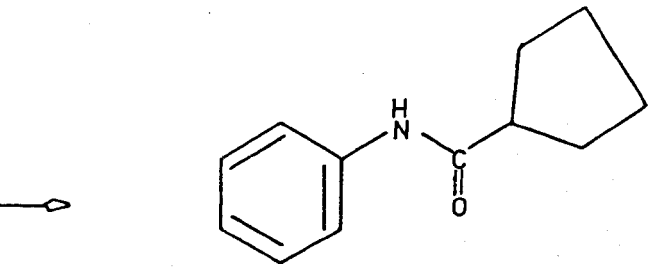




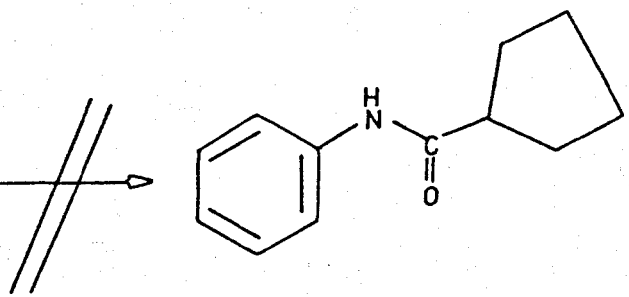
(200)



(202)



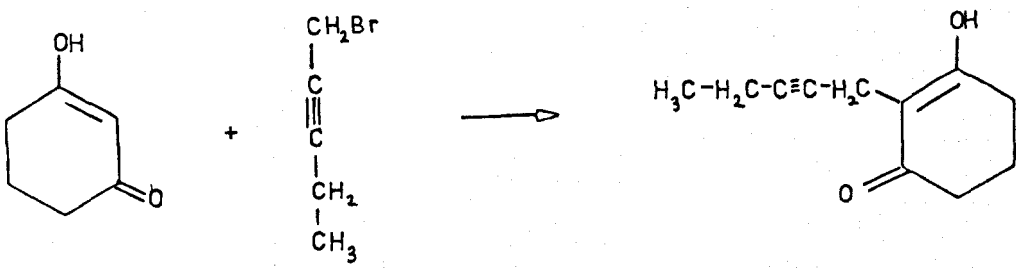
(201)



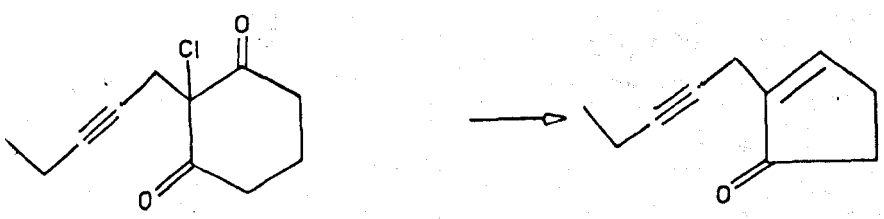
(201)

ATTEMPTED SYNTHESES OF SUITABLY SUBSTITUTED CYCLOPENTENONES.

Buchi and Egger[93] have reported the synthesis of the enolic 2-(2-pentynyl)-1,3-cyclohexanedione (206) by alkylation in aqueous potassium hydroxide solution of 1,3-cyclohexanedione (205) with 1-bromo-2-pentyne (204).



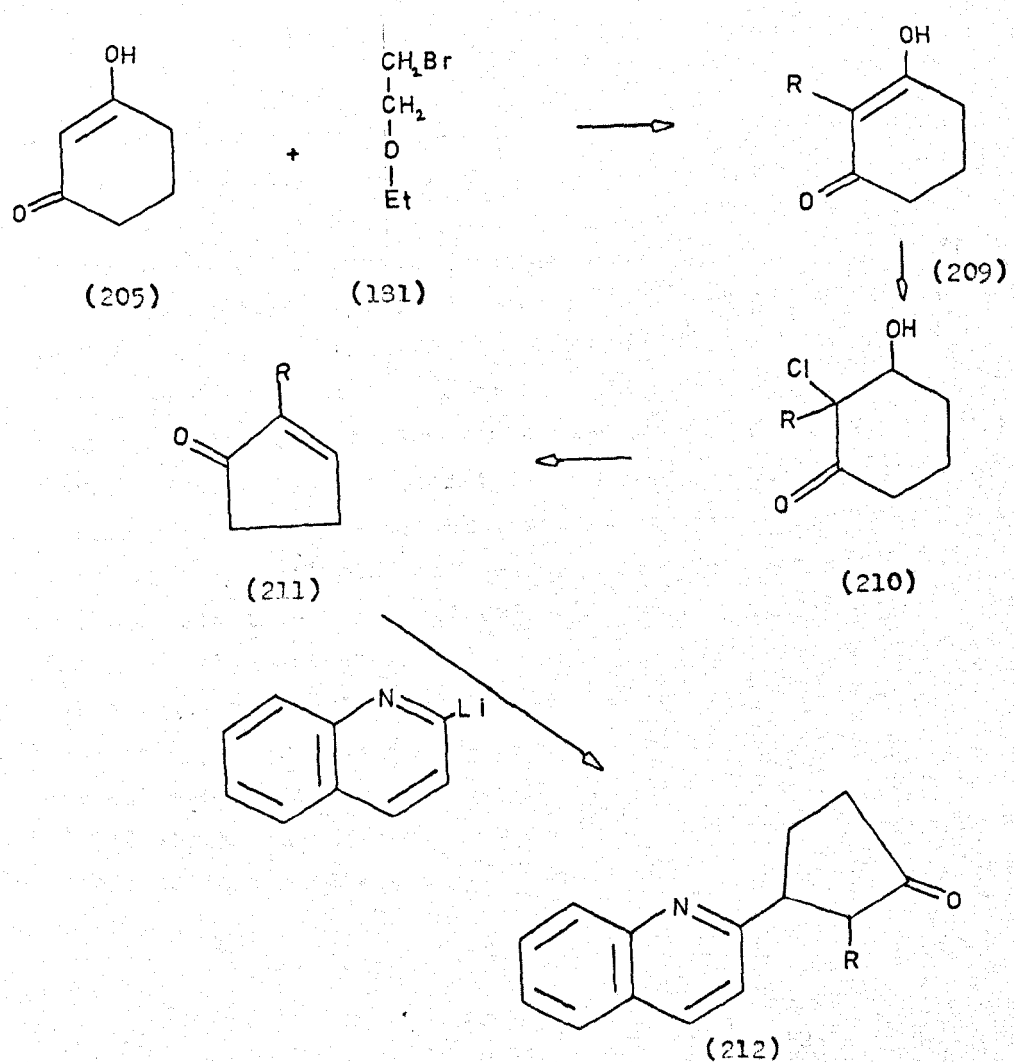
(205) (204) (206)



(207) (208)

They then found that ring contraction to a five membered ring could be brought about using the following procedure. Chlorination of the enol (206) with tertiary butyl hypochlorite gave the non-enolised dione 1-chloro-1-(2-pentynyl)-2,6-cyclohexanedione (207). Simultaneous dehydrochlorination and ring contraction were achieved by boiling in xylene in the presence of anhydrous sodium carbonate to give the cyclopentenone (208).

It was decided to prepare 2-(2-ethoxyethyl)-1,3-cyclohexanedione (209) by a similar route involving alkylation of cyclohexane-1,3-dione with 2-bromoethoxyethane and use of the same method to bring about ring contraction to give the cyclopentenone (211) via the chloro compound (210).

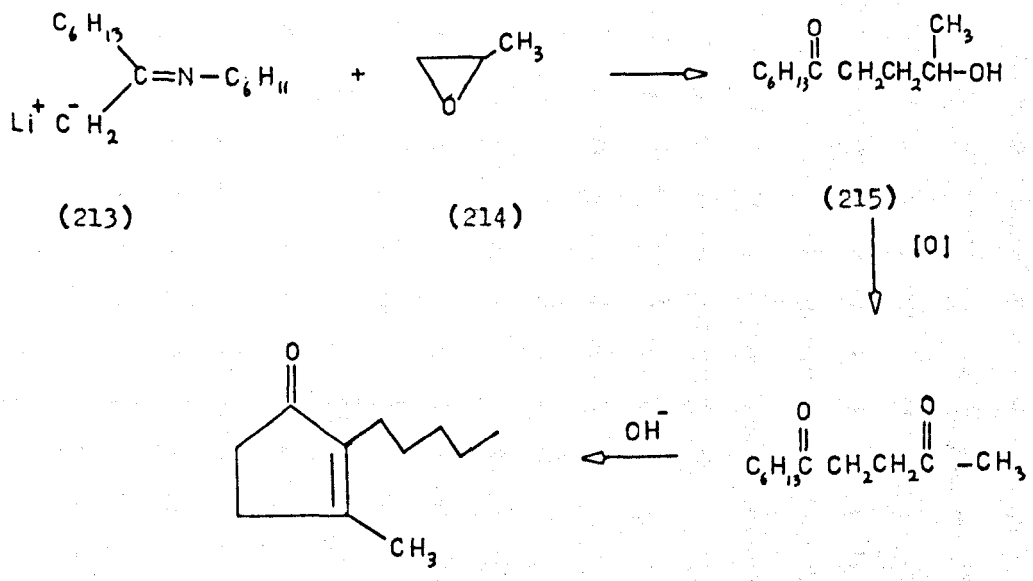


Reaction of this cyclopentenone with 2-quinolyl lithium could give the tricyclic ketone (212) where the future D ring of the aza-steroid is suitably substituted for formation of the C ring. Further reaction would then involve reduction of the nitrogen ring and of the C 17 carbonyl group.

Due to the insolubility of 2-bromoethoxyethane in aqueous potassium hydroxide, the conditions for alkylation of cyclohexane-1,-3-dione were altered slightly. The base used was sodium ethoxide and the solvent ethanol. Boiling the sodium salt of cyclohexane-1,3-dione with 2-bromoethoxyethane for 24 hours gave only a small amount (approx. 5%) of alkylated material. To obtain a higher yield the conditions were changed to use sodium hydride as base with dimethoxy-ethane as solvent (24 hr.). This time a red oil was obtained which proved to be a mixture of two compounds, the major one being product and the other one unchanged dione. Preparative layer chromatography eluting in 90% chloroform/10% ethyl acetate separated the product.

N.M.R. spectrum showed the cyclohexane-1,3-dione alkene proton at 5.2 p.p.m., no hydroxyl proton, which in the enolised dione occurs at 10 p.p.m., and the remaining dione protons at 1.8-2.55 p.p.m. In additon there was a two proton quartet at 3.6-4.1 p.p.m. and a three proton triplet at 1.18-1.5 p.p.m. The alkene proton was not exchangeable in D_2O. If alkylation had proceeded as expected to give the C-alkylated product (209) then a hydroxyl proton exchangeable in D_2O instead of an alkene proton would have been observed in the N.M.R. This fact together with the downfield shift of the methylene group corresponding to a $-O-\underline{CH_2}-$ signal leads to the deduction that O-alkylation rather than C-alkylation had occurred. Because of these difficulties this line was not further investigated.

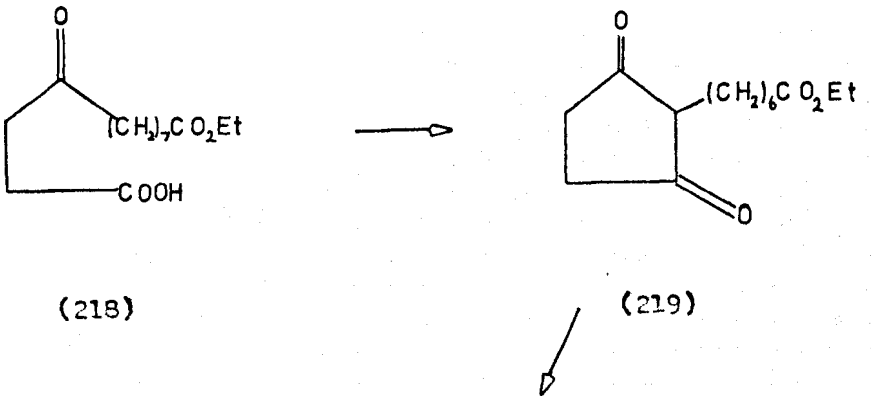
Very recently Larcheveque et al[94] have reported by high yield a three step route to substituted cyclopentenones. Dihydrojasmone (216) has been prepared in an overall yield of 75%. Condensation of the relevent epoxide (214) with the lithiated imine (213) gave the ketol (215) which was oxidised by a solution of sodium dichromate in sulphuric acid to the diketone (217) which was cyclised to dihydrojasmone (216).



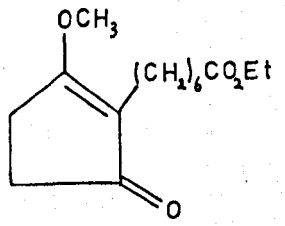
(213) (214) (215) (216) (217)

ATTEMPTED PREPARATION OF 2-(2-ETHOXYETHYL)-1,3-CYCLOPENTANEDIONE

Yura and Ide[95] have reported a synthesis of the straight chain carboxylic acid (218) which underwent internal Friedel Craft cyclisation to give the 2-substituted cyclopentanedione (219). Methylation of the dione with diazomethane gave the enolic methyl ether (220) in 85% yield.



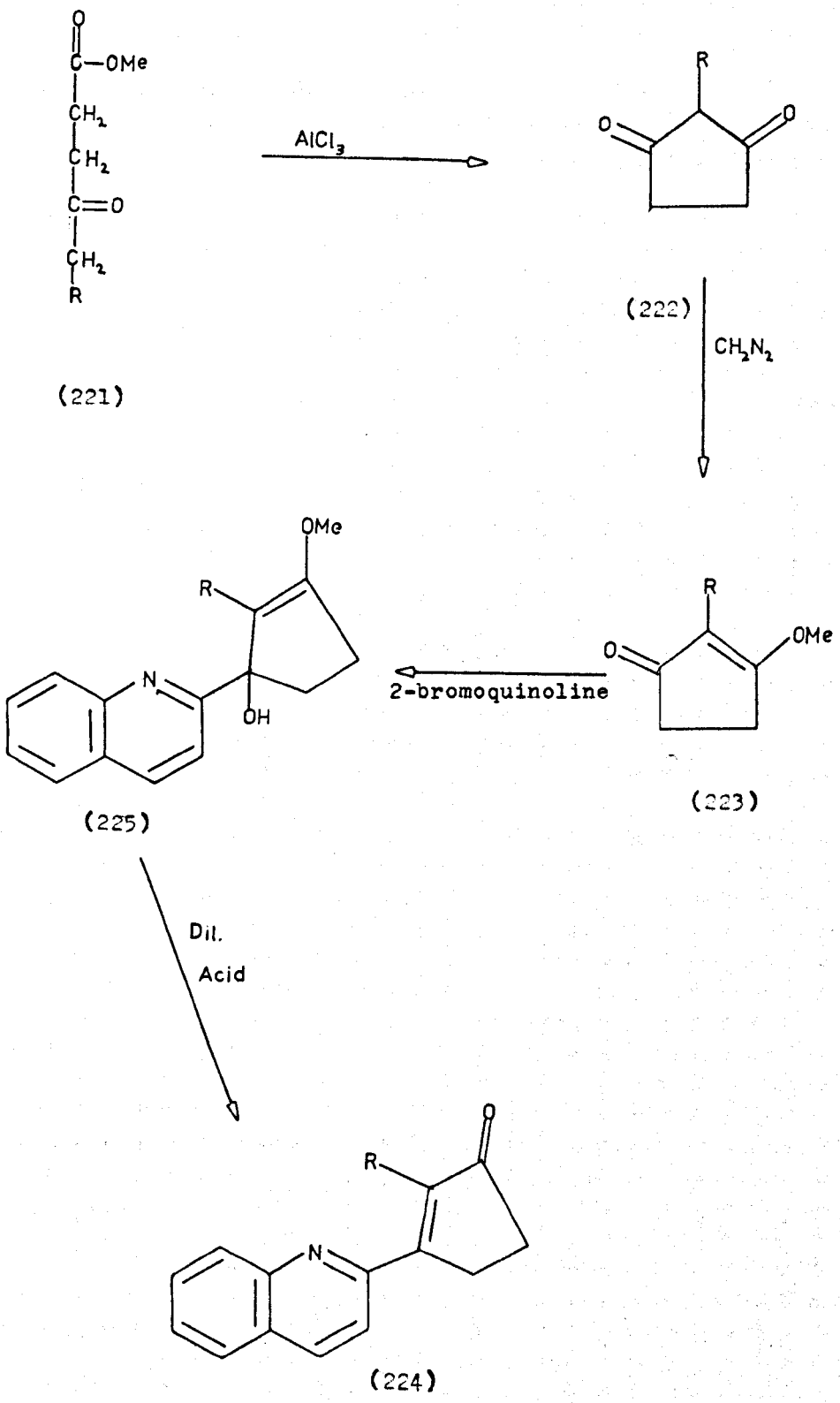
(218) (219)



(220)

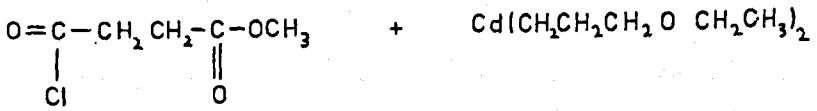
By a similar reaction pathway it was hoped to prepare the methyl ether (223), Grignard reaction of (223) with 2-bromoquinoline could give the tricyclic alcohol (225). Treatment with dilute mineral acid could give the ketone (224).

The ester (221) was thought to be best prepared from monomethyl-succinyl chloride (226) and the cadmium reagent of 6-ethoxypropyl bromide (227) which could be prepared from and is less reactive than its magnesium counterpart. The cadmium reagent of 6-ethoxypropyl bromide was prepared from the corresponding Grignard reagent with

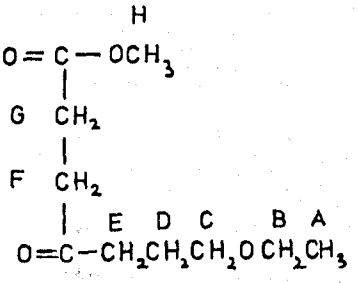

O
C—OMe
CH2
CH2
C=O
CH2
R
AlCl3
R
O
O
(221)
(222)
CH2N2
OMe
R
N
OH
2-bromoquinoline
R
O
OMe
(225)
(223)
Dil.
Acid
O
R
N
(224)

R = CH_2CH_2OEt

the use of anhydrous cadmium chloride[96]. The reaction procedure was then followed using monomethylsuccinyl chloride and the cadmium reagent. Reaction using the monoethylsuccinyl chloride proved unsuccessful.



(226) (227)



(221)

After work up and distillation (at a temperature to be expected from the required product - 74°/3mm.) of the crude material, the pure product gave an N.M.R. spectrum difficult to interpret. The N.M.R. spectrum of compound (221) would be expected to show a 3 proton triplet at 1.1 p.p.m. (methyl group A), a 2 proton multiplet at 2 p.p.m. (methylene group D), a 4 proton singlet at 2.55 p.p.m. (methylene groups G and F), a 2 proton triplet at 2.4 p.p.m. (methylene group E), a 4 proton multiplet at 3.4 p.p.m. (methylene groups C and B) and a 3 proton singlet at 3.6 p.p.m. (methyl group H). However the N.M.R. spectrum of the actual product showed a 6 proton multiplet at 1.2 p.p.m., a 4 proton singlet at 2.6 p.p.m., a 2 proton triplet at 3.4 p.p.m., a 3 proton singlet at 3.65 p.p.m. and a 2

proton quartet at 4.1 p.p.m. Apart from the different spectrum obtained, there was a loss of two protons. Furthermore the mass spectrum showed a molecular ion peak at 188 (14 less than the expected value of 202) indicating possible loss of a methylene group. The I.R. spectrum showed broad carbonyl absorption at 1730 $cm.^{-1}$ which could cover both ester and ketone absorption, and ether absorption at 1155 $cm.^{-1}$.

An attempt was made to cyclise the product from the previous reaction in a similar manner to that used by Yura and Ide[96] to prepare their dione (219). The N.M.R. spectrum of the product showed a 6 proton multiplet at 1.1-1.3 p.p.m., a sharp 2 proton doublet at 1.94 p .p.m., and a broad 4 proton multiplet at 2.05-2.64 p.p.m. Again there were two protons less than expected and no acid hydroxyl protons were found further downfield. The mass spectrum showed a molecular ion peak at 164 which is a loss of 24 in the reaction instead of the expected loss of 30. From the two sets of spectral evidence available it seemed that the reactions had not proceeded as planned.

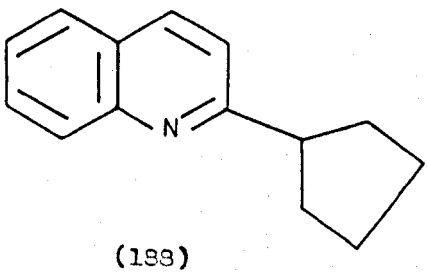
SYNTHESIS OF SOME THIOPHEN AND FURAN COMPOUNDS

The compound 2-quinolyl cyclopentane (188) can be easily synthesised from quinoline and the Grignard reagent of bromocyclopentane but when the bromocyclopentane possesses a substituent in the α-position, the yield of product (160) is significantly reduced. The main cause of the lower yield is probably the steric hindrance of the ether side chain. The side chain was to be used as a method of incorporating a two carbon fragment into the azasteroid precursor which could cyclise to form ring C.

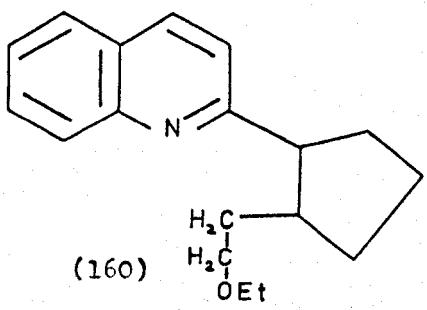
The next step was to synthesise a cyclopentanone derivative possessing such a two carbon fragment in the α-position but which would not be capable of causing any steric problems. Such a cyclopentanone would be bicyclic compounds (216,217) in which the heterocyclic ring acts as a good example of "latent functionality". The thiophen or furan ring will be less obstructive than a long side chain. Reaction of the cyclopentanones (216,217) with 2-quinolyl lithium could give the corresponding alcohols (218,219). Because steric problems play a lesser part in the reaction, the yield could be higher than for the synthesis of compound (160). The two carbon side chain could be generated by ring cleavage of the thiophen or furan nucleus to give compound (220). The next steps would be reduction of the nitrogen ring (hydrogenation in ethanol over platinum oxide catalyst), followed by cyclisation.

Consider compound (216) (X = S): there have been several methods reported of syntheses of thiophen derivatives which possess a suitable substituent in the α-position that on cleavage of the thiophen ring would give a two carbon fragment capable of forming the C-ring of the azasteroid. Use has also been made of the ability to introduce substituents into the α-position of the thiophen which could not be done after ring opening. The methods of ring cleavage follow a general procedure viz: reductive desulphurisation by Raney nickel catalyst.

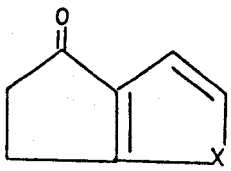
Goldfarb and Korsakova [97] synthesised a dialkylated thiophen (221) by condensation of dimethylphenyl carbinol with thiophen in 70% sulphuric acid, which gave a symmetrically branched octane (222)after reductive ring opening with Raney nickel. Wynberg[98] has used thiophens for ascending a homologous series of fatty acids by five carbon atoms. Thiophen is acylated by the carboxylic acid (223) to give the



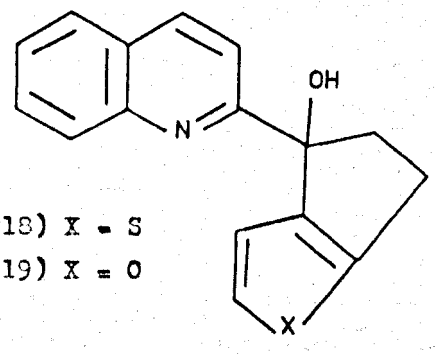
(188)



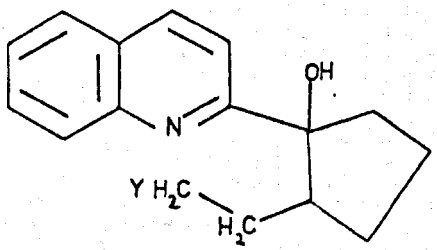
(160)



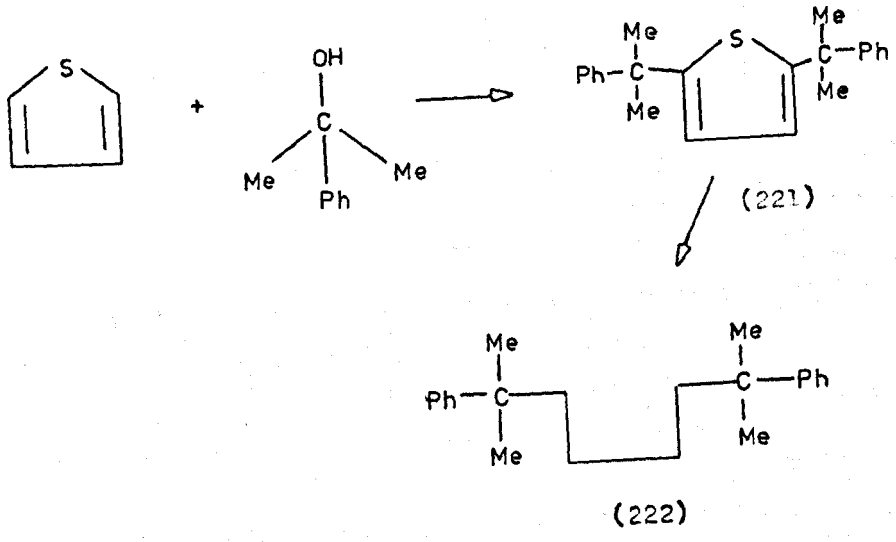
(216) X = S
(217) X = O



(218) X = S
(219) X = O

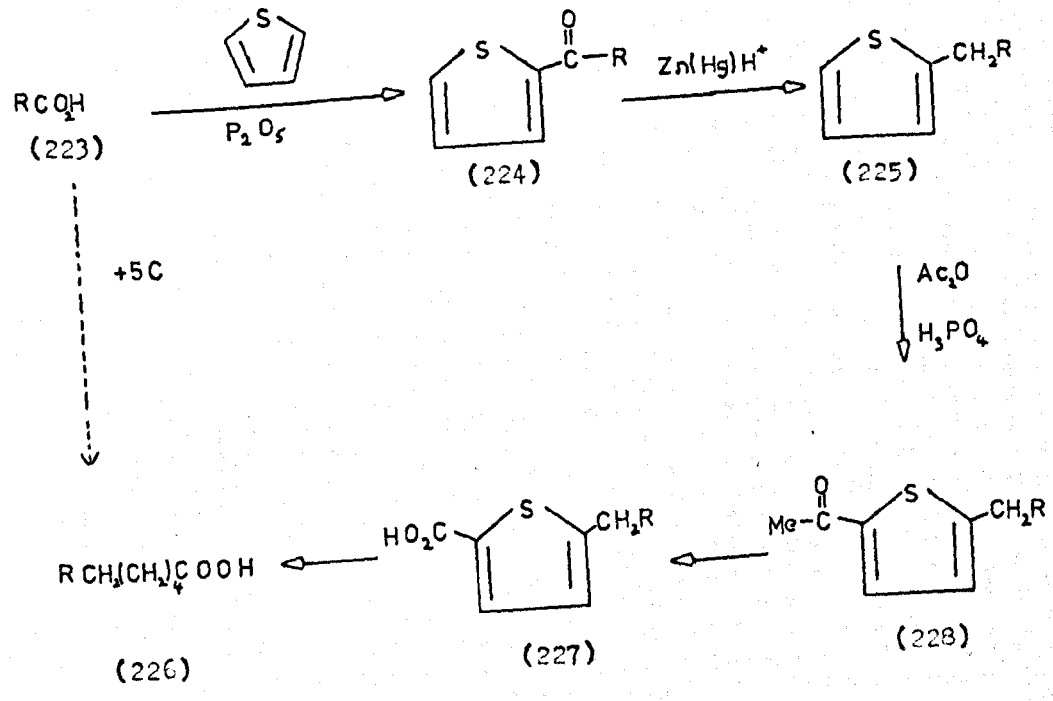


(220)



(221)

(222)



(223)

(224)

(225)

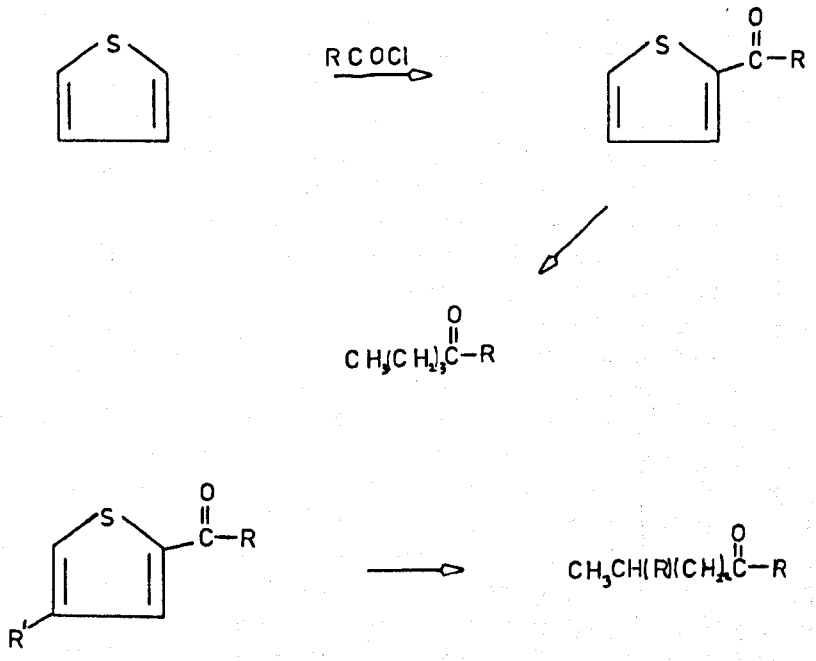
(226)

(227)

(228)

acyl thiophen (224) which undergoes Clemmensen reduction to give the alkyl thiophen (225). Reacylation with acetic anhydride to give 2-acetyl-5-alkyl thiophen (228) followed by the haloform reaction formed the carboxylic acid (227) which on ring opening gave the alkyl carboxylic acid (226).

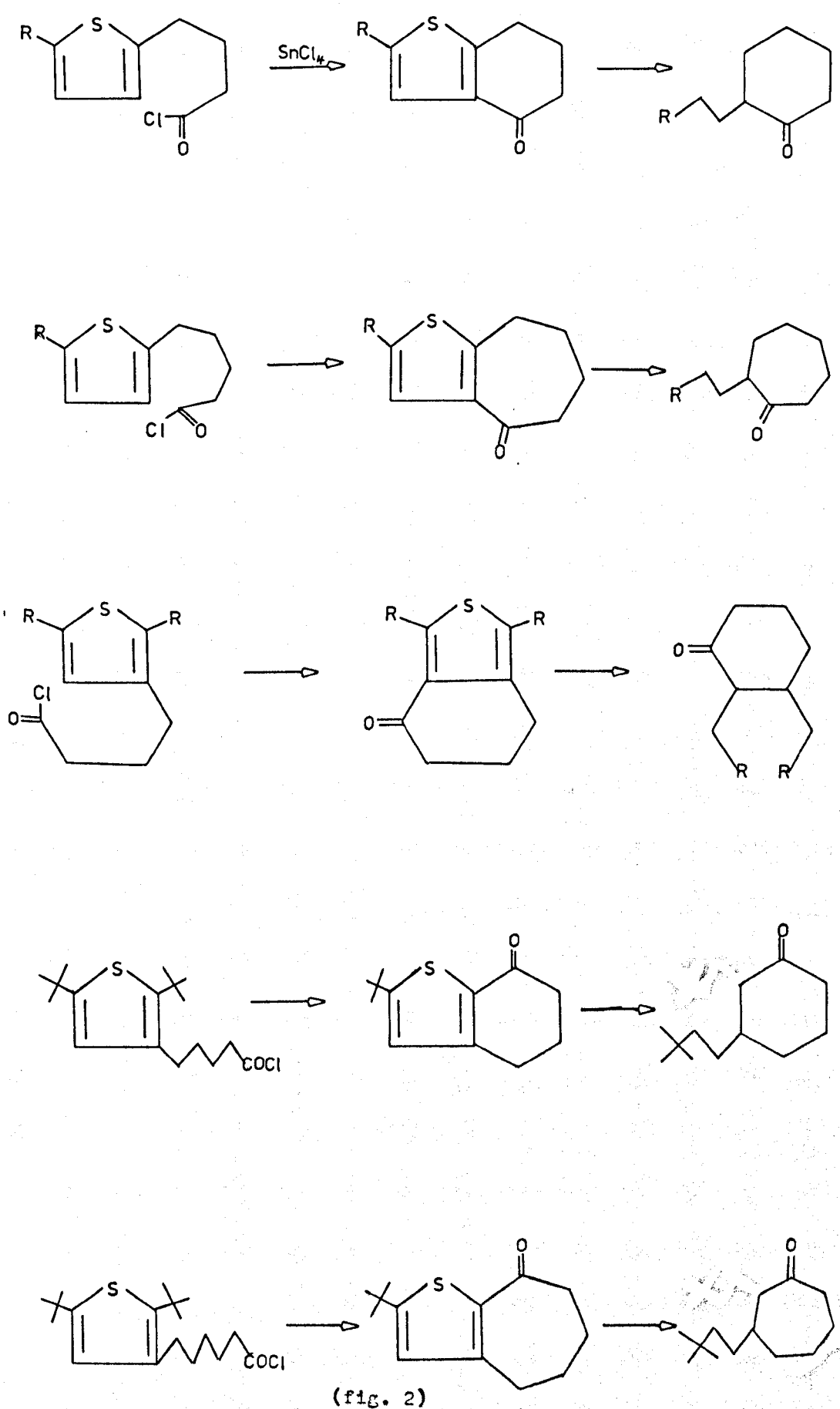
The ability of the thiophen nucleus to readily undergo Friedel-Craft acylation to give good yields of 2-acyl derivatives has been extensively used. An example of this is a general synthesis by Wynberg and Logothetis[98] who followed the Friedel-Craft acylation and subsequent alkylation of the deactivated nucleus with ring opening (fig.1). Some instances have been reported[99] of the carbonyl group



(fig. 1)

also being reduced by the Raney nickel but this can be avoided in such cases by the formation of an ethylene ketal.

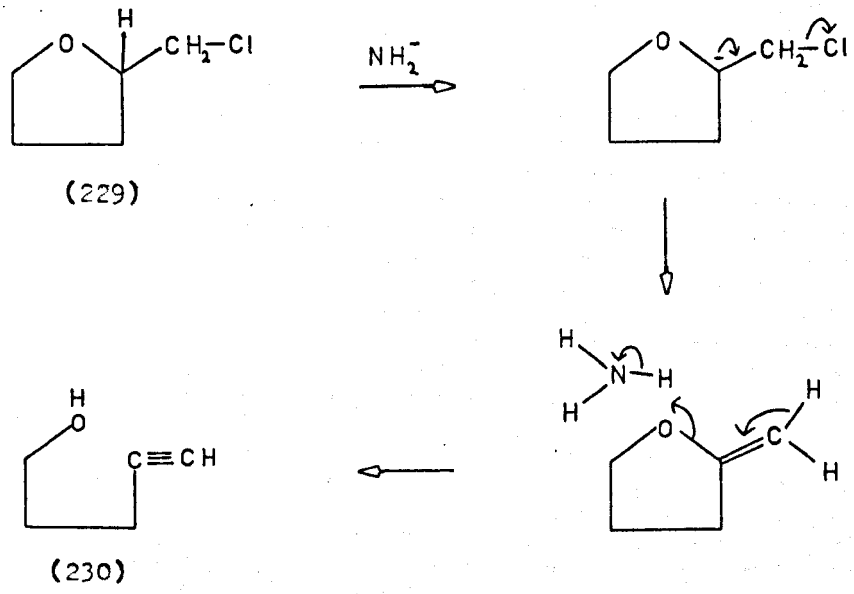
Cagniant et al[100] have synthesised a number of alkyl cycloalkanones by the same general procedure (outlined in fig. 2) which involved an internal Friedel-Craft cyclisation of the corresponding


R
S
Cl
O
SnCl4
R
S
O
R
O
R
S
Cl
O
R
S
O
R
O
R
S
R
Cl
O
R
S
R
O
O
R
R
S
COCl
S
O
O
S
COCl
S
O
O

(fig. 2)

acid chloride followed by reductive ring opening with Raney nickel.

Less work has been reported on the cleavage of furans which can also be considered as cyclic ethers. By treatment with sodium amide in liquid ammonia[101], 2-chloromethyltetrahydrofuran (229) has been converted into the corresponding acetylenic alcohol (230).



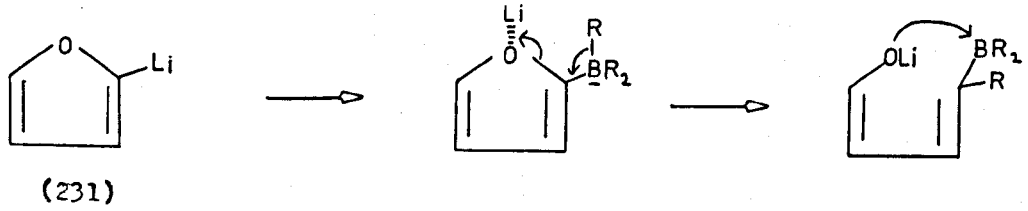
(229)

(230)

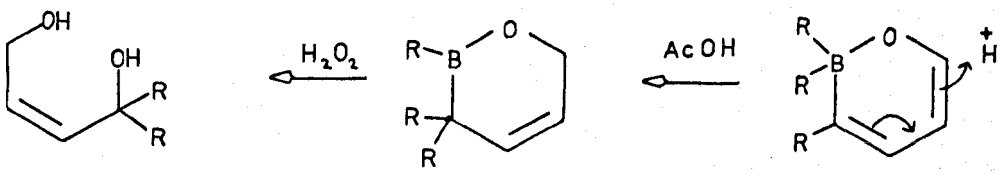
Insertion of an organoborane into a furan nucleus has been used[102] to facilitate ring opening. Reaction of 2-furyllithium (231) with organoborane gave the cyclic borate (233), oxidation of which gave the cis diols (232) in good yield. The reaction only proceeds satisfactorily if R is not a bulky group.

In their review on furan chemistry Bossard and Eugster[103] have suggested the synthesis of 1,4-diketones (236) by conversion of the furan to 2,5-dimethoxy dihydrofurans (234) and then to the tetrahydrofuran (235) before hydrolysis. This is a better route than direct hydrolysis of the furan which leads to extensive polymerisation. Using an adaptation of this procedure, Finch and co-workers[104] have synthesised the prostaglandin precursor (237). Johnson[105,106] has performed the cleavage of furans in ethylene glycol-benzene containing a small amount of p-toluene sulphonic acid.

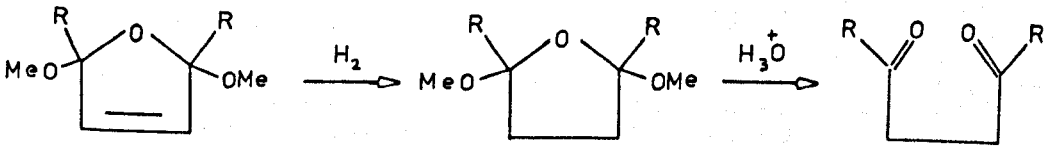
Substituted levulinic esters have been prepared[107,108] from α-furfuryl alcohols (238). Ring cleavage is achieved with alcoholic hydrogen chloride to (240) followed by rearrangement to (239).



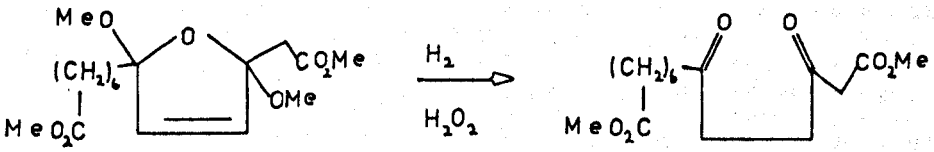
(231)

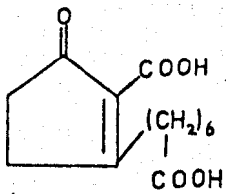


(232) (233)



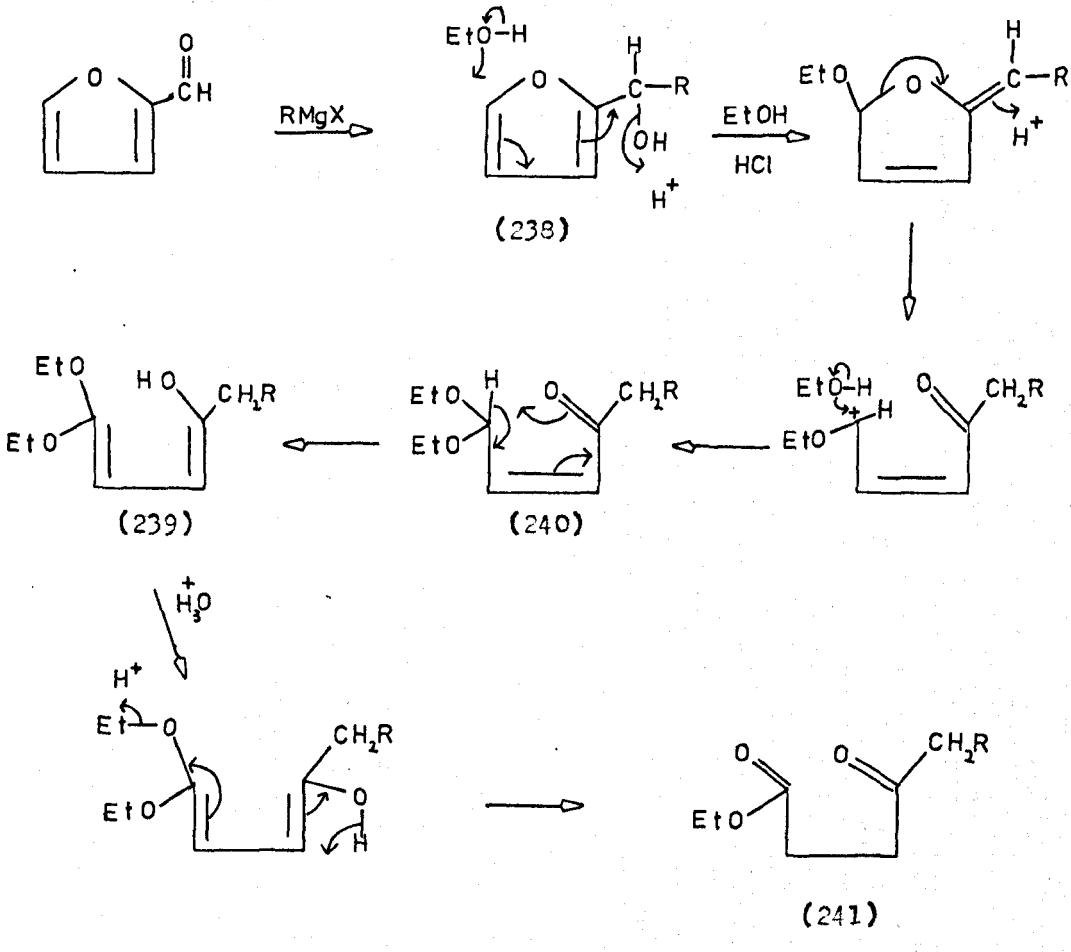
(234) (235) (236)





(237)

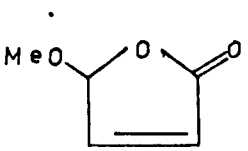
Intramolecular oxidation - reduction then takes place to give the ester (241). Acid catalysis in alcoholic medium has also been used



to cleave the unsaturated lactone[109] (242) to give the unsaturated acetal (243). Shechter[110] has studied the thermal decomposition of readily prepared α-diazofurans (244) to give moderate yields of the acetylenic-α,β-unsaturated ketones (245,246).

Karger and Mazur[111] have used mixed sulphonic carboxylic anhydrides (prepared by the method of Baroni[112]) for the cleavage of open chain and cyclic ethers. Tetrahydrofuran (247), 2,5-dihydrofuran and 2-methyl tetrahydrofuran have undergone ring opening employing acetyl p-toluenesulphonate under relatively mild conditions to give the corresponding acetyl tosylate (248) in high yield.

The first of the cyclopentanone derivatives to be prepared was the ketone (216). A synthetic route analogous to that successfully employed by Cagniant and Deluzarche[113] for the synthesis of 5,6,7,-8,-tetrahydro-4H-cyclohepta(3,2b)thiophen-4-one was attempted. A



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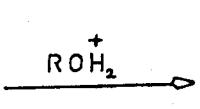
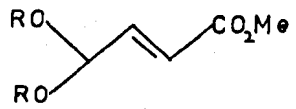
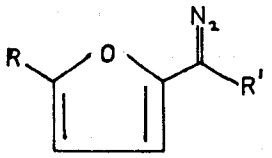
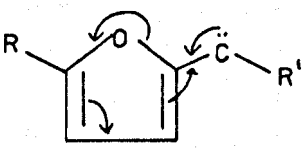


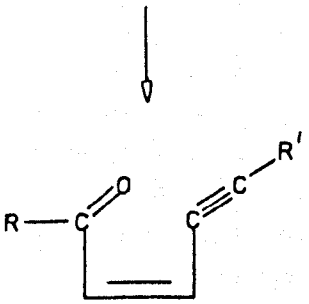


(243) R = Me, Et, $-CH_2CH_2-$

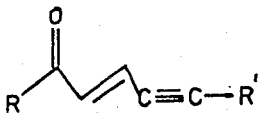


(244)

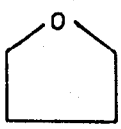




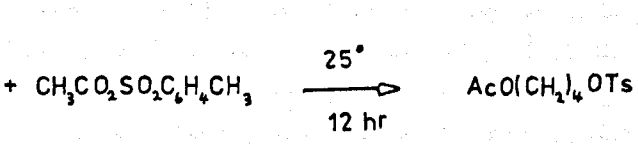
(246)



(245)

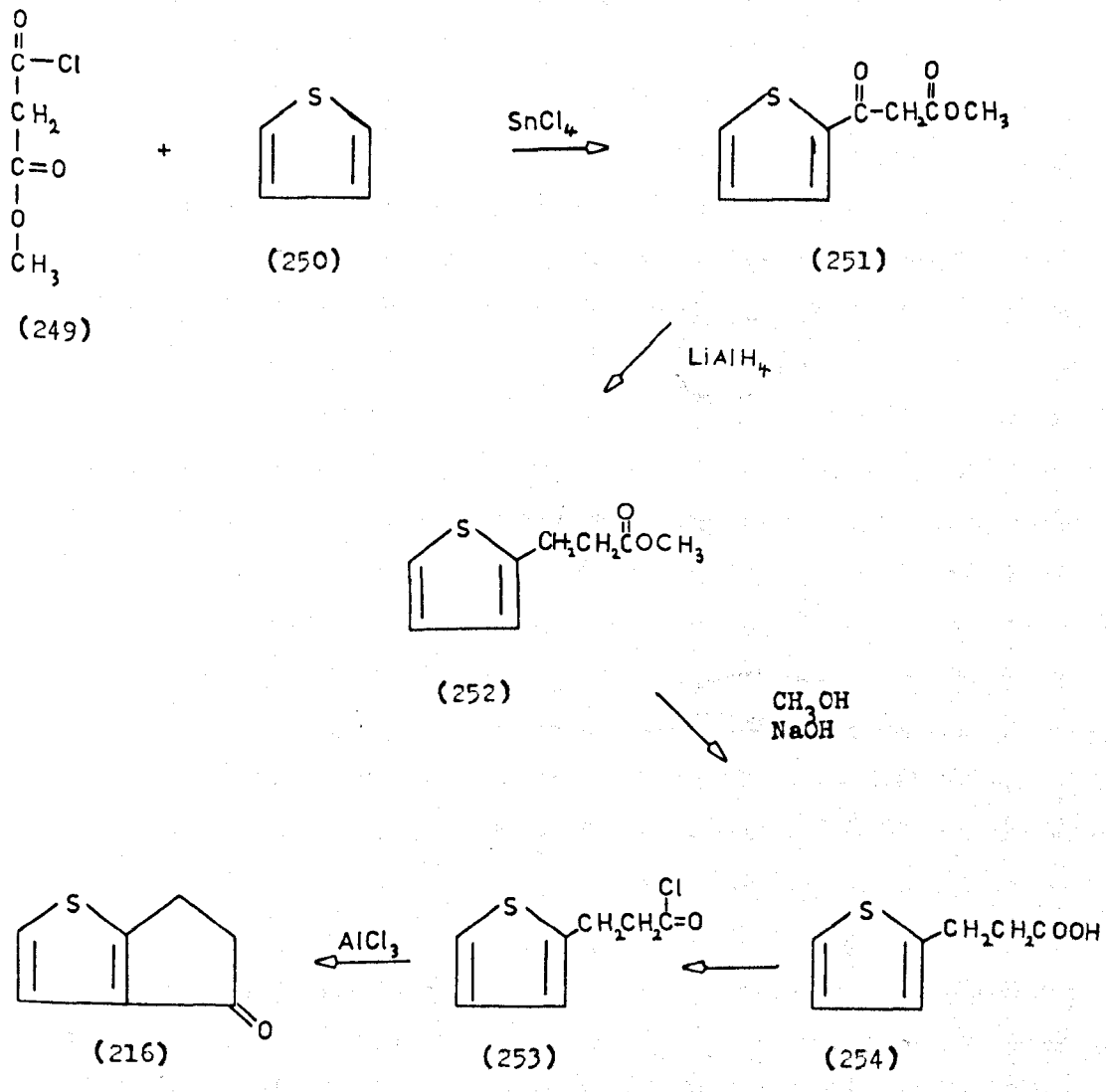


(247)



(248)

Friedel-Craft reaction of mono-methyl malonyl chloride (249) with thiophen (250) could give the ester (251) which could undergo reduction to give the ester(252). Basic hydrolysis of compound (252) could give β-(2-thienyl) propionic acid (254) whose acid chloride (253) could cyclise in a Friedel-Craft reaction to give the cyclopentanone (216).



(249) (250) (251) (252) (253) (254) (216)

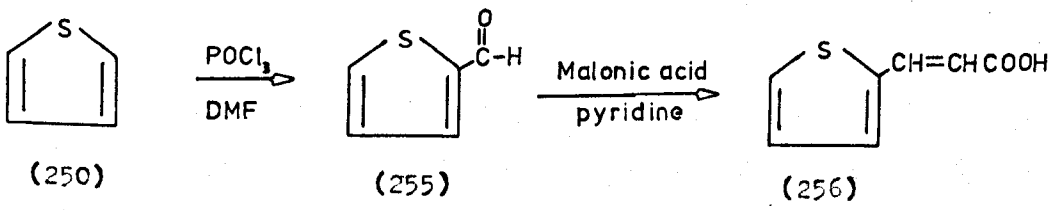
It was preferable to prepare the acid (254) by acylation of the thiophen nucleus followed by reduction of the carbonyl group, instead of direct alkylation, due to the problems of polyalkylation that would be introduced. The Friedel-Craft reaction of monomethylmalonyl chloride (249) with thiophen did not give the keto-ester (251) but 2-thienyl methyl ketone. The keto-ester (251) was thought to be very susceptible

to hydrolysis and decarboxylation which presumably happened in the work up stage.

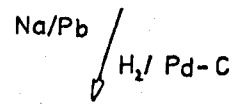
Other methods have been reported for the synthesis of β-(2-thienyl) propionic acid (254)[114-119] and the two most promising routes were by Sam and Thompson[114] and Poirier et al[119]. The former prepared the acid by two methods: a) reduction of β-(2-thienyl) acrylic acid by sodium-lead alloy in sodium hydroxide (64% yield) and b) hydrogenation with 10% palladium on charcoal catalyst of β-(2-thienyl) acrylic acid (256) under pressure (80% yield). Poirier et al have prepared the acid by only one method - reduction of β-(2-thienyl) acrylic acid. Both groups of workers have reported successfully synthesising the ketone (216). Sam and Thompson[114] report that the ketone (216) could be prepared from the acid (254) in 36% yield by heating with polyphosphoric acid but other dehydrating agents (sulphuric acid and liquid hydrogen fluoride) gave negligible results. They found that Friedel-Craft cyclisation of the acid chloride (253) was unsuccessful using aluminium chloride but they were able to synthesise the cyclohexanone analogue (257) by the same procedure and other workers[100,114] have been able to synthesise the cycloheptanone analogue (258) by this method.

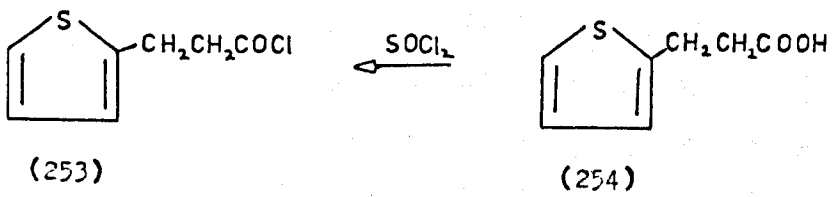
In contrast Poirier et al[119] have prepared the ketone (216) by a Friedel-Craft reaction of the acid chloride (253) using aluminium chloride but claim that the ketone (216) could only be synthesised in 2% yield by treatment of the acid (254) with polyphosphoric acid. More success has been obtained in the preparation of ketones (260,-262,263) bearing at least one other substituent in the thiophen or cyclopentanone ring. Poirier et al[119] have synthesised several of these, one being 6,7-dihydro-5H-cyclopenta(b)3-methyl thiophen -5-one (260) which was prepared by two methods: a) heating 2-isopropylidene-cyclopentanone (259) with sulphur gave a 10% yield of the ketone (260) b) treatment of the acid chloride (261) with polyphosphoric acid gave the ketone (216) in 30% yield. Meth-Cohn and Gronovitz[120] have prepared the ketone (263) by treatment of compound (262) with polyphosphoric acid.

The Friedel-Craft reaction of the acid chloride (253) was found, using either aluminium chloride or stannic chloride to give a low yield (17%) of product. Intermolecular reaction was minimised by the separate simultaneous addition of catalyst and acid chloride to a large volume of solvent (carbon disulphide). Attempted dehydrative

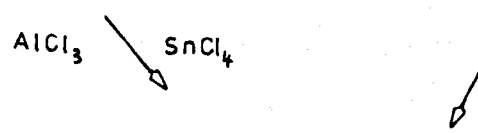


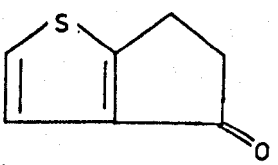
(250) (255) (256)





(253) (254)





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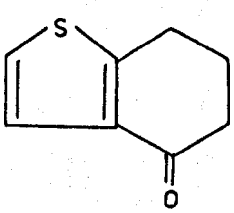

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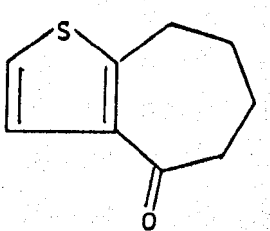

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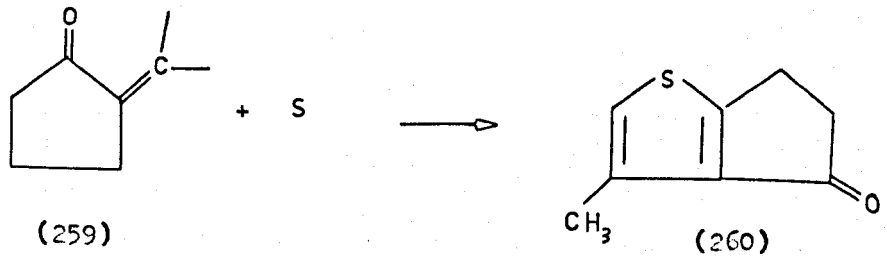

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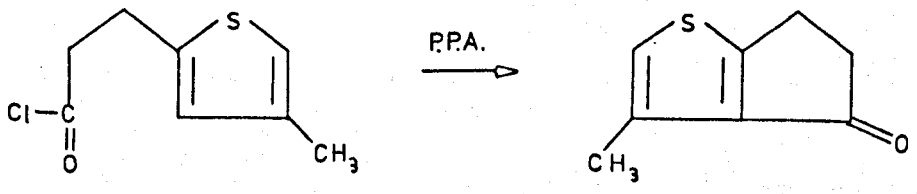
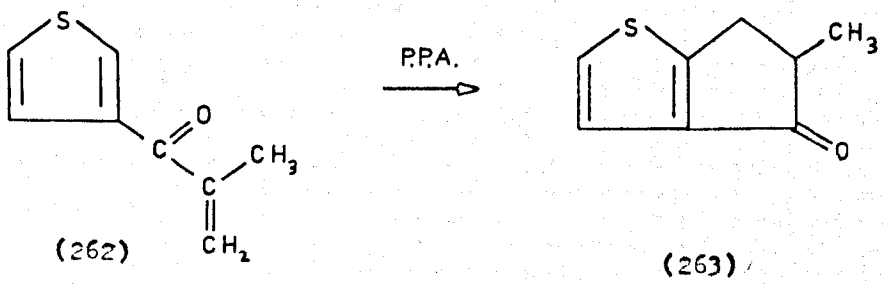


(261) (260)



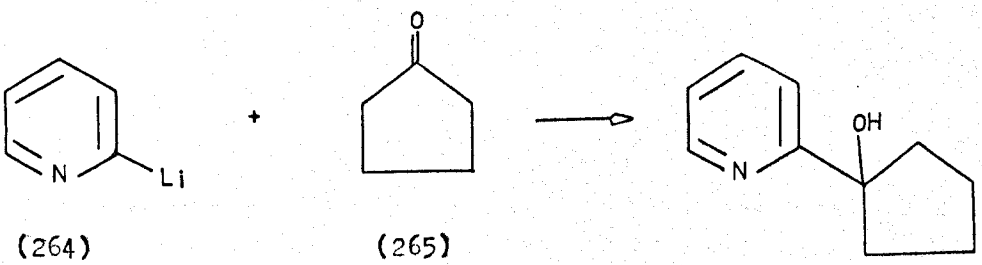
(262) (263)

cyclisation of the acid (254) by the methods of Sam and Thompson[114] and by the method of Poirier et al[119] all failed.

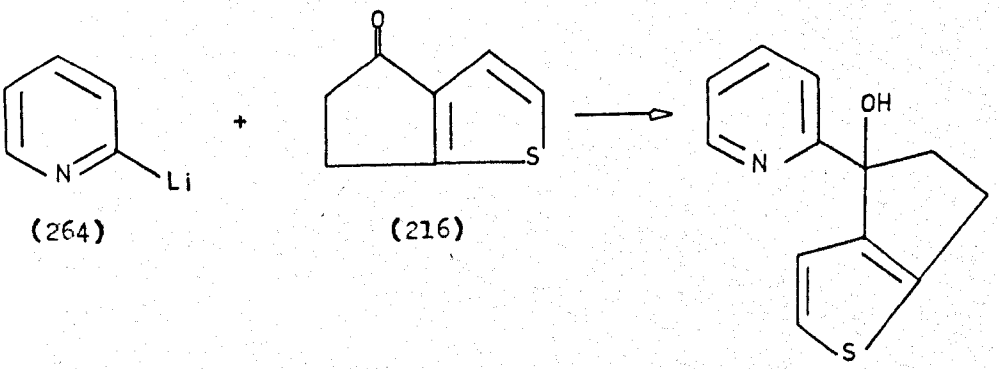
As a forerun to the reaction of 2-quinolyl lithium with the ketone (216), model reactions were performed. Cyclopentanone (265) was reacted with 2-pyridyl lithium (264) (prepared from 2-bromopyridine which is more readily obtainable than 2-bromoquinoline) to give 1-(2-pyridyl) cyclopentanol (266) in good yield. Using similar reaction conditions 2-pyridyl lithium (264) was reacted with the ketone (216) to give a low yield of 4-(2-pyridyl)4,5-dihydro-6H-cyclopenta (b) thiophen-4-ol (267). Reaction of 2-quinolyl lithium (268) with the ketone (216) using a variety of conditions failed to give any expected product (218) but only 2-2'biquinolyl (269) and a very small amount of ketone (216).

In a final attempt to synthesise a tetracyclic condensation product, the following synthetic route was envisaged. The ketone (216) could be reduced to give the alcohol (270) which with phosphorus tribromide could give the corresponding bromo-compound (271). The Grignard reagent of this compound could either undergo reaction with quinoline or quinoline-1-oxide to give compound (272) or if this failed then it could react with phenyl isocyanate to give the amide (273). Meth-Cohn and Gronowitz[120] have successfully reduced the ketone (263) to the corresponding alcohol (274). They report that unless basic conditions are maintained during the work up procedure, the alcohol (274) will undergo an acid catalysed dehydration and the colourless products rapidly turn brown. Their conditions were followed for the reduction of ketone (216) but although slightly basic conditions were maintained during work up, the only product was a red resin.

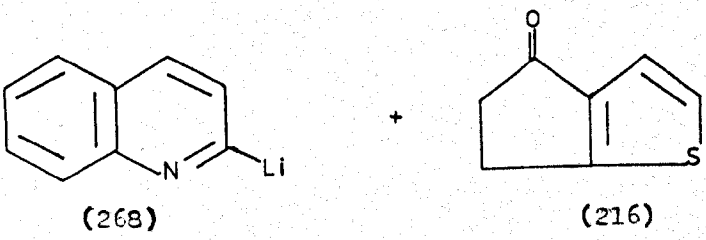
Due to the lack of success with the thiophen compounds the furan derivatives were examined. The first compound whose synthesis was attempted was 2-(2-chloroethyl) cyclopentane-1,3-dione (285) which could be cyclised to give the ketone (216). The initial synthesis of cyclopentane-1,3-dione (278) was that of Merenzi and Nilsson[121,122]. This involved reaction of succinic anhydride (275) with isopropenyl acetate (276) in the presence of aluminium chloride to give 2-acetyl cyclopentane-1,3-dione (277) which was heated for 24 hours in dilute hydrochloric acid to give the cyclopentane-1,3-dione (278). Both of these reactions proceeded poorly giving overall yields varying from 3½-5%.



(264) (265) (266)



(264) (216) (267)



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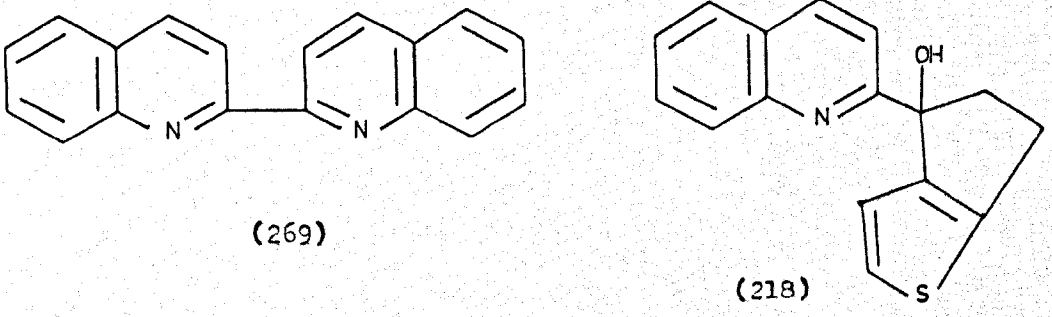
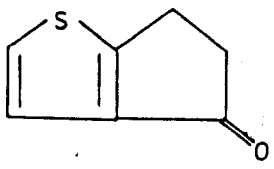
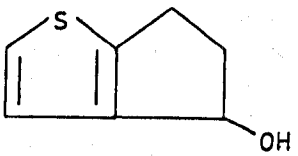


(269) (218)



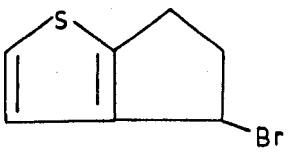
(216)

$LiAlH_4$



(270)

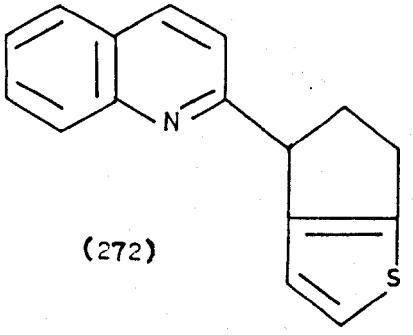
PBr_3



(271)

QUINOLINE OR Q.N.O. Mg or Li

Mg PhNCO



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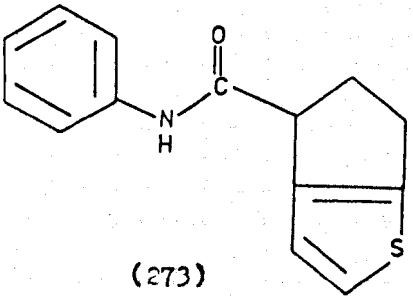

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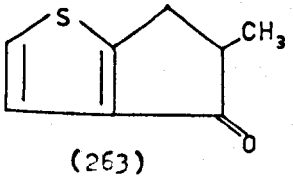
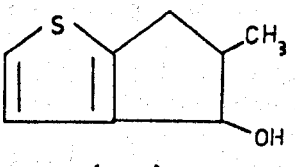


(263)

$LiAlH_4$



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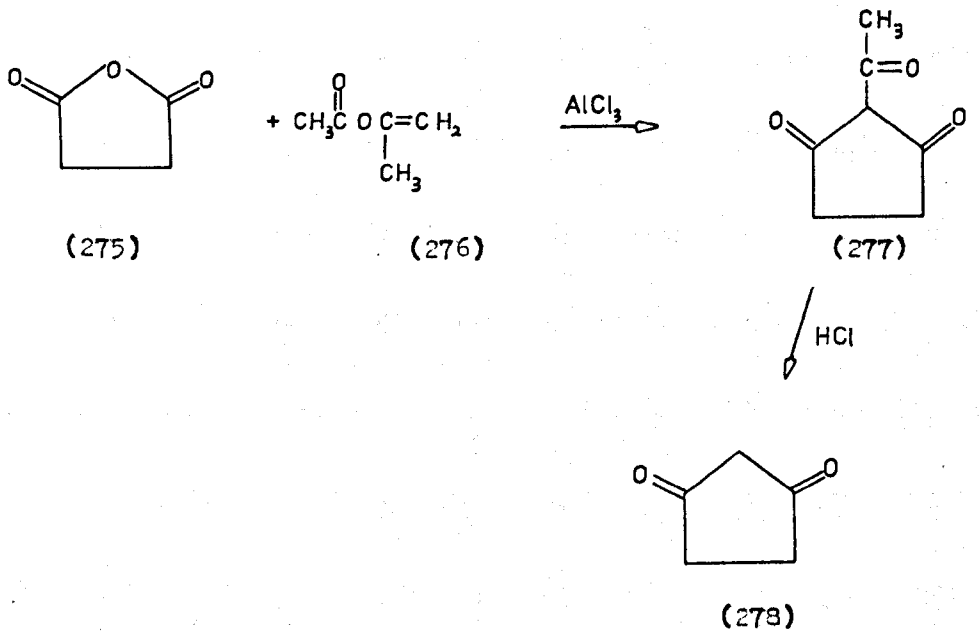
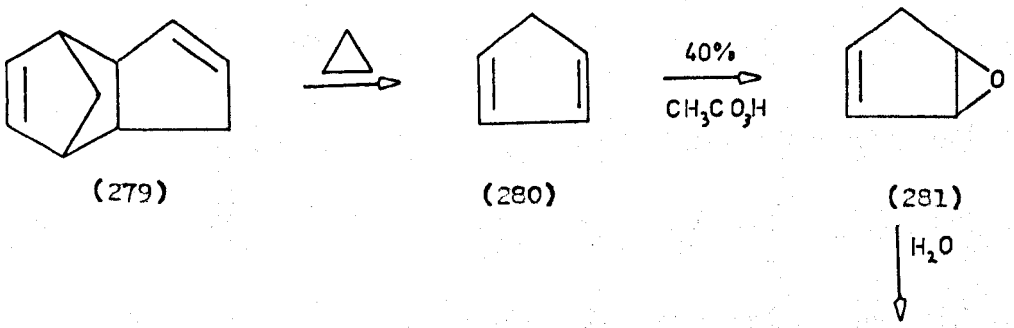
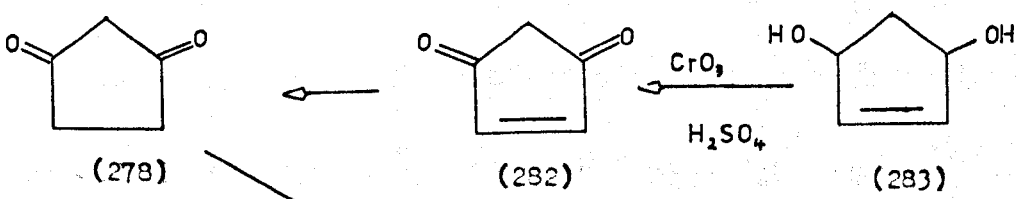


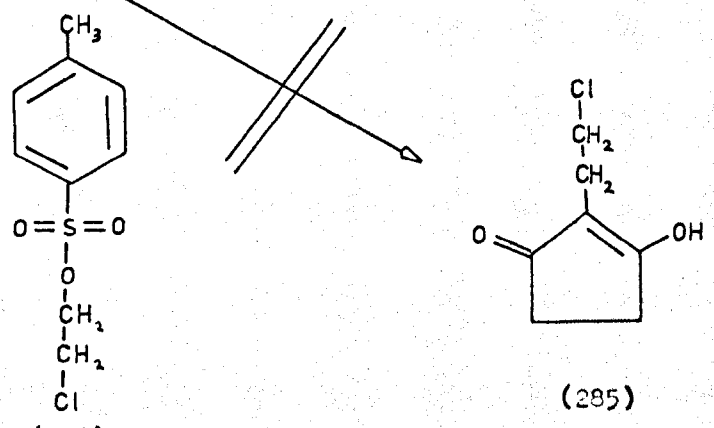
(275) (276) (277) (278)



(279) (280) (281)



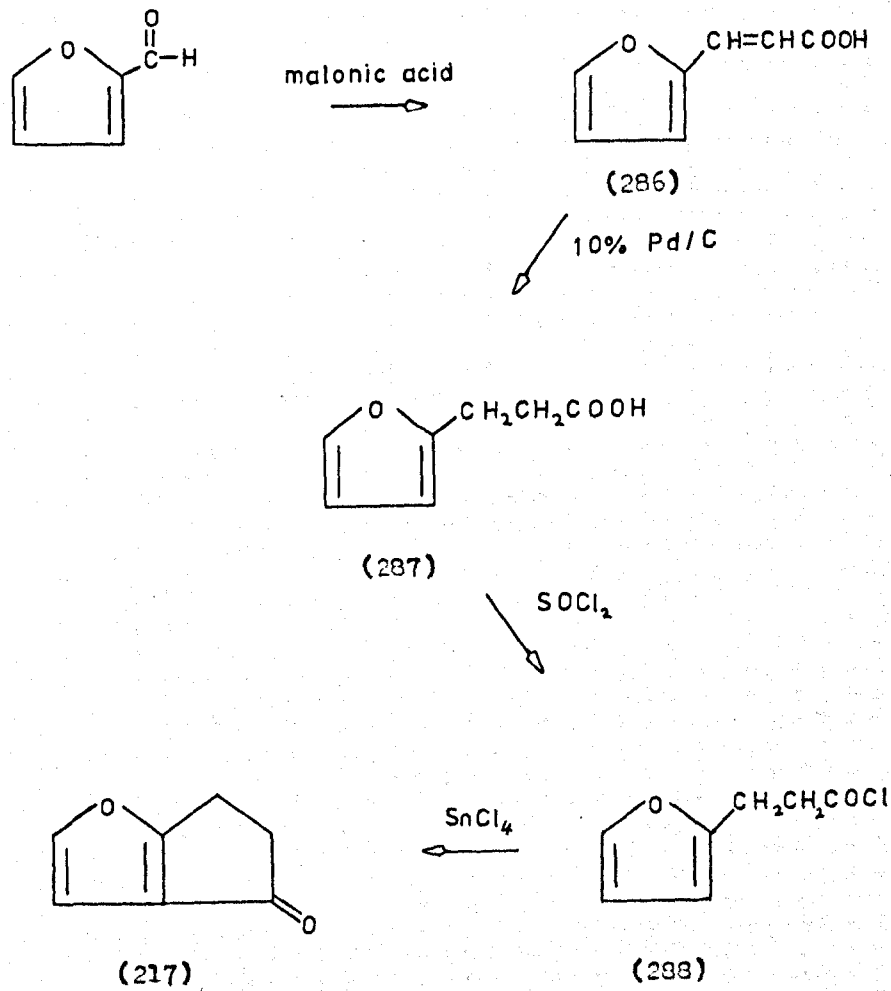
(278) (282) (283)



(284) (285)

Very recently McIntosh and Beaumier[123] have reported the reduction of cyclopentene-1,3-dione (282) with activated zinc in hot acetic acid to give the cyclopentane-1,3-dione (278) in high yield. Cyclopentene-1,3-dione was prepared in a four step synthesis[124,125] starting from dicyclopentadiene (279) which on heating gave the monomer (280) which was oxidised with 40% peracetic acid to the epoxide (281) hydration of which gave the diol (283). Oxidation of the diol (283) gave the cyclopentene-1,3-dione (282). The overall yield (36%) of the dione (278) was much better than that by the former method. Alkylation of the dione (278) with 2-chloro-ethyl tosylate (284) failed.

Furans are less stable to Friedel-Craft reaction conditions than thiophens but because of the failure to synthesise compound (285), the synthesis of the ketone (217) was attempted by an analogous method to the preparation of the ketone (216). Preparation of furyl acrylic acid[126,127] (286) was followed by reduction to furyl propionic acid (287) whose acid chloride (288) could cyclise to give the ketone (217).



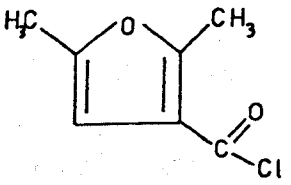
Rahlings and Smith[128], and Jones and Taylor[129] report that the synthesis of W-2'-furylalkanes from furfural through compounds of type $C_4H_3O(CH{=}CH)nCH_2X$ is hindered by the instability of the furan nucleus. There have been several methods reported for the reduction of the side chain of the furyl acrylic acid (287), for example, using hydrazine hydrate[130], sodium amalgam[131,137], palladised strontium carbonate[128] or Raney nickel[133,134]. Plisov and Bykovets[135] report that hydrogenation over 10% palladium on charcoal catalyst reduced the side chain double bond while Mitsui[133] reports that 5% palladium on charcoal catalyst reduced the furan ring as well as the side chain.

The method of Plisov and Bykovets[135] was found to be successful for the reduction of the furyl acrylic acid (286). Reaction of the acid (287) with thionyl chloride in ether was unsuccessful, merely leading to extensive polymerisation. This method has however been successfully employed by Triebs and Heyer[136] to prepare furanyl-2,3-cycloheptan(b)-4-one in 60% yield. A reason for the failure of the formation of the acid chloride (288) could be as Rahlings and Smith[128] further report that the furan nucleus has great sensitivity to acids, thionyl chloride and phosphorus, aluminium and tin halides. For this reason the Friedel-Craft reaction has not been used with success; not many of the $\omega;\alpha$ furylalkyl halides have been prepared and iodides are unknown. They further state that all furyl derivatives are unstable to acids.

In view of the difficulty in preparing the furyl cyclopentanone (217) a different approach was adopted which involved the synthesis of compound (289). Furan is preferentially substituted in the 2- and 5- positions rather than the 3- and 4- positions, thus a 2,5-disubstituted furan would have to be used in the preparation of compound (290) so that further substitution could only occur in the 3- position.

Two ways in which compound (290) could be prepared are: a) by reaction of 2,5-dimethyl furoic acid (289) chloride with 2-quinolyllithium (268) and b) reaction of 2,5-dimethyl furan (291) with quinaldinic acid chloride (292).

Acheson and Robinson[137] report that they synthesised ethyl-2,5-dimethyl-3-furancarboxylate (289) by treatment of ethyl α-acetyl-laevulate (294) with sodium ethoxide. They reported that ethyl α-acetyl-laevulate (294) is best prepared from bromoacetone and ethyl sodio acetyl acetate (293) by the method of Stevenson and Johnson[138]. How-



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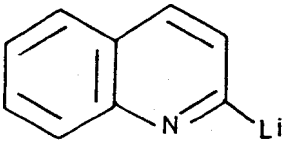

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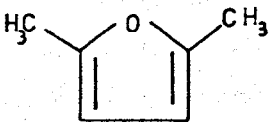

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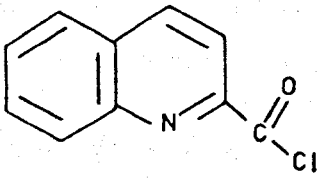
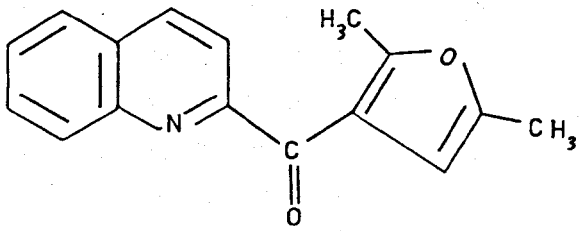


(292)



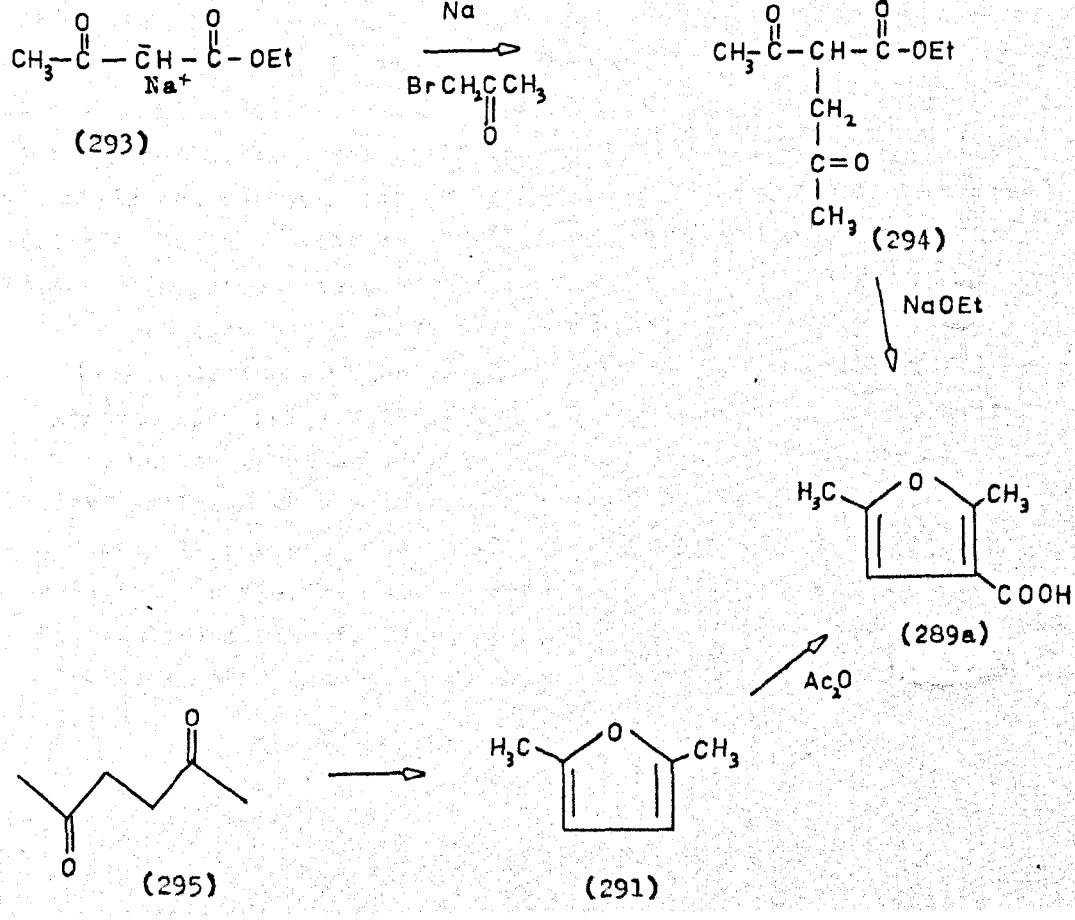
(290)

ever this latter method was found to give a compound other than that expected.

There have been several other straight forward syntheses of the acid(289a) reported[139-143]. Scott and Naples[144] have recently reported that 2,5-dimethyl furan (291) could by synthesised by heating hexane-2,5-dione (295) with an ion exchange - resin catalyst in high yield. Hurd and Wilkinson[145] have reported the synthesis of 2,5-dimethyl-3-furoic acid(289a) in good yield by treatment of 2,5-dimethylfuran (291) with acetic anhydride to give the 3-acetyl derivative, the iodoform reaction then giving the acid(289a). This synthesis was successfully followed to give the acid (289a).

A Friedel-Craft reaction was attempted using quinaldinic acid chloride(292) and 2,5-dimethyl furan (291). Separation of the crude mixture by T.L.C. showed that none of the required product had been formed. The N.M.R. spectrum of one of the products showed the presence of a large number of aliphatic protons indicating that possibly ring opening of the furan nucleus could have occurred. The other compound separated was quinaldinic acid.

Reaction of 2,5-dimethyl-3-furoic acid with quinolyl lithium gave biquinolyl as the only product.



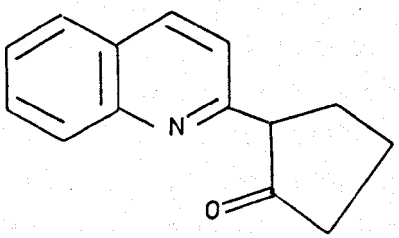
ETHYL 2-(2-CYCLOPENTANONYL)-1,2,3,4-TETRAHYDROQUINOLINE-1-β-PROPIONATE AND ITS ATTEMPTED CYCLISATION

A highly promising route to a 9-azasteroid would start from 2-(2-quinolyl) cyclopentanone (163) previously prepared by Baty et-al[66]. This route would involve catalytic reduction of the nitrogen ring and the carbonyl group to give the secondary amine (164). Alkylation with 2-bromoethylpropionate would give the tertiary amine (167). Oxidation under mild conditions in order that the ester group and the nitrogen containing ring are not affected would give the ketone (160) which would be capable of cyclisation to form the C ring to give the tetracyclic compound (165).

PREPARATION AND REDUCTION OF 2-(2-QUINOLYL) CYCLOPENTANONE

Baty and co-workers[66] reported a yield of 80% in the preparation of 2-(2-quinolyl) cyclopentanone (163) which they separated by recrystallisation from 60-80° petroleum ether. Initial attempts to copy this work gave yields varying from 7-15% and difficulties in isolation of the product. After work up the crude material was a black oil not a solid and recrystallisation attempts using various solvents failed to yield a crystalline material. It was found that the reaction temperature was critical and for an optimum yield (75-80% based on quinoline-1-oxide) the reaction temperature was best kept between -5° and 0°C. The reaction was slightly exothermic and if the reaction temperature was allowed to rise to between 0-5°C. then the yield was cut to below 25%. The product could still not be separated by recrystallisation but either chromatography on Woelm alumina or distillation at very low pressures gave the pure product as orange needles.

The next step was reduction of the ketone (163) to give the alcohol(164). Attempts at catalytic reduction of the amine (163) or its hydrochloride using both 5% and 10% palladium on charcoal catalyst were unsuccessful at both atmospheric and high pressure. Rylander[146] has found that reduction of quinolines using platinum oxide catalyst proceeds more readily on an acid salt or quaternary compound than on the free base. Reduction of the amine (163) as its hydrochloride also failed using platinum oxide catalyst. Rylander has also found that reduction of quinolines are unusually sensitive to poisons.



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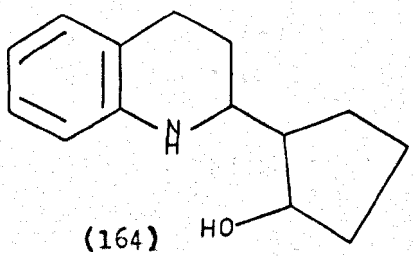
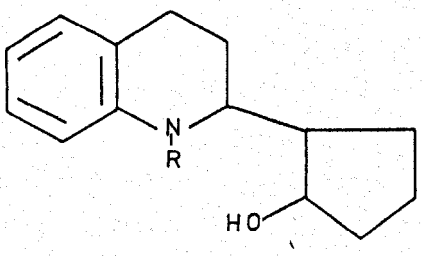
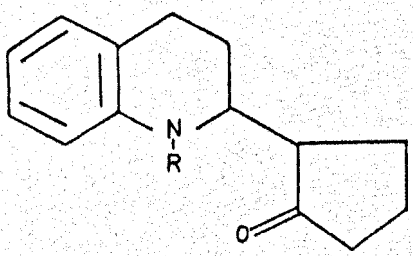


(164)

$BrCH_2CH_2CO_2Et$

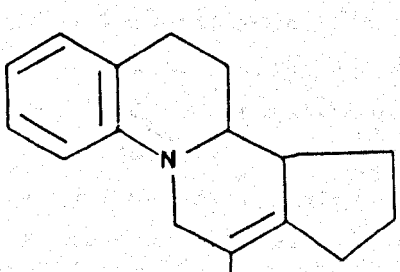


(167)



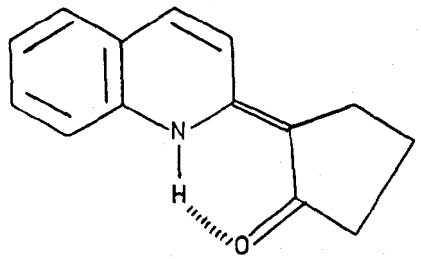
R = CH_2CH_2COOEt

(166)

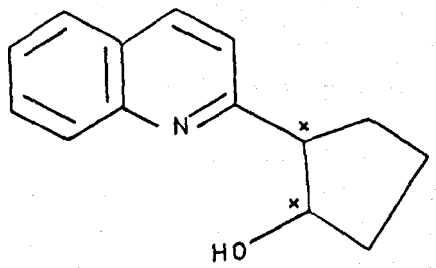


(169)

The reason for the lack of success in the reduction of the ketone(163)is probably due to the potential conjugation between the quinoline and ketone. Baty and co-workers[66] consider the structure of ketone(163)to be(163à)which would explain the observed physical properties. A method of removing this conjugation would be to reduce the ketone(163à)to the corresponding alcohol(296).



(163a)



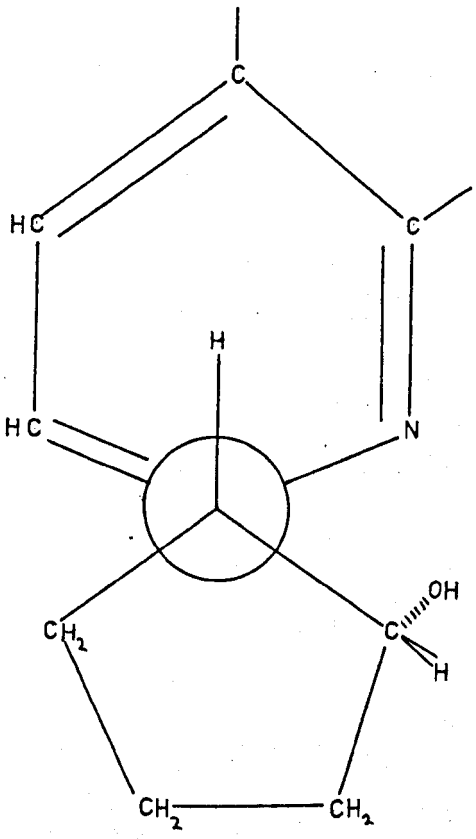
(296)

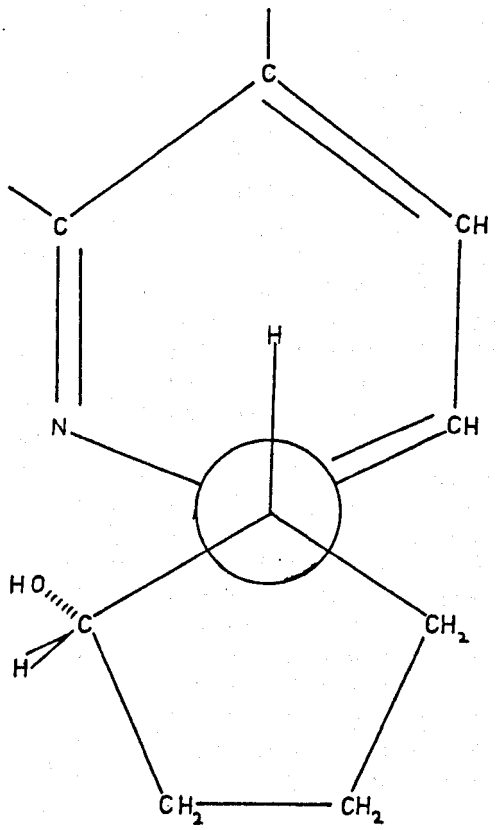
This reduction was carried out using the method of Baty and co-workers[66] to give two racemates, cis(296à)and trans(296b) one showing intramolecular hydrogen bonding and the other not.

STEREOCHEMICAL FEATURES OF 2-(2-QUINOLYL) CYCLOPENTANOL

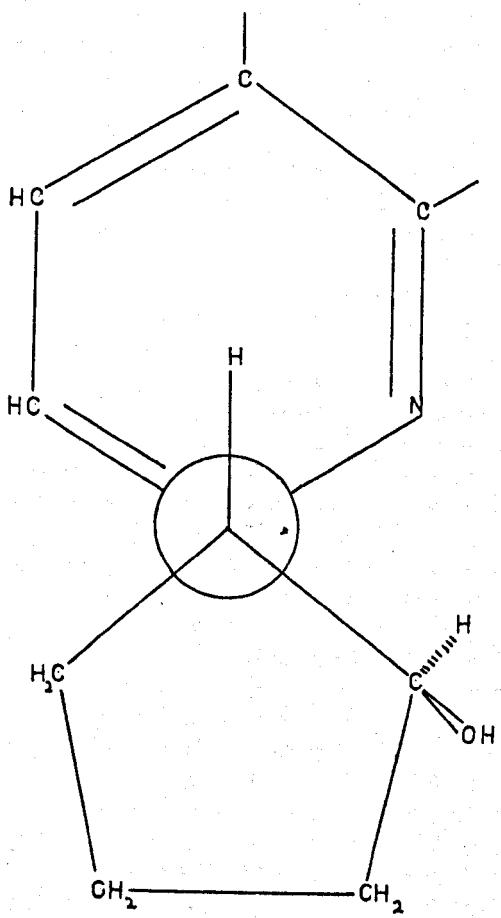
The alcohol(296)possesses two chiral centres (starred) and hence there is a possible total of 2^n optical isomers (n = number of chiral centres) ie four. These are the two optical isomers of each of the two racemates. It can be seen from models and page 95 . that the racemate showing intermolecular hydrogen bonding is in the trans configuration(296b)and the racemate showing intramolecular hydrogen bonding is in the cis configuration(296à). As expected racemate(296à)had a greater R.f. value and lower melting point than racemate (296b).

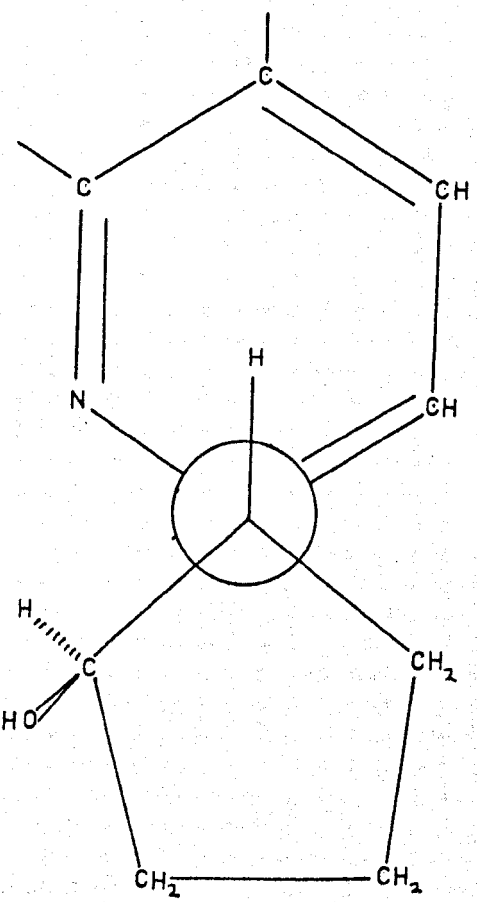
Reduction using 5% and 10% palladium charcoal catalyst on the mixed or separate racemates of the alcohol(296)failed to give any products. Reduction using Adams' platinum oxide catalyst in ethanol was slow giving one racemate of the tetrahydroquinolyl cyclopentanol(164)and tetrahydroquinolyl cyclopentane (300). In



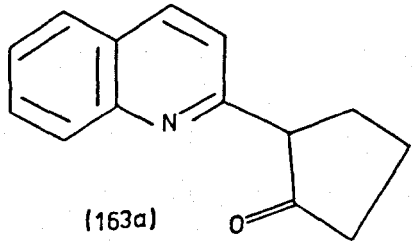


d and l isomers of compound (296a) cis

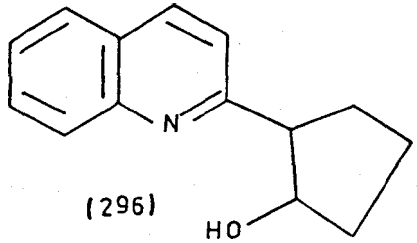




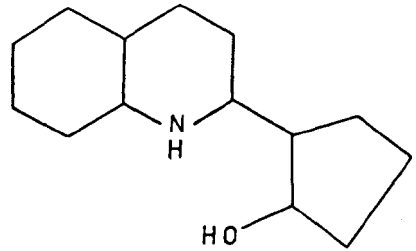
d and l isomers of compound (296b) trans



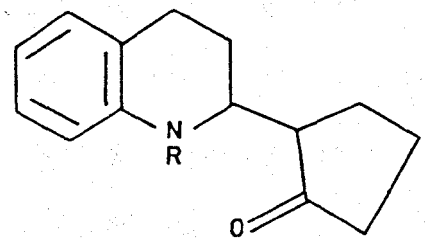
(163a)



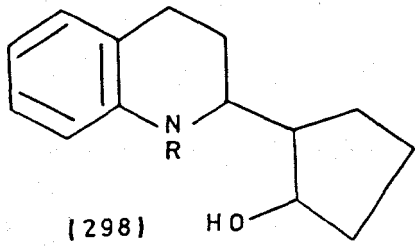
(296)



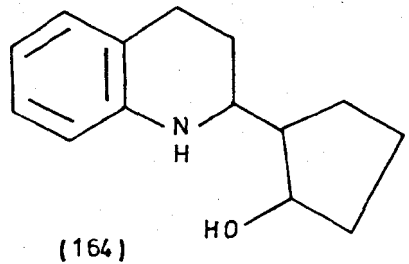
(297)



(166)

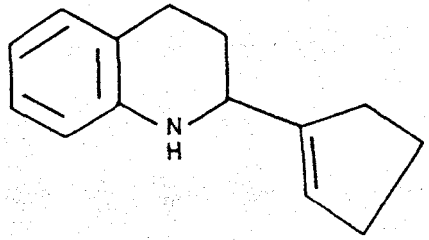


(298)

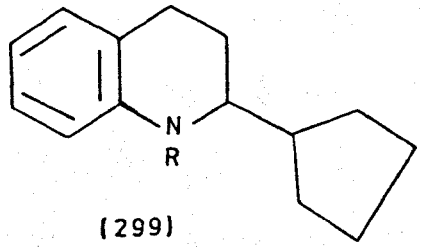


(164)

+

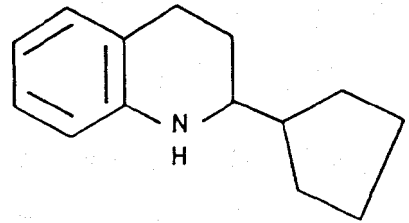


(301)



(299)

R = CH_2CH_2COOEt



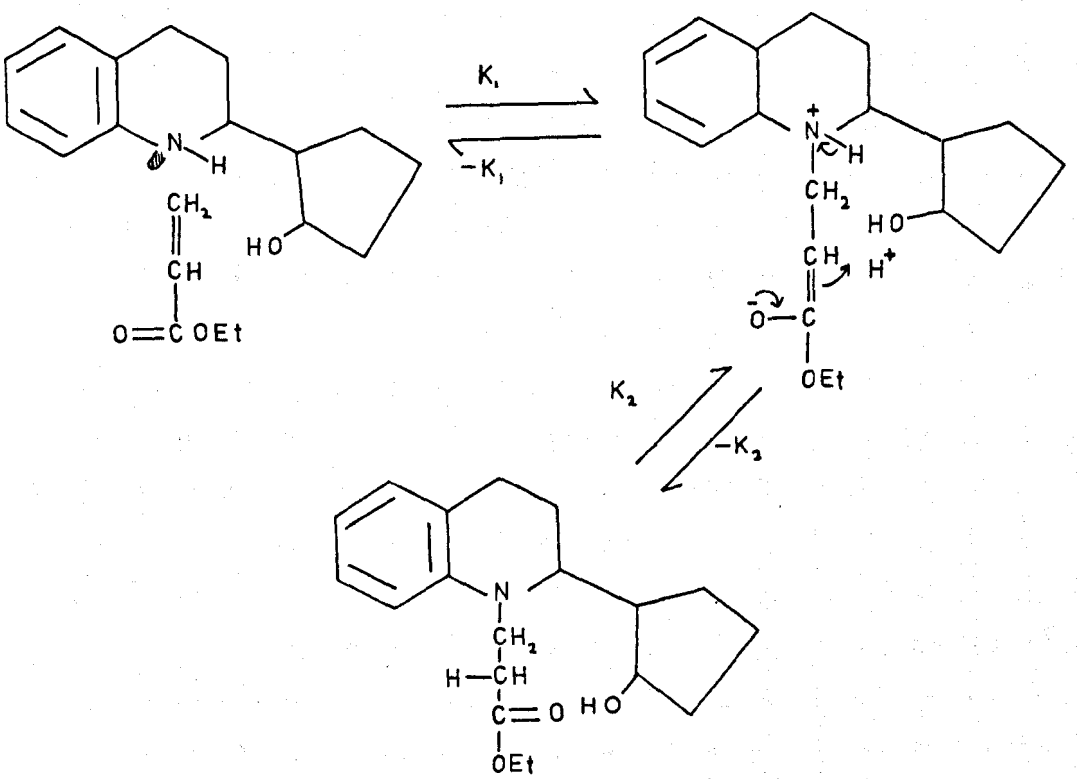
(300)

an attempt to reduce the reaction time and possibly to obtain a greater proportion of the required product (164), the solvent was changed to glacial acetic acid but reduction then gave only one racemate of the decahydroquinolyl cyclopentanol (297).

Quinolines are reduced preferentially in the hetero-ring except when platinum catalysts[147] and acid media are used and Gilman and Cohn[148] have suggested that alkyl substituents in the nitrogen ring of quinoline should increase the relative ease of saturation of the benzene ring and vice versa. However no evidence for the presence of a 2-[2-(5,6,7,8-tetrahydro) quinolyl]cyclopentanol has been found. Hydrogenolysis of the carbon-oxygen bond had occurred to give rise to compound (300), which might have been formed by dehydration to give the corresponding alkene (301). Under the reaction conditions reduction of this double bond would have been very rapid. This amounts to an overall loss of oxygen which can be verified by observation of a molecular ion peak at 201 instead of the expected 217 in its mass spectrum. Facile hydrogenolysis has been observed to occur when elimination would give rise to alkene formation as in the reduction of ketals[149]. Hydrogenolysis of the carbon-oxygen single bond has also been observed when the bond is activated, for example in alkyl and benzyl compounds and phenyl ethers[150]. The alcohol (164) was shown to be intermolecularly hydrogen bonded.

Alkylation of the alcohol (164) using ethyl β-bromopropionate in the absence of solvent was successful. Excess of the alkylating agent was used because at the reaction temperature (140°) there is firstly a possibility of the product undergoing a Michael retrogression reaction (fig. 3; $-K_1$,$-K_2$) back to the amine and ethyl acrylate and secondly dehydrobromination of the ethyl β-bromopropionate to ethyl acrylate occurs to some extent. The reaction was performed in the presence of sodium carbonate in order to prevent the formation of an acidic medium which could cause hydrolysis of the ester-group of the product. The reaction could not be followed by thin layer chromatography because the product had approximately the same R.f. value as the reactant. The product (298) was separated by column chromatography on Woelm alumina (activity 4) and showed intermolecular hydrogen bonding. Compound (300) was also alkylated to give the ester (299).

The next stage was oxidation of the alcohol (298) to the corresponding ketone (166) by methods using mild conditions. Two such methods are the Oppenauer and Sarett procedures. The Oppenauer



(fig. 3)

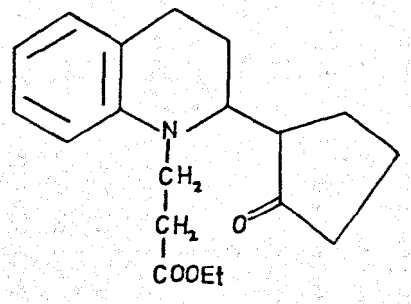
oxidation involves the use of a hydrogen acceptor and originally acetone was the one most widely used. The disadvantage of acetone is that it has a low oxidation potential (0.129 volt) but this could be offset by using it in a large excess. With the introduction of cyclohexanone which has a higher oxidation potential than acetone (0.162 volt) and the use of solvents such as toluene and xylene higher reaction temperatures and shorter reaction times were achieved. Cyclohexanone is particularly useful with involatile compounds such as steroids since it can be separated from the reaction product by steam distillation. Of the three most common catalysts - aluminium t-butoxide, isopropoxide and phenoxide - the t-butoxide is the most difficult to prepare and decomposes in solution at 115°. The Sarett oxidation employs a

chromic anhydride-pyridine complex as a solution in pyridine. Ellis and Petrow[151] have successfully used this reagent to oxidise cholesterol α-oxide to the corresponding ketone although when oxidising cholesterol β-oxide the epoxide ring was opened as well. The original preparation of the complex[152] was potentially hazardous but recently a safer method for its preparation has been formulated by Ratcliffe and Rodehurst[153] involving the formation of the chromic anhydride-pyridine complex in a solution of methylene chloride.

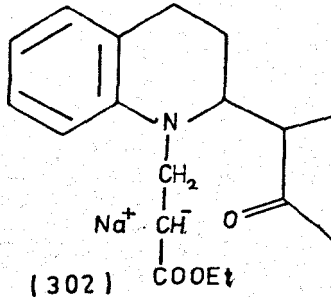
Both methods of oxidation were attempted on 2-(2-quinolyl) cyclopentanol as a model and yields of 55% for the Sarett procedure and 60% for the Oppenauer procedure were obtained. Because of the slightly higher yield the Oppenauer procedure was attempted on the alcohol (298) but failed. The Sarett procedure oxidised the alcohol (298) in 55% yield to the ketone (166). Surprisingly these two compounds were difficult to separate chromatographically, the ketone only having a slightly greater R.f. value than the alcohol.

The next stage was the Dieckmann condensation to give the tetracyclic compound (165).

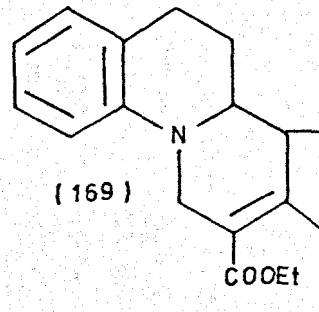
Initially mild conditions were tried for the cyclisation because of the possibility of loss of the side chain to give the amine (304). The conditions first tried were sodium ethoxide in ethanol at room temperature for twenty four hours. This went as far as forming the sodium salt (302) but cyclisation did not occur as could be judged from the fact that the product had identical spectra, the same molecular ion in the mass spectrum and the same G.L.C. retention time. More vigorous conditions using sodium ethoxide in refluxing ethanol for six hours or sodium tertiary butoxide in tertiary butanol were next used. Both methods only went as far as forming the sodium salt (302). Because the sodium salt (302) is actually formed it would be expected that due to polarisation of the ketone group of the cyclopentanone ring, the anionic centre would attack the electron deficient ketone carbon atom. The degree of polarisation of the ketone group would thus affect the rate of reaction as would the stereochemistry.



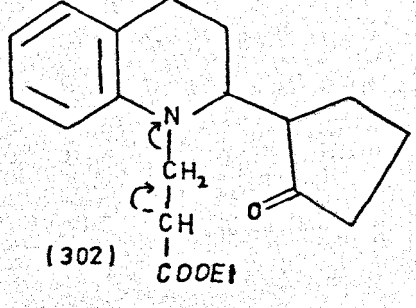
(165)



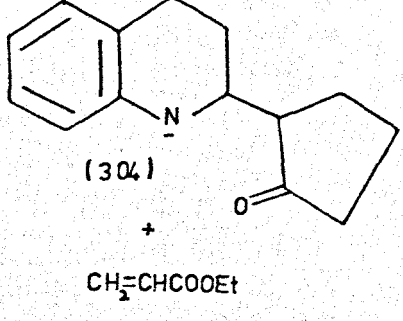
(302)



(169)



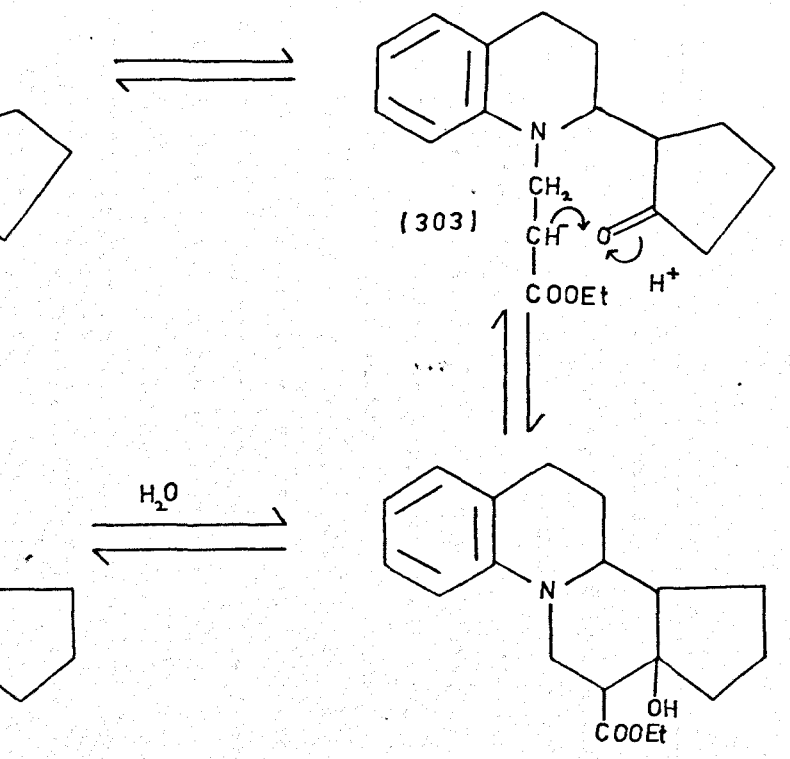
(302)



(304)

+

CH_2=CHCOOEt



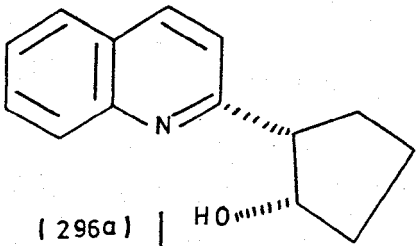
(165)

STEREOCHEMICAL FEATURES OF THE REDUCTION OF 2-(2-QUINOLYL)-CYCLOPENTANOL

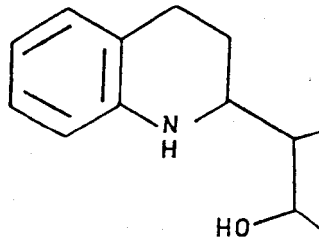
Depending on the relative rates of hydrogenolysis and hydrogenation, loss of oxygen could occur before or after reduction of the hetero-ring. If hydrogenolysis occurred first to compound (296a) then one alkene (305) would be formed. The reduction of the double bond of this compound would give the alkane (306) which could undergo reduction of the nitrogen containing ring to give one racemate of compound (300) which in these circumstances would have originated from the reduction of compound (296a). If compound (296b) was not de-oxygenated in the reduction, only one of a possible total of two racemates (164c or 164d) would be formed. Diagrams of all compounds are shown in the energetically more favourable form in which the five membered ring is equatorially bonded to the reduced nitrogen-containing ring.

If the reduction of the nitrogen-containing ring occurred prior to hydrogenolysis then the cis racemate (296a) could be reduced to give one or both of the alcohols (164a and 164b). Dehydration could then occur to give the alkene (301) which could be reduced to the alkane (300). Likewise the trans racemate (296b) could be reduced to give one or both of alcohols (164c or 164d).

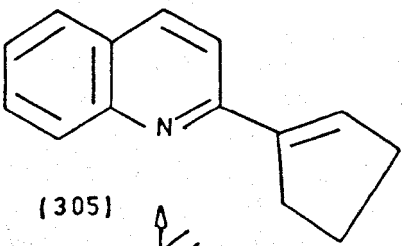
The several alternatives that could give the observed products [one alcohol (164) and one de-oxygenated product (300)] are summarised in scheme 2. The one racemate of alcohol (164) formed in the reaction was shown to form intermolecular hydrogen bonds. It can thus be assigned either the configuration (164c) or (164d) and can only have come from compound (296b). Compound (300) could have come either from compound (296b) alone or from both compound (296a) and (296b) but not from compound (296b) alone. If compound (296b) was reduced to give two racemates of compound (164), one racemate was probably further converted to the alkane (300) [only one racemate of compound (164) was found in the products]. In these circumstances compound (300) would have come from both compound (296a) and (296b). If compound (296b) was reduced to give only one racemate of compound (164) then compound (300) would have come only from compound (296a). Similar arguments could be applied if one racemate of compound (296) underwent hydrogenolysis prior to hydrogenation and the other racemate underwent hydrogenation prior to hydrogenolysis.



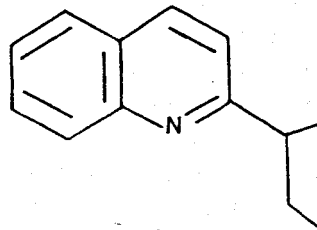
(296a)



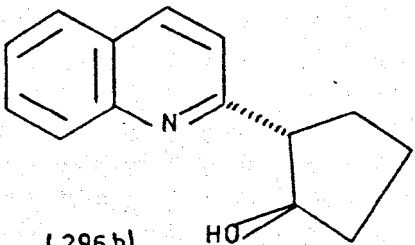
(164a)



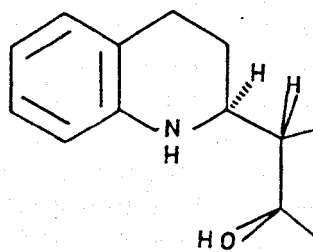
(305)



(306)



(296b)



(164c)

SCHEME 1

(164b)

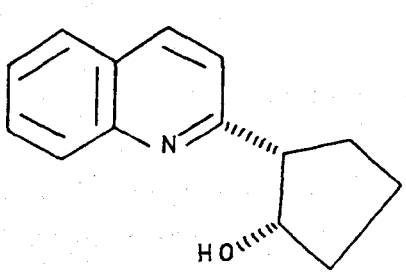
(300)

OR

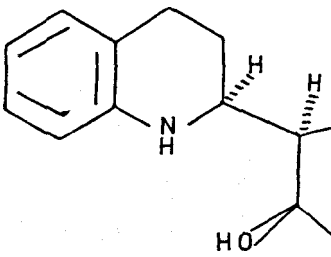
(164d)

(300)

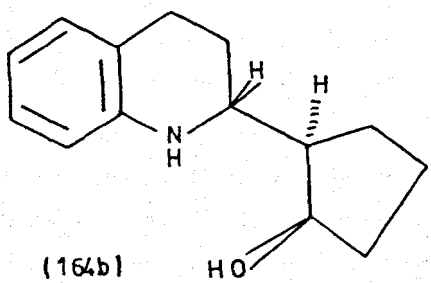
(301)



(296a)

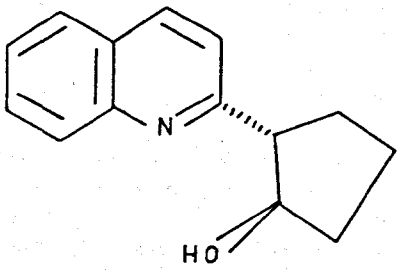


(164a)

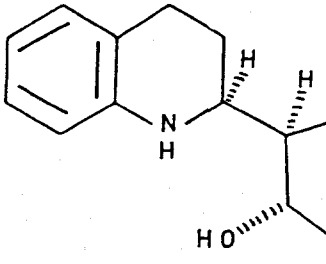


(164b)

SCHEME 2

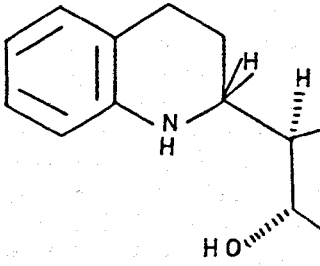


(296b)



164c

AND/OR

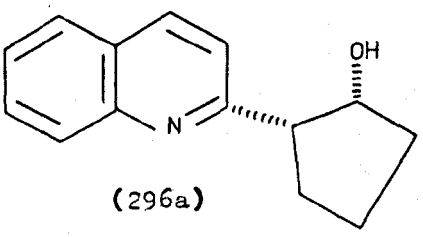


(164d)

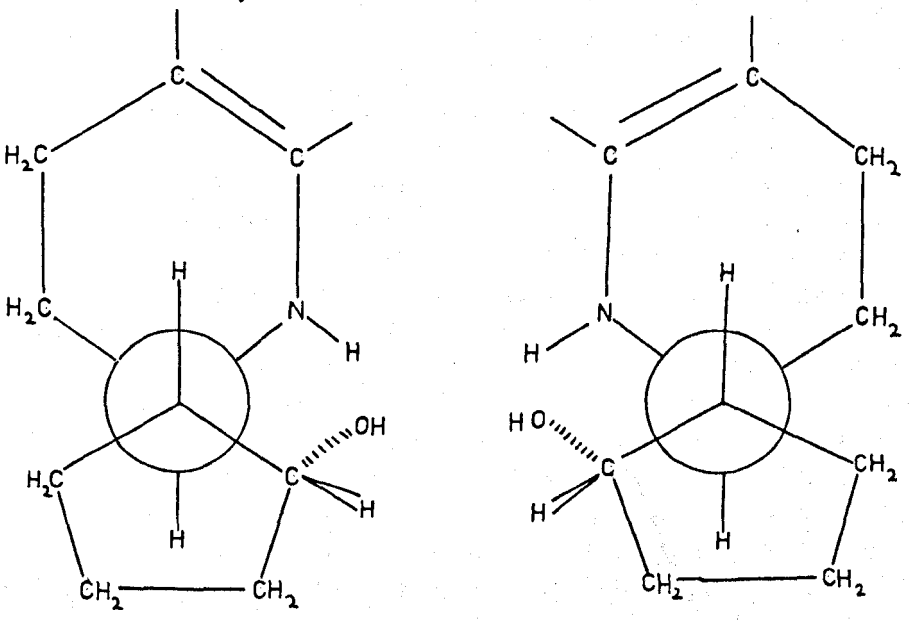
SCHEME 2

(301)

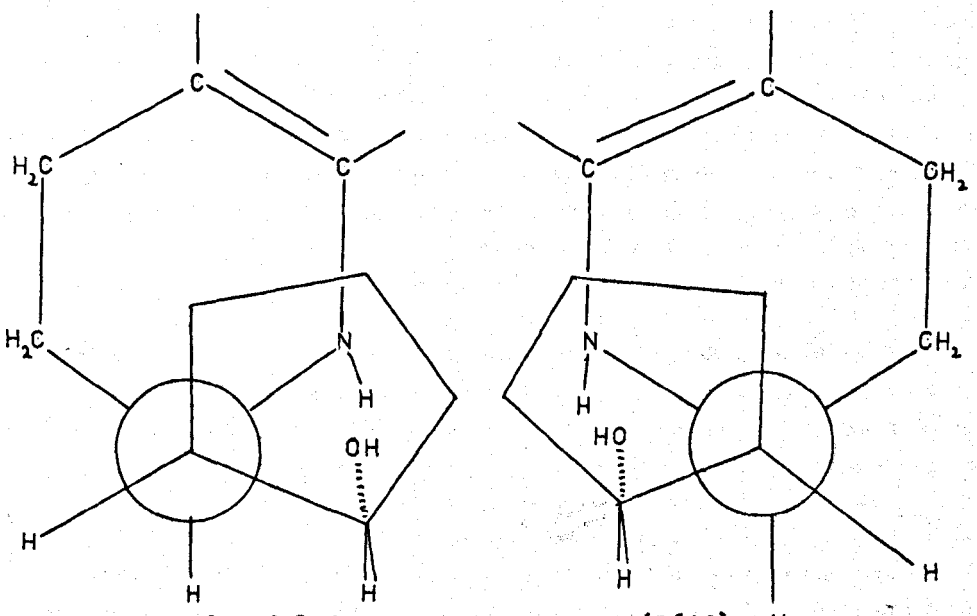
(300)



(296a)

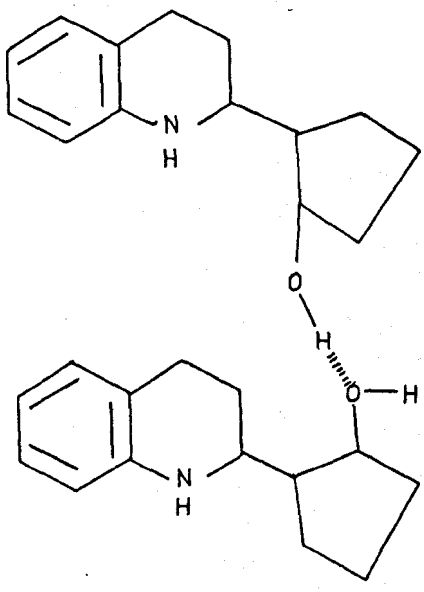


d and l isomers of compound (164a)



d and l isomers of compound (164d)

Compounds (164a) and (164b) are capable of intramolecular hydrogen bonding



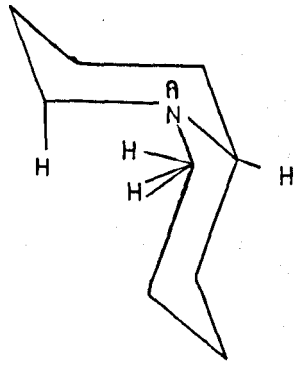
(fig. 6)

STEROCHEMICAL FEATURES OF THE REDUCTION OF 2-(2-QUINOLYL) CYCLOPENTANOL IN GLACIAL ACETIC ACID.

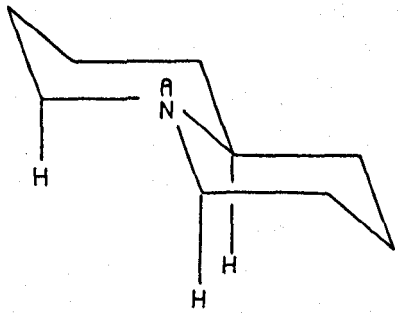
The reduction of compound (164) using Adams' catalyst in glacial acetic acid gave compound (297) which possesses five chiral centres and hence a possible total of sixteen racemates. The actual compound found shows intermolecular hydrogen bonding and so the number of possibilities is reduced to sixteen.

It has been known since 1957[155-156] that quinolizidines (312a and 312b) and related compounds are capable of showing high wavelength C-H I.R. absorption stretching bands (Bohlmann bands) depending on their configuration. Wenkert and Roychaudhuri[157] have shown that indoles (313) in which the C/D ring fusion is trans show two or more peaks of medium intensity on the high wavelength side of the major band. The cis epimers were found to show only shoulders. Absorption at this wavelength is due to interaction between the nitrogen dipole and adjacent axial hydrogen atoms and only is shown if there are at least two such hydrogen atoms. This phenomenom has since been used in assigning configuration to such compounds and could be applied to the decahydroquinolyl cyclopentanol

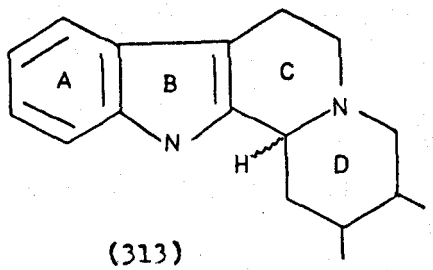
(297). The quinolizidine in the trans (312b) configuration possesses



(312a) cis

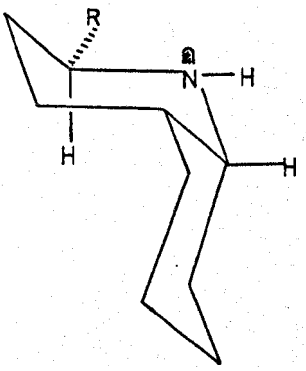


(312b) trans

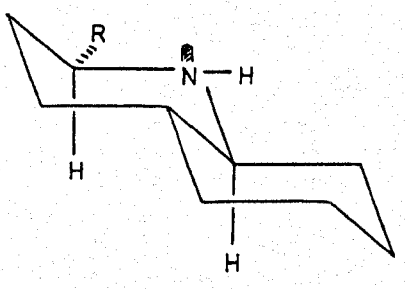


(313)

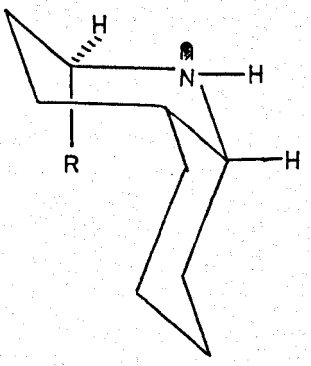
three axial hydrogen atoms adjacent to nitrogen but the cis (312a) only has one. The decahydroquinolyl cyclopentanol (297) in the trans configuration (297c 297d) has at least one such hydrogen atom (two if the cyclopentanol ring is equatorially bonded) whereas the molecule in the cis configuration (297a,297b) has a maximum of one adjacent axial hydrogen atom (but none if the cyclopentanol ring is in the less favoured axial configuration). The I.R. of compound (297) does not show Bohlmann bands, thus the configurations (297b, 297c and 297d) are unlikely (two axial hydrogens adjacent to nitrogen in297c) and the more likely configuration is (297a) where the A/B ring fusion is cis and the cyclopentanol ring is equatorially bonded to the nitrogen ring.



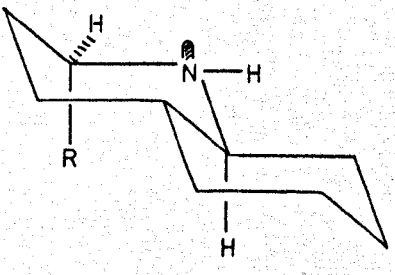
(297a)



(297c)

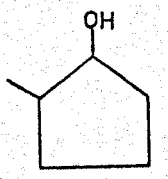


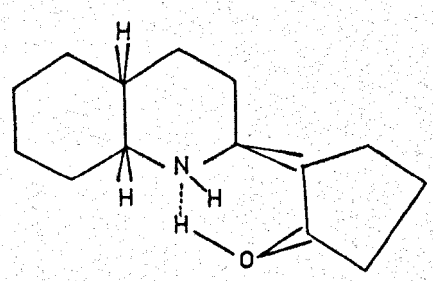
(297b)



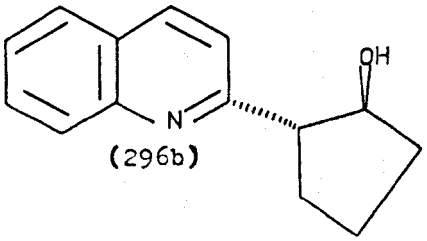
(297d)

R =

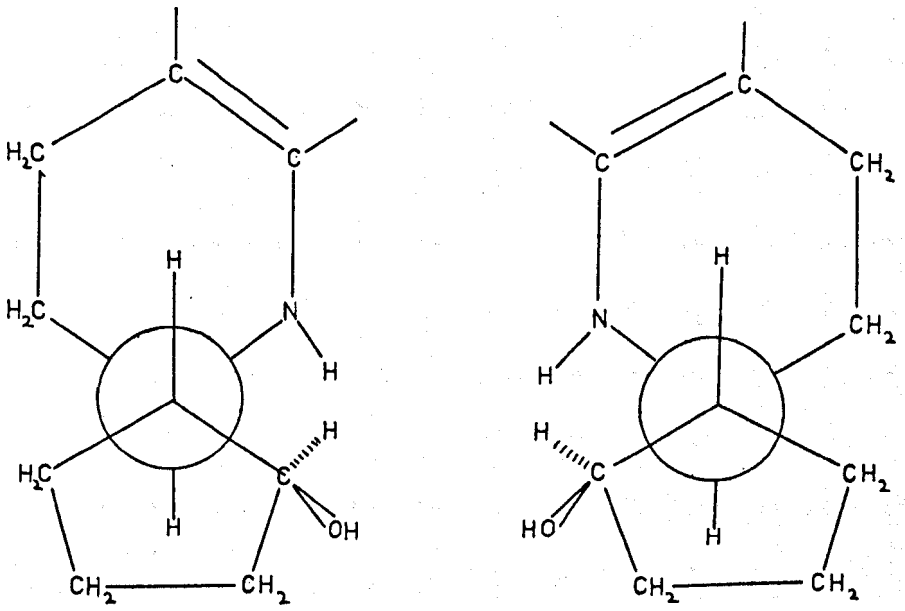




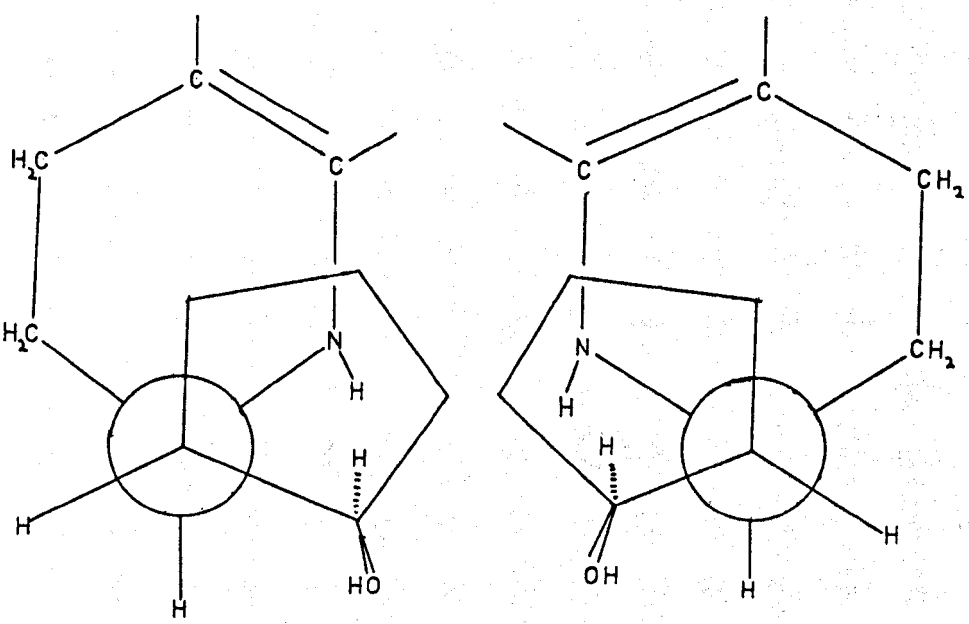
(297a)



(296b)



d and l isomers of compound (164c)



d and l isomers of compound (164d)

Compounds (164c) and (164d) are not capable of intramolecular hydrogen bonding

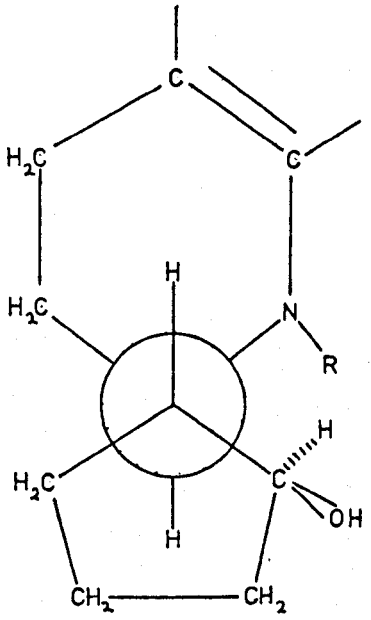
STEREOCHEMICAL FEATURES OF ALCOHOL (298), KETONE (166) AND THE DIECKMANN CONDENSATION REACTION.

Alkylation of alcohol (164) to give the tertiary amine (298) does not influence the stereochemistry previously considered. Oxidation of compound (298) to the ketone (166) causes the loss of one chiral centre to bring a reduction in the possible total number of racemates from four to two. The two possible configurations of the ketone (166) are (166c) and (166d).

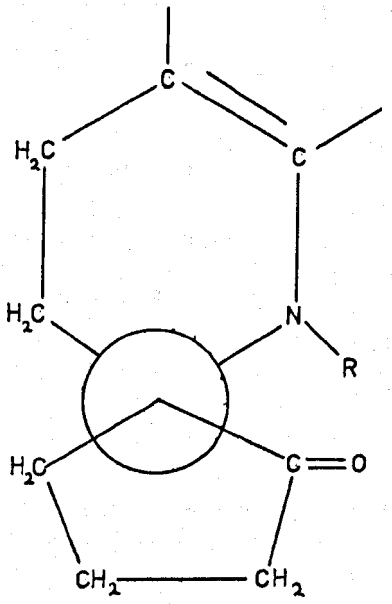
On the basis of the assignment of configuration to alcohol (164), the amine (298) can be assigned the configuration of either (298c) or (298d). Oxidation of the alcohol (298) does not assist in assigning a configuration to ketone (166).

Condensation of the ketone (166) would initially give the alcohol (307) which possesses four chiral centres and thus there would be a possible total of eight racemates. There is a point of equilibration involved in the reaction at C-12, where the ester-group could be either axial or equatorial. The latter configuration would be energetically favoured and it is assumed that the molecule would equilibrate to give mainly this configuration. This reduces the number of chiral centres to three and the possible total number of racemates to four.

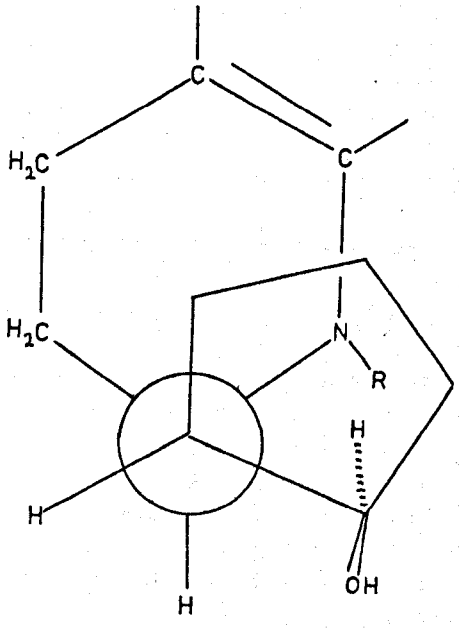
During the reaction the carbanion can approach C-13 from either side of the carbonyl group in compound (166c) to give a possible mixture of compound (307a) (C/D cis) and compound (307b) (C/D trans). Similarly compound (166d) could give a possible mixture of compound (307c) (C/D cis) and compound (307d) (C/D trans).



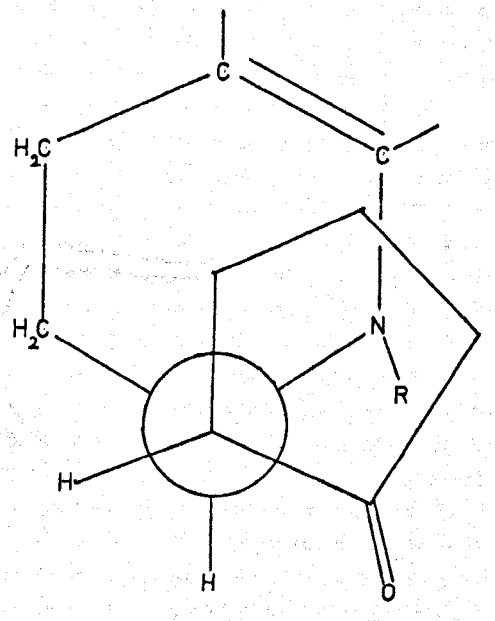
Compound (298c)



Compound (166c)

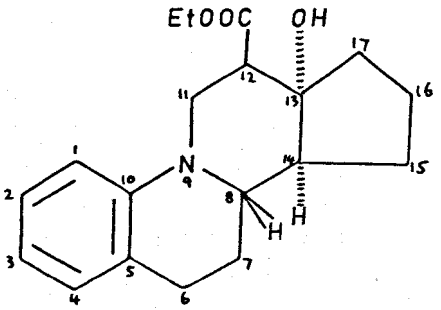


Compound (298d)

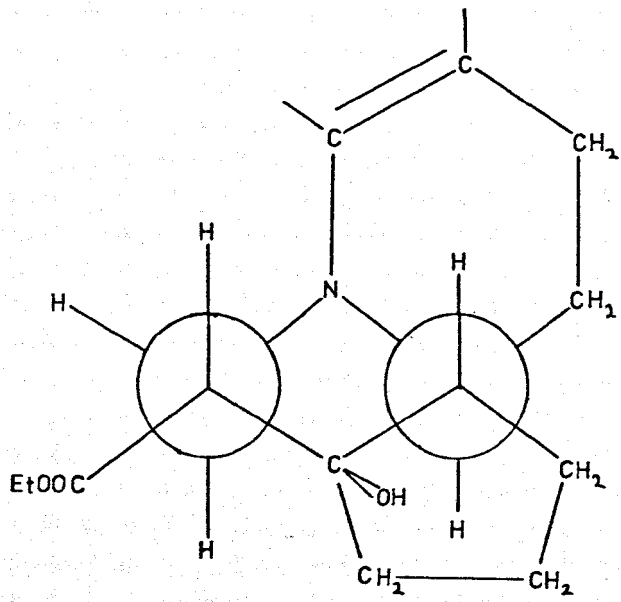


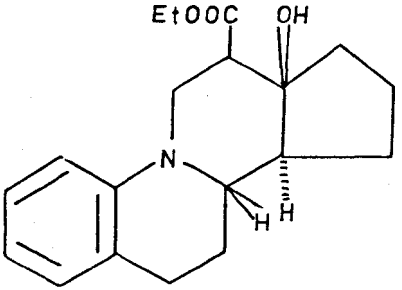
Compound (166d)

$R = CH_2CH_2CO_2Et$

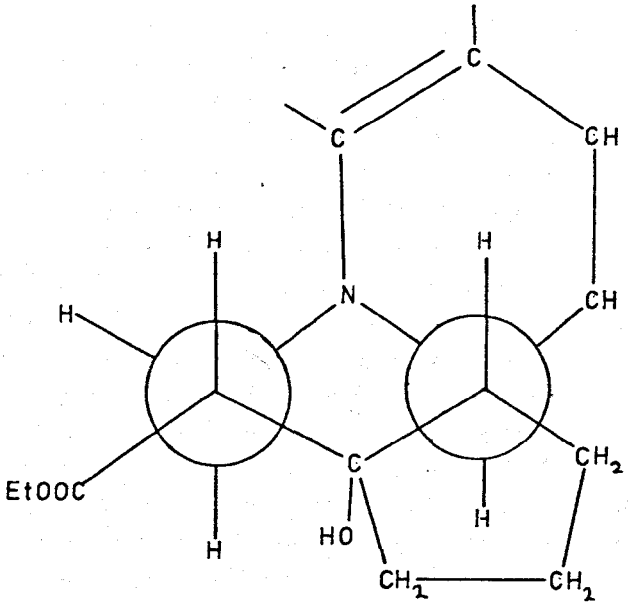

EtOOC
OH
17
16
15
12
13
11
14
1
10
N
9
8
2
H
H
3
5
7
4
6

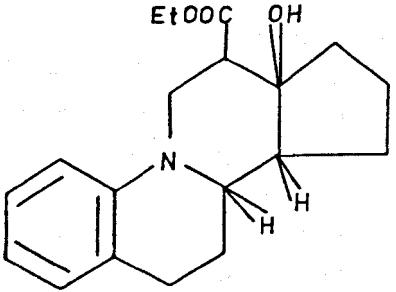
(307a)


C
C
CH2
H
N
H
H
CH2
EtOOC
C
OH
CH2
H
H
CH2
CH2

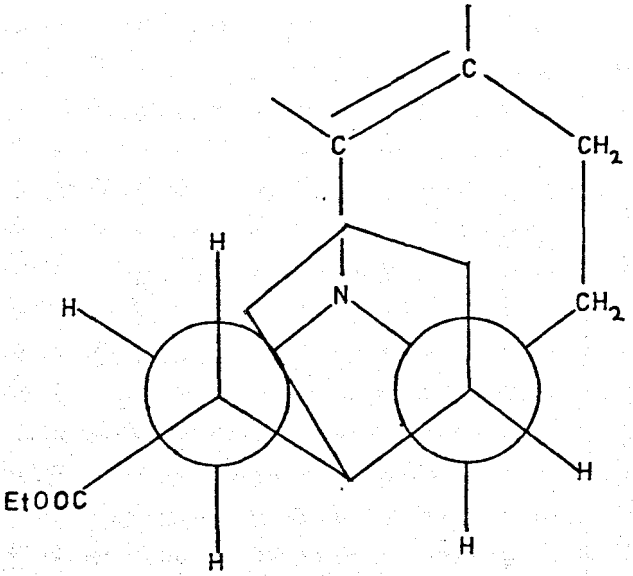


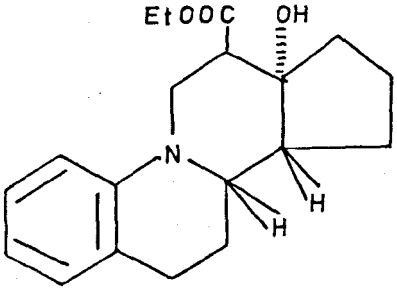
(307b)



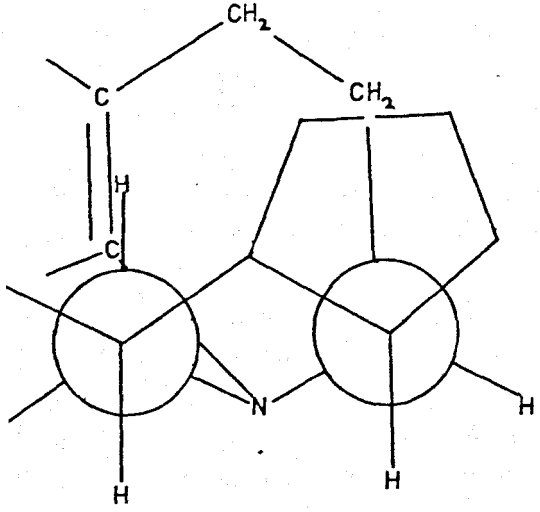


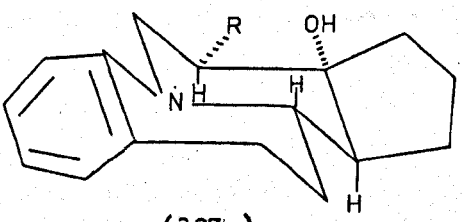
(307c)



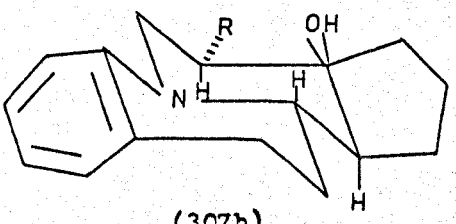


(307d)

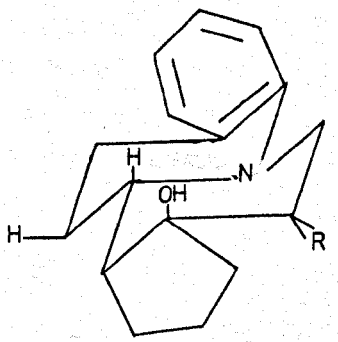




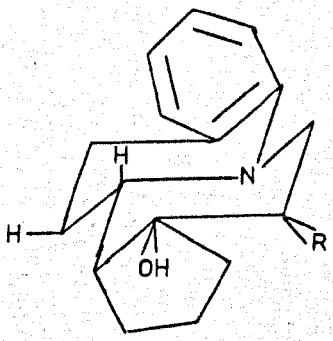
(307a)



(307b)



(307c)

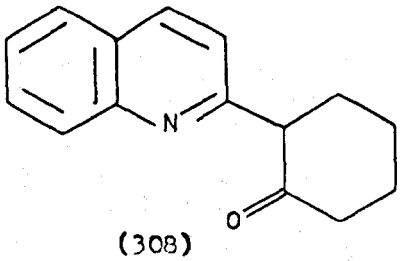


(307d)

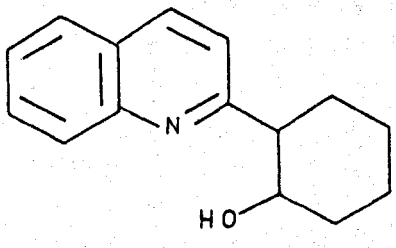
R = CO_2Et

PREPARATION AND REDUCTION OF 2-(2-QUINOLYL) CYCLOHEXANONE

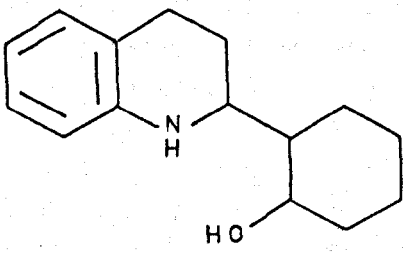
Because of the initial lack of success in obtaining a high yield of ketone (163), the 2-(2-quinolyl) cyclohexanone (308) synthesised by Hamana and Noda[154] was prepared in high yield and used as a model for the further reactions. Reduction to the alcohol (309) was successful using the method of Hamana and Noda but further reduction proved more difficult than with the cyclopentanol analogue (296). Reduction using 5% and 10% palladium charcoal catalyst failed. Using Adams' catalyst in ethanol at atmospheric pressure, reaction proceeded very slowly and not to completion. By changing the solvent to glacial acetic acid the reaction went to completion to give three products (310, 311) - two racemates with the nitrogen containing ring reduced and one racemate with the benzene ring reduced. Of the two alcohols (310) one showed intermolecular hydrogen bonding and one did not. Compound (311) showed intramolecular hydrogen bonding. The alcohol (309) existed as two racemates, one showing intermolecular hydrogen bonding and one not.



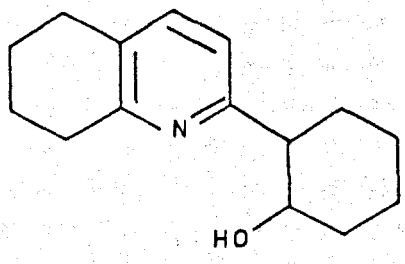
(308)



(309)



(310)

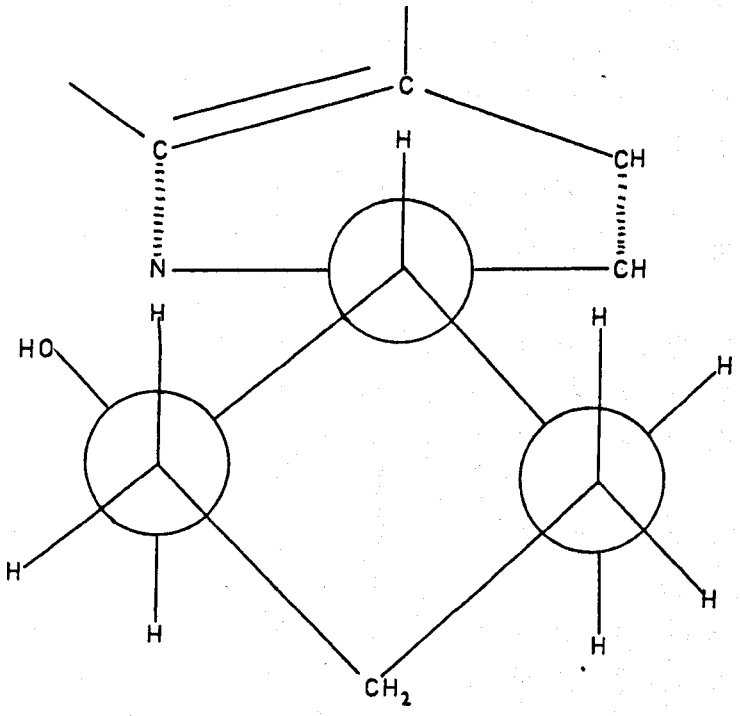


(311)

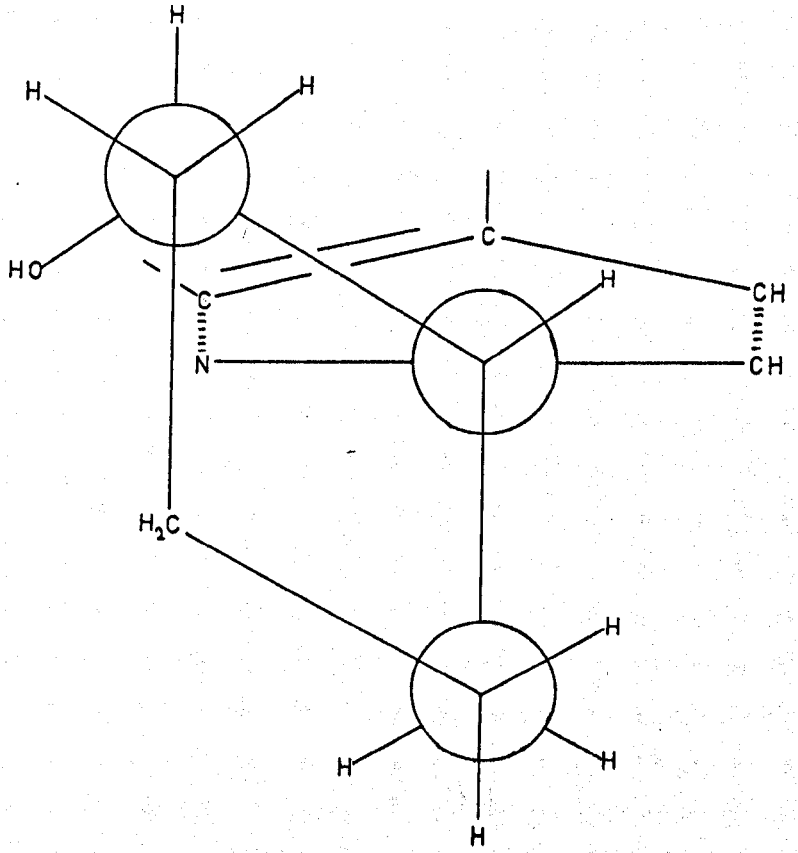
STEREOCHEMICAL FEATURES OF THE REDUCTION OF 2-(2-QUINOLYL) CYCLOHEXANONE (308)

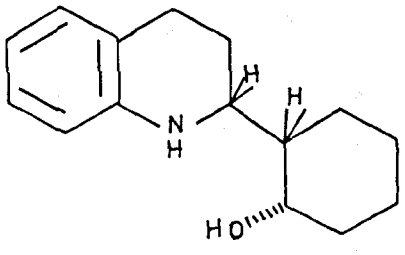
Both 2-(2-quinolyl) cyclopentanol (296) and 2-(2-quinolyl) cyclohexanol (309) can exist as stereoisomers - for the cyclohexanol cis (309a) and trans (309b). One of the racemates showed intramolecular hydrogen bonding and the other showed intermolecular hydrogen bonding. The former had a greater R.f. value and lower melting point than the latter. Models show that both the cis and trans racemates are capable of showing intramolecular hydrogen bonding. In compound (309a) the hydroxyl group and the nitrogen ring are equatorially and axially bonded to the cyclohexane ring. In compound (309b) the hydroxyl group and the nitrogen ring are either both equatorially bonded or less likely both axially bonded to the cyclohexane ring. On this evidence it is not possible to assign configurations to the intra - and intermolecularly hydrogen bonded racemates. On reduction of the nitrogen-containing ring to give compound (310) another chiral centre is introduced creating a possible total of four pairs of racemates. Compound (309a) would be reduced to compounds (310a and 310b) and compound (309b) would be reduced to compounds (310c and 310d). All four racemates of compound (310) are capable of intramolecular hydrogen bonding however the molecule in the cis configuration (310a and 310b) must adopt the sterically hindered arrangement of C-2 - C-2′ bond being eclipsed rather than staggered for this bonding to occur. Thus it seems more likely that the one racemate found showing intramolecular hydrogen bonding is in the trans configuration and can be assigned the structure either (310c) or (310d). Consequently the one racemate found showing intermolecular hydrogen bonding is more likely to be in the cis configuration and can be assigned the structure either (310a) or (310b). This is the opposite to that found with the four possible racemates of 2-[2-(1,2,3,4 tetrahydro) quinolyl] cyclopentanol (164). Only one racemate of alcohol (311) out of a possible total of two was found and did not show intramolecular hydrogen bonding. The sterochemical features of this compound are similar to those of 2-(2-quinolyl) cyclohexanol and hence it is not possible to assign either a cis or trans configuration to it on the evidence.

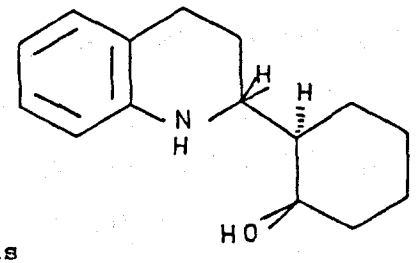
(309b) trans



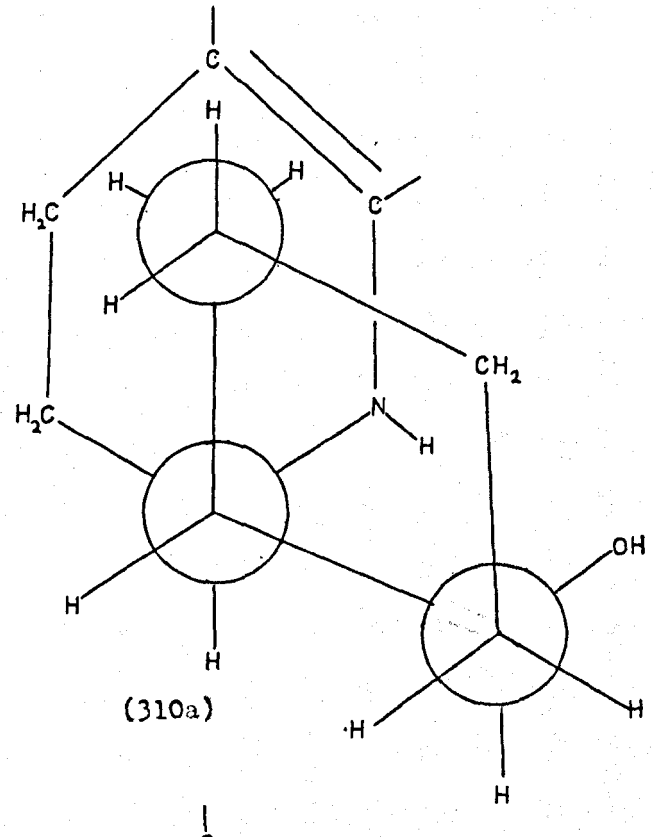
(309c) cis



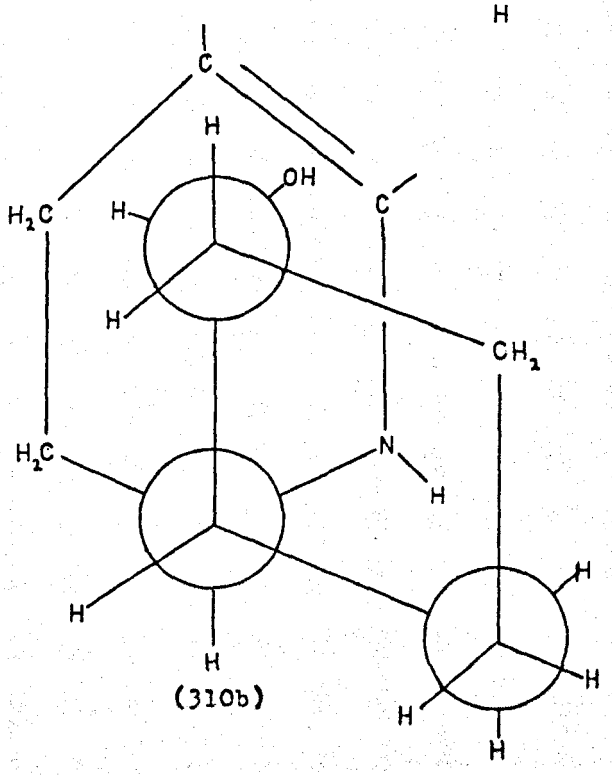




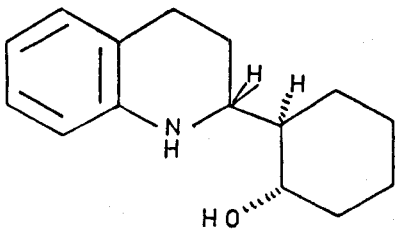
(310) cis



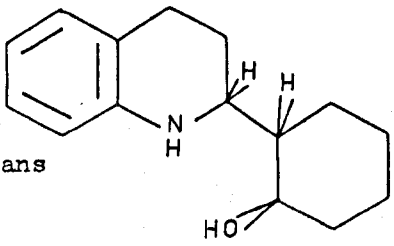
(310a)

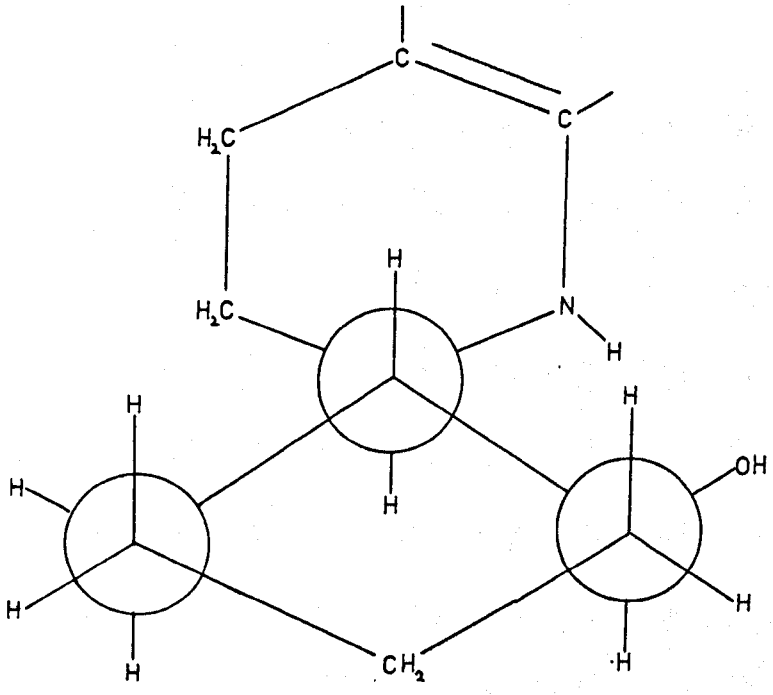


(310b)

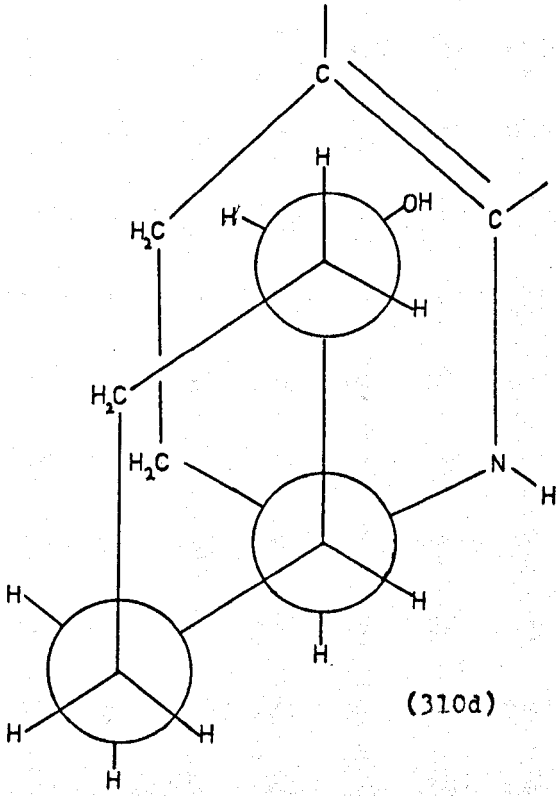


(310) trans



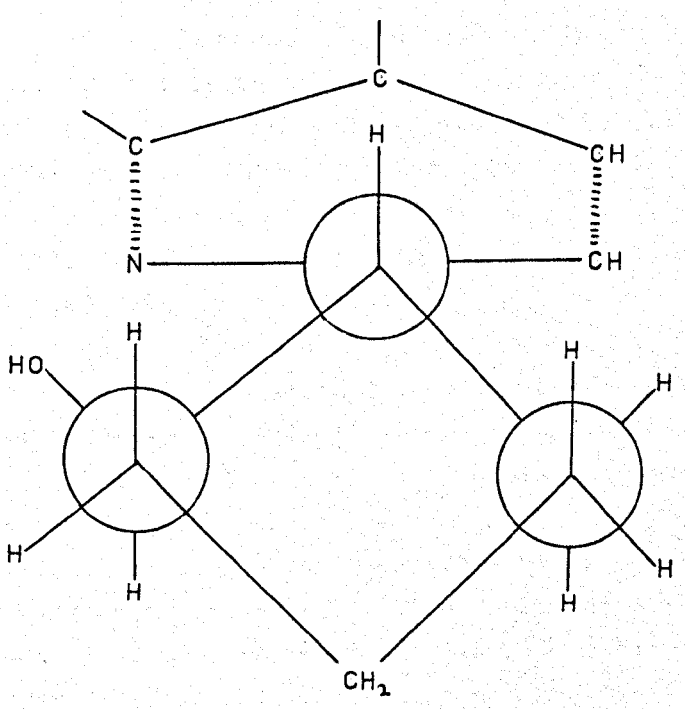


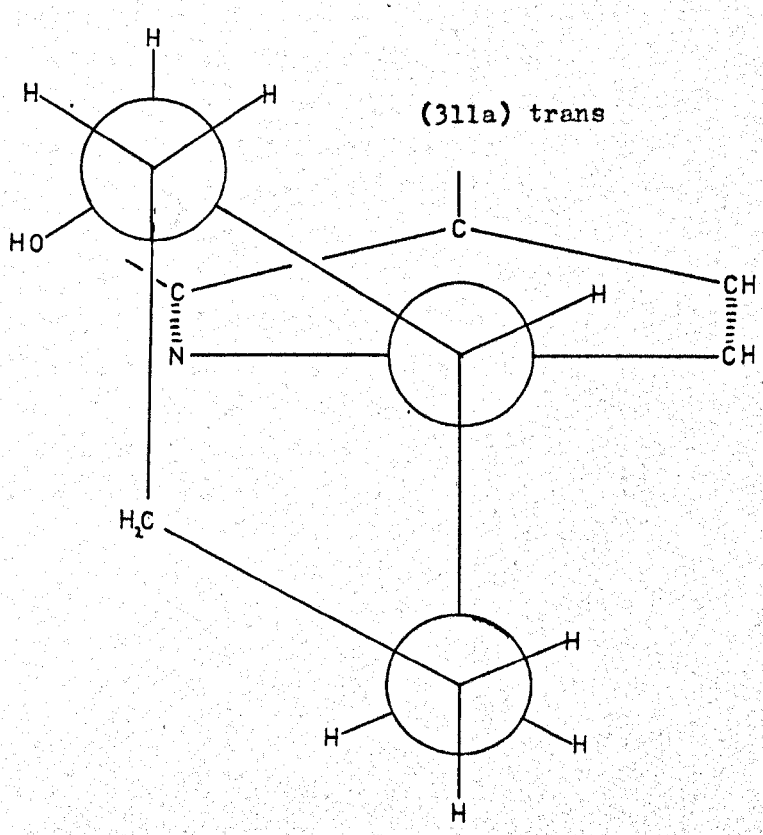
(310c)



(310d)

(311b) trans



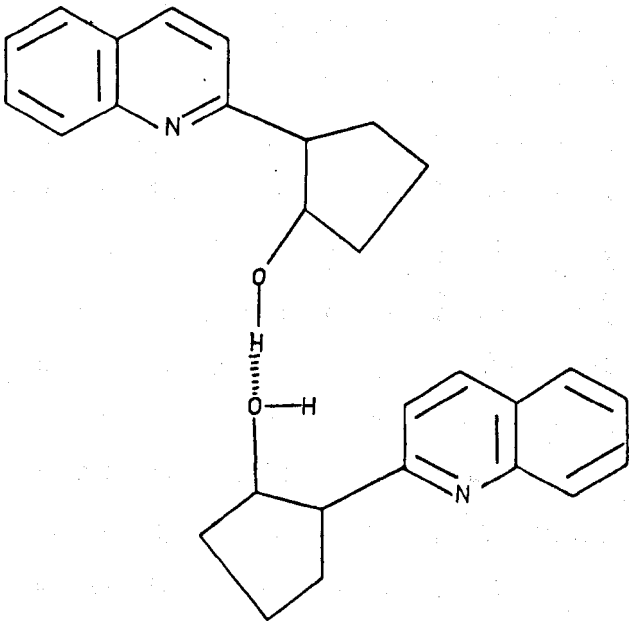


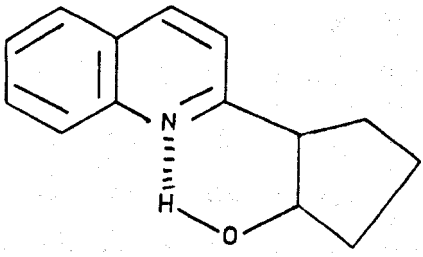
It can be seen that compound (311) was derived only from the racemate of compound (399) which showed intermolecular hydrogen bonding. Compound (310a or310b) could only have come from compound (309a) and compound (310c or310d) could only have come from compound (309b). From this it is possible to reason that the intramolecular hydrogen bonded racemate of compound (309) can be assigned the trans configuration (309b) and that the intermolecular hydrogen bonded racemate of compound (309) can be assigned the cis configuration (309a). Likewise compound (311) can be assigned the cis configuration (311a).

In compounds (296,309,311) the nitrogen-containing ring is aromatic and intramolecular hydrogen bonding occurs between the hydroxyl hydrogen and the nitrogen. The intermolecular hydrogen bond is more likely to be between the hydroxyl hydrogen and the hydroxyl oxygen (oxygen is more electronegative than nitrogen - the difference is increased by the nitrogen lone pair being delocalised over the aromatic system) than between the hydroxyl hydrogen and nitrogen. This is illustrated in fig. (4) by compound (296).

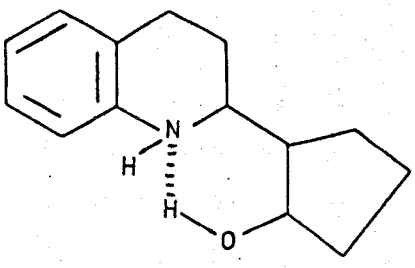
In compounds (164) and (310) the nitrogen-containing ring is saturated and intramolecular hydrogen bonding could occur between the hydroxyl hydrogen and the nitrogen (fig.5a) or between the oxygen and the amine hydrogen fig. (5b). This is illustrated by compound (164). The more likely arrangement is in fig. (5b) where the oxygen would have a greater electron affinity than nitrogen even though the nitrogenlone pair is not delocalised over an aromatic ring. For the same reason intermolecular hydrogen bonding is more likely to be between the hydroxyl hydrogen and the oxygen, illustrated in fig. (6) page 106.

Hydrogen bonding causes shifts to lower frequencies in the I.R. absorption of the hydroxyl group and the amine group. Intramolecular hydrogen bonding causes greater shifts than intermolecular hydrogen bonding. Because these frequency shifts are proportional to the strength of the hydrogen bond it follows that the intramolecular bond is stronger than the intermolecular bond.

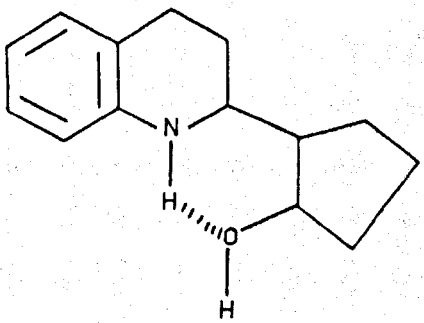




(fig. 4)



(fig. 5a)



(fig. 5b)

PREPARATION AND ATTEMPTED CYCLISATION OF THE MONO-ETHYL MALONIC ACID AMIDE OF 2-(2-CHLOROCYCLOPENTYL)-1,2,3,4-TETRAHYDROQUINOLINE AND RELATED COMPOUNDS

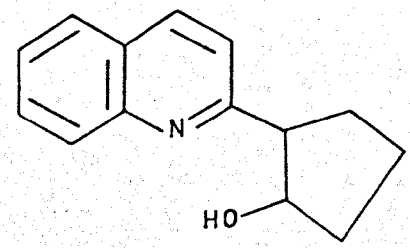
Because of the failure of compound (166) to undergo condensation it was decided to change the substituent on the nitrogen atom and use a different substituent on the cyclopentane ring. The compound chosen was the mono-ethyl malonic acid amide of 2-(2-chlorocyclopentyl)-1,2,3,4-tetrahydroquinoline (316). Because of the presence of two carbonyl groups, the amide (316) possesses a more active methylene group than does compound (314) and chlorine provides a ready leaving group.

PREPARATION OF 2-(2-CHLOROCYCLOPENTYL)-1,2,3,4-TETRAHYDROQUINOLINE

A suitable method of obtaining 2-(2-chlorocyclopentyl)-1,2,3,4-tetrahydroquinoline was considered to be by catalytic reduction of compound (296) to the tetrahydroderivative (164) followed by reaction with thionyl chloride. The alcohol (164) was treated with purified thionyl chloride in ether in the presence of a trace of pyridine. This procedure led to extensive polymerisation probably due to the fact that during work up the ether distills off before the excess thionyl chloride does leaving the product in the presence of undiluted thionyl chloride. To overcome this difficulty a higher boiling solvent (toluene) was used in the reaction and one racemate of product (315) was obtained..

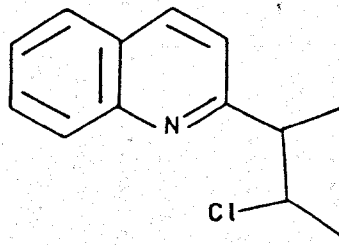
A second method of obtaining compound (315) was visualised by reaction of alcohol (296) with thionyl chloride first to give compound (314) followed by catalytic reduction to give the chloro-compound (315) (though there is the possibility of the reductive removal of chlorine). Reaction of compound (296) with thionyl chloride gave 2-quinolyl cyclopentane (306) which on catalytic reduction gave one racemate o f 2-(1,2,3,4-tetrahydroquinolyl) cyclopentane (300) having identical spectra and the same G.L.C. retention time as the product (300) of the catalytic reduction of 2-(2-quinolyl) cyclopentanol (p. 94).

This second route was not further pursued. Acylation of the secondary amine (315) with monoethylmalonyl chloride in ether gave the amide (316).



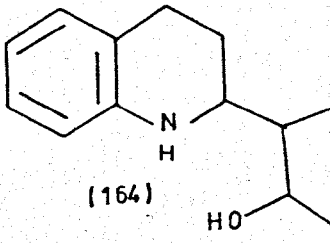
(296)

$SOCl_2$

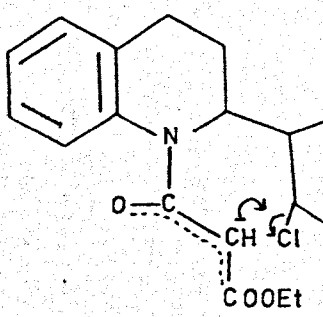


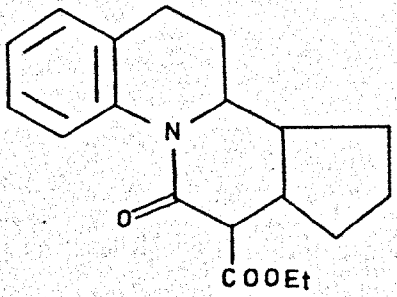
(314)

PtO_2/H_2

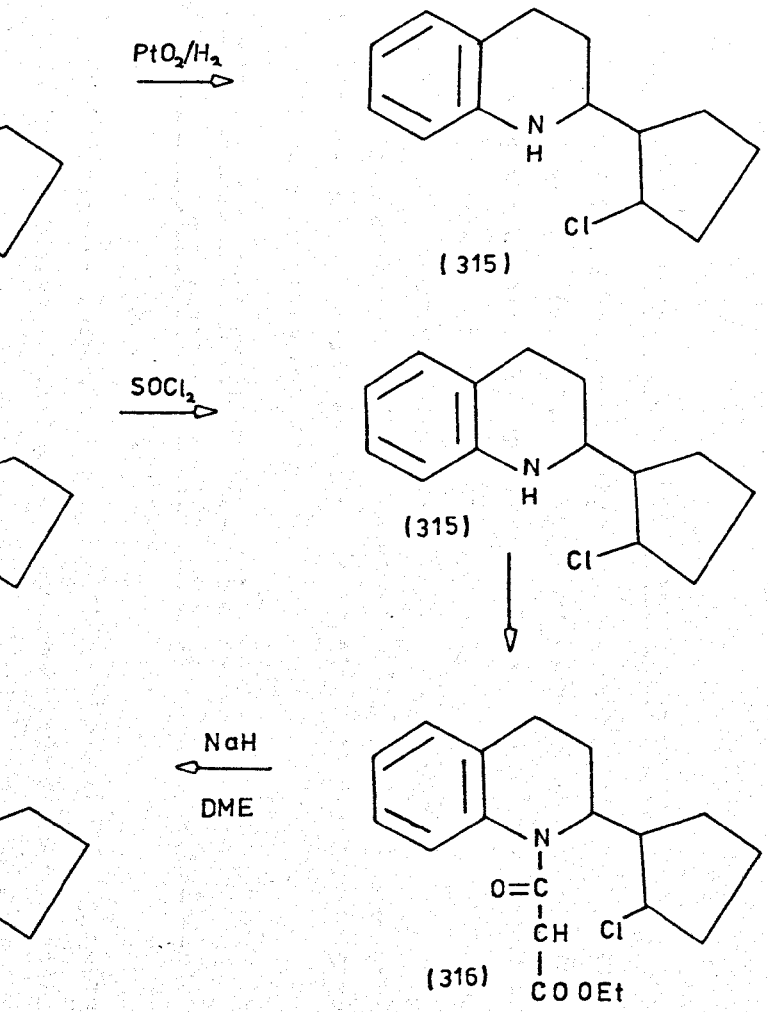


(164)





(317)


PtO2/H2
N
H
Cl
(315)
SOCl2
(315)
NaH
DME
(316)
CO OEt

STEREOCHEMICAL FEATURES OF COMPOUND (315) AND COMPOUND (316)

Compound (164) has previously been assigned the trans configuration (164c or164d) (p.109). Reaction of compound (164) with thionyl chloride in the presence of pyridine follows an Sn2 type mechanism leading to inversion of configuration. This gives rise to compound (315) in the cis configuration (315c or315d).

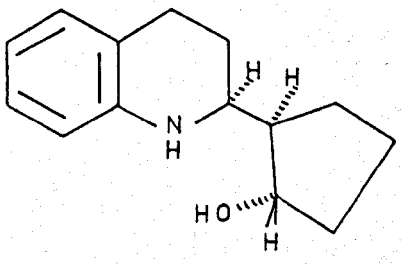
Acylation of compound (315) to give amide (316) does not affect the relative configuration of compound (316) which can be assigned the configuration (316c or316d).

REACTIONS OF THE MONO-ETHYL MALONIC ACID AMIDE OF 2-(2-CHLORO-CYCLOPENTYL)-1,2,3,4-TETRAHYDROQUINOLINE (316) AND THEIR STEREOCHEMICAL FEATURES

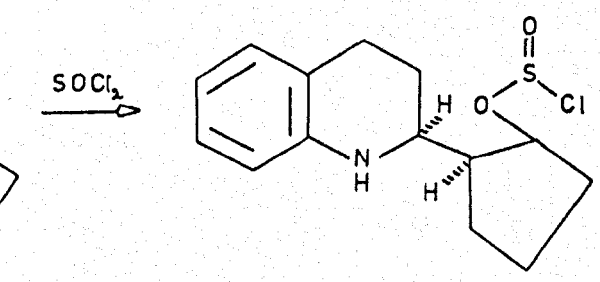
Cyclisation of compound (316) was first attempted using sodium hydride in dimethoxy ethane initially at room temperature and then in boiling solvent but these were not successful. This reaction has an Sn2 mechanism and models show that neither compound (316c) nor (316d) can take up a suitable position for an Sn2 substitution.

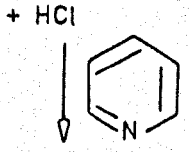
If the racemate of amide (316) obtained had had the chlorine atom in the alternative position (316a) or (316b) then reaction could have taken place. Because of this possible difficulty reaction conditions were changed to encourage an Sn1 type reaction where the attack of the nucleophilic centre takes place after the chlorine has left and can take place from the same side. Thus a more polar solvent (dimethylformamide) was used but this also failed to bring about cyclisation. Hexamethylphosphoric triamide has been widely used as a reaction medium because of its excellent properties as a dipolar aprotic solvent[158] and this solvent was also used for the reaction but the amide (316) still failed to cyclise. The product after attempted cyclisation had the same G.L.C. retention time, mass spectral molecular ion, and N.M.R. spectrum as the reactant.

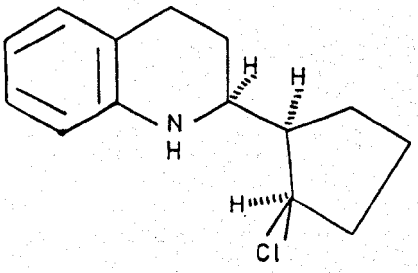
A possible method of obtaining two or more racemates of the alcohol (164) (only one is obtained and at least one is destroyed) would be to protect the hydroxyl group of alcohol (296) and then attempt the catalytic reduction. Such a procedure could be envisaged involving the formation of the tetrahydropyrans of the two racemates of alcohol (164) which could be reduced catalytically and then the hydroxyl group regenerated giving a possible total of four



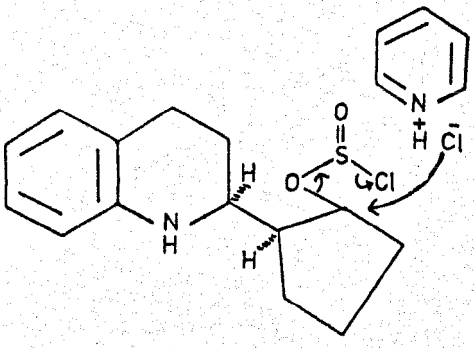
(164d)

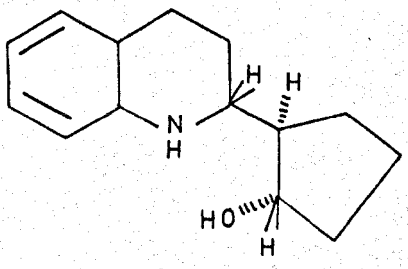




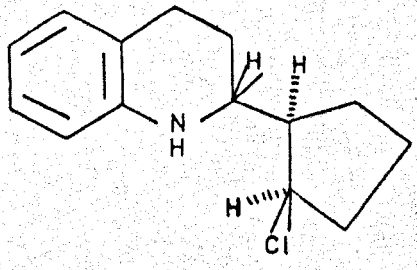


(315c)

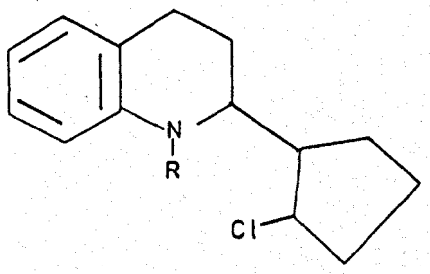


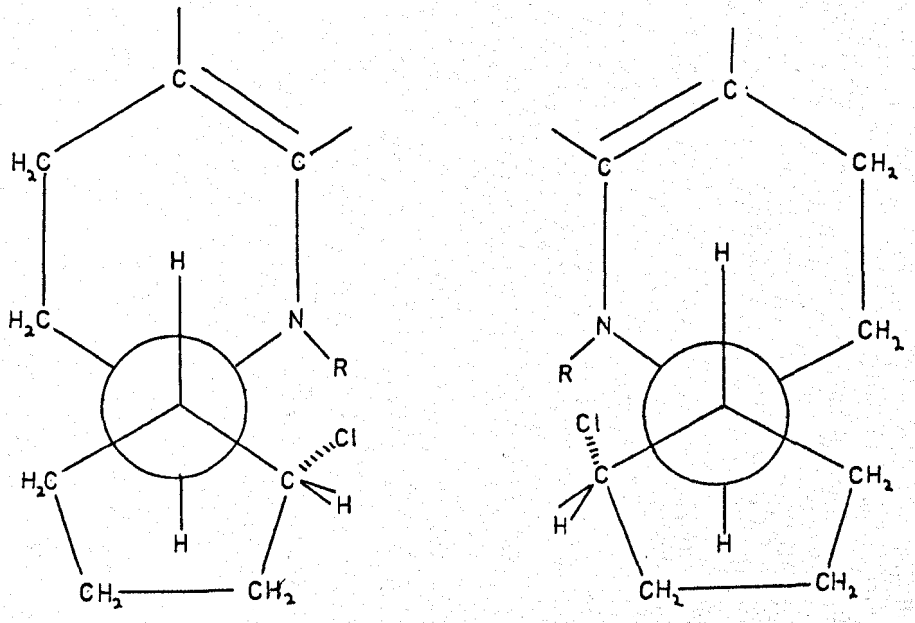


(164c)

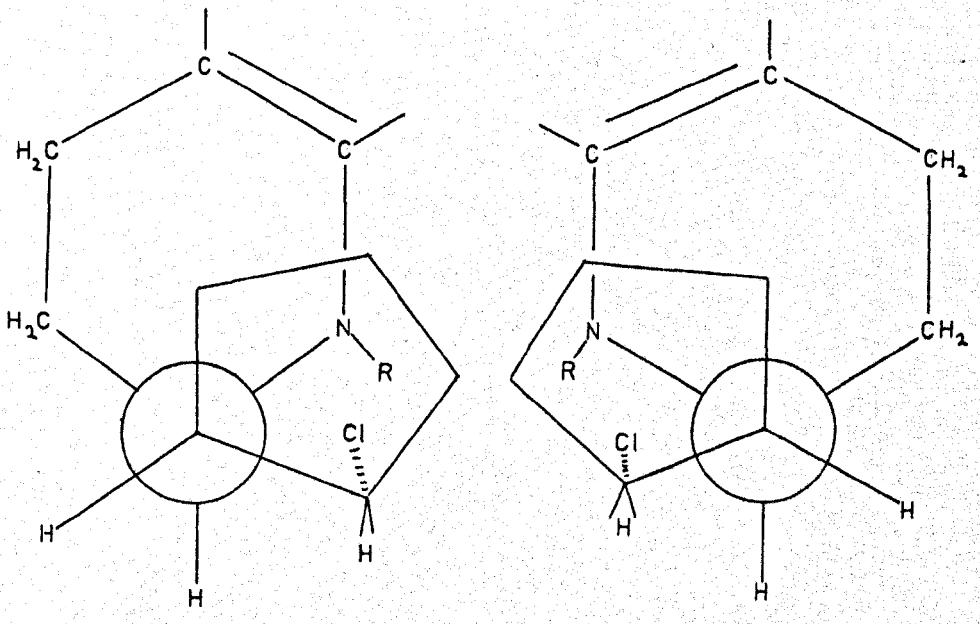


(315d)

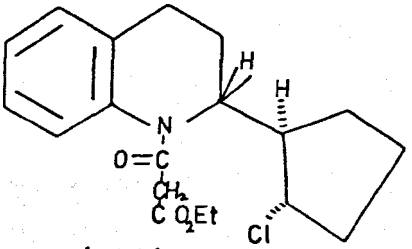




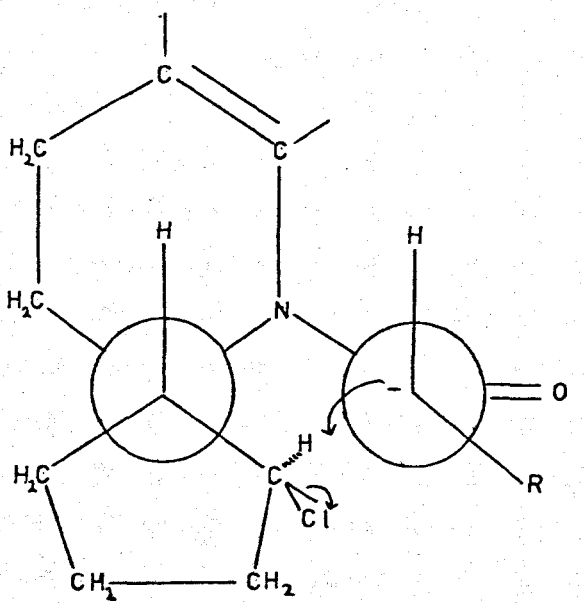
d and l isomers of compound (315d) (R = H) and compound (316d) (R = O = CCH_2CO_2Et)



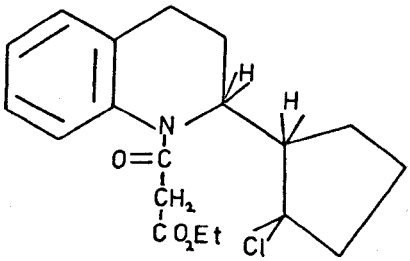
d and l isomers of compound (315c) (R = H) and compound (316c) (R = O = CCH_2CO_2Et)



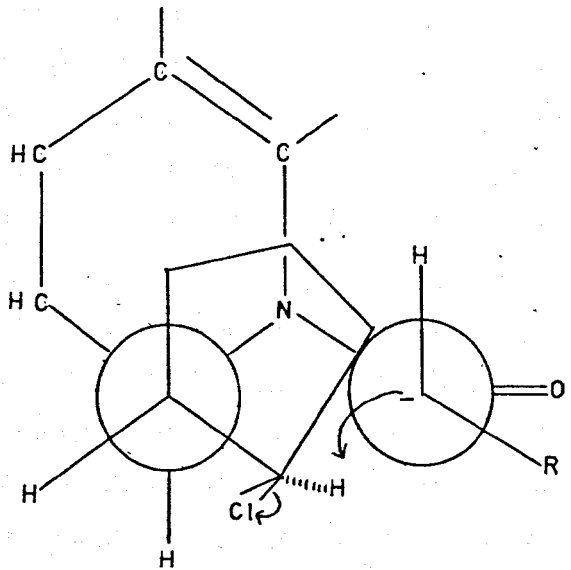
(316b)

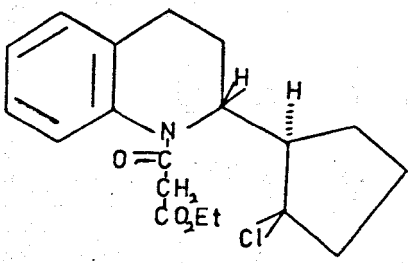


R = OEt

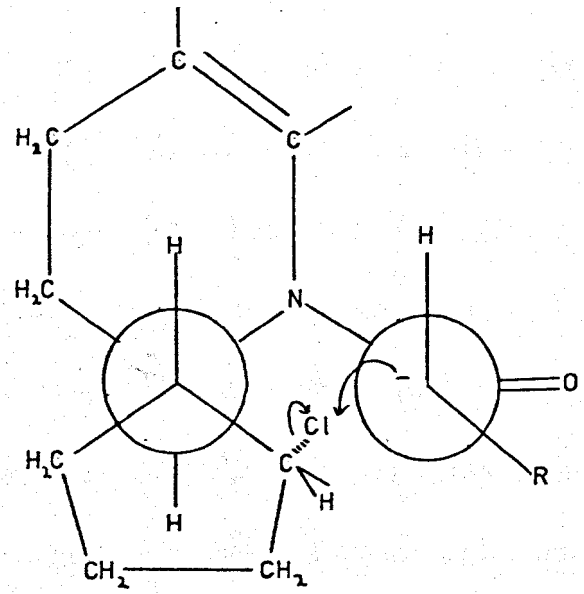


(316a)





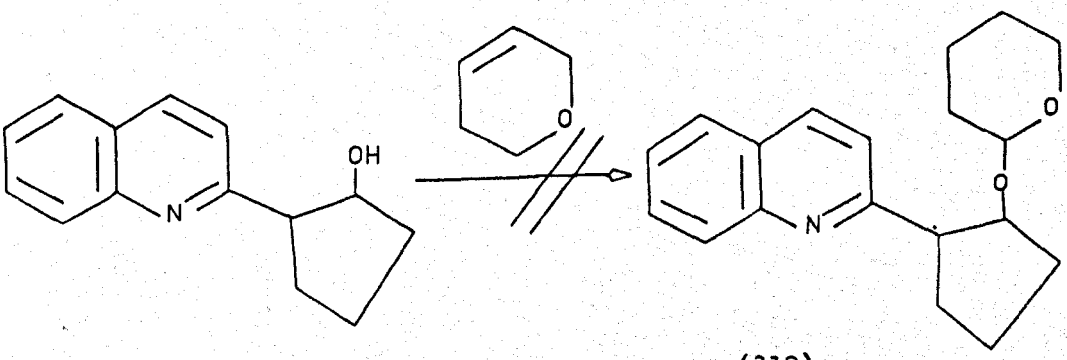
(316d)



R = OEt

[316c]

racemates of the alcohol (164). This, in further reactions in the synthetic route, could give rise to four racemates of the amide (316a-d) with the chlorine atom in both configurations, one suitable for cyclisation.



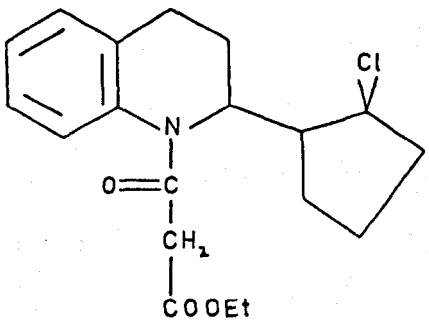
(296) (318)

However attempts to form the tetrahydropyran derivative (318) by reaction of the alcohol (296) with 2,3-dihydropyran gave only the reactant and a polymeric oil. Reacting the hydrochloride of the alcohol (296) with 2,3-dihydropyran gave similar results. Performing the reaction again but omitting the alcohol (296) gave a high boiling oil whose N.M.R. spectrum indicated that the 2,3-dihydropyran had probably reacted with itself in the acidic reaction conditions to give a polymeric oil.

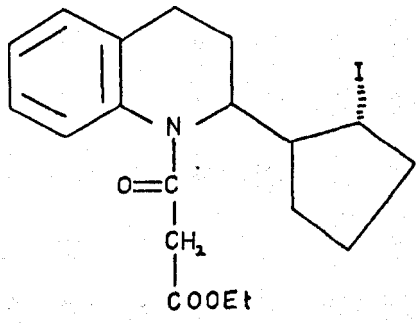
Although dihydropyran has been widely used for protecting alcohols, its disadvantage is that a new assymetric centre is introduced into the compound. This gives a mixture of isomers which make N.M.R. studies difficult. Recently Fuji et al[159] have reported protection of alcohols by methoxymethylation using methylal, by an acid catalysed acetal exchange reaction under mild conditions. This method has the advantage of not introducing another assymetric centre into the molecule.

Because a change in configuration of the chlorine in the amide (316) could not be achieved by protection of the hydroxyl group in the alcohol (296), the one racemate of the amide (316) obtained was reacted with sodium iodide in an attempt to form the corresponding

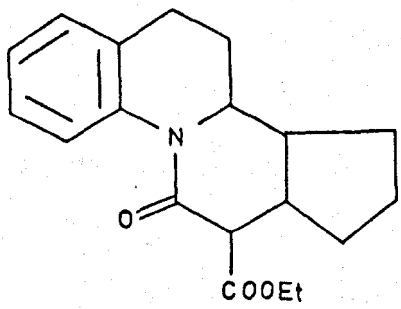
iodo compound (319). This reaction would have an Sn2 mechanism and hence inversion of configuration about the future C-13 atom would occur. The reaction proceeded to give a low yield of product (identified by a molecular ion of 441 in the mass spectrum of the crude reaction mixture) but loss of the acyl side chain (to give the corresponding acid) occurred at a greater rate. Separation of the products and reactant by chromatography caused dehalogenation and loss of the ester ethyl group of the iodo compound (319).



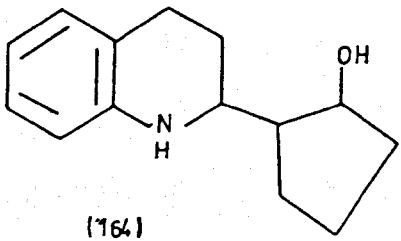
(316)



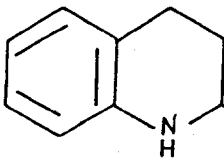
(319)



(317)

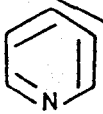


(164)

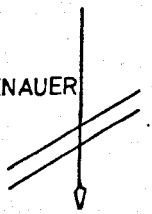


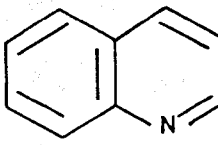
(320)

CrO_3

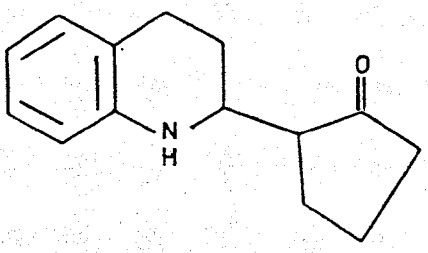


OPPENAUER

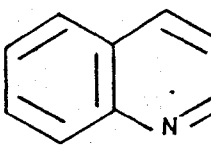




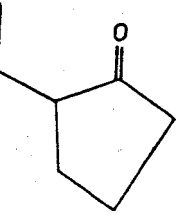
(163)$^+$



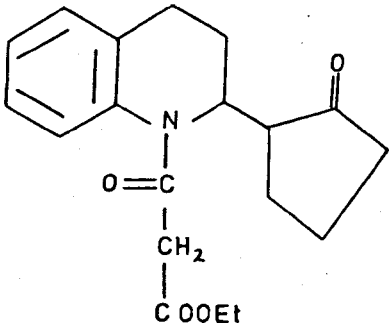
(320)



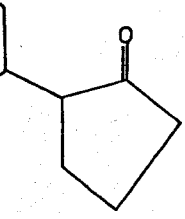
(296)

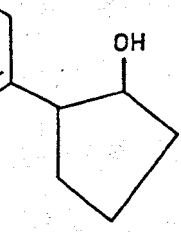


$ClCOCH_2COOEt$



(321)





If the tetracyclic compound (317) had been successfully synthesised then the next steps would have been hydrolysis and decarboxylation to remove the ester group followed by a Wolff-Kishner reduction of the ketone group to a methylene group.

Because of these difficulties over the configuration of the leaving group it was decided to use a cyclopentanone so that a condensation reaction could be attempted on the amide (321). The first step would be oxidation of the hydroxyl group of the alcohol(164) to give the corresponding ketone (320) acylation of which with monethylmalonyl chloride could give the amide (321).

The Oppenauer and Sarett oxidation procedures had previously been tried on 2-(2-quinolyl) cyclopentanol (296) (p.99) and the Sarett procedure had proved to be the more satisfactory. This latter procedure was tried on alcohol (164) but the reaction conditions were too vigorous, oxidation of the nitrogen ring occurring preferentially to oxidation of the hydroxyl group to give a mixture of ketone (163) and the alcohol (296). The Oppenauer procedure with toluene as solvent and cyclohexanone as hydrogen acceptor was used in an attempt to oxidise alcohol (164) but failed to give any product after a reaction time of three days. Oppenauer oxidation with benzene as solvent and acetone as hydrogen acceptor also failed. This line of approach was thus abandoned.

EXPERIMENTAL

PRELIMINARY NOTES

Melting points were determined on a Kofler hot - stage apparatus and are uncorrected.

Infra red absorption spectra were recorded on a Perkin Elmer 257 spectrophotometer. The spectra of solids were determined in solution (e.g. $CHCl_3$). The spectra of liquids were determined as liquid films (film) or in solution.

Ultra violet and visible absorption spectra were recorded on a Unicam SP 800 instrument.

Nuclear Magnetic Resonance (N.M.R.) spectra were recorded on a Perkin Elmer R10 60 MHz instrument and Hitachi-Perkin Elmer R24 60 MHz instrument.

Micro-analyses were carried out on an F and M carbon/hydrogen/nitrogen analyser and Perkin Elmer Elemental Analyser 240 at the University of Keele.

Mass spectra were recorded on a Hitachi-Perkin Elmer R.M.U.-6 instrument using a heated inlet.

Gas Liquid Chromatography was performed on a Pye Series 104 instrument equipped with a 1.5m. x 4mm. glass column packed with a support material coated with 3% loading of stationary phase. The stationary phases were: OV101 (dimethyl silicone fluid) and OV17 (phenyl silicone fluid). Detection of the eluted components of a mixture was by a hydrogen flame conisation detector. The chart speed was normally 1cm./min.

Thin Layer Chromatography was carried out on microscope slides (7.5cm. x 2.5cm.) coated with silica gel (Merck Kieselgel PF_{254}). The components were visualised under U.V. light or developed in iodine vapour.

Preparative Layer Chromatography was carried out on glass plates

(40cm. x 20cm.) coated with a 1.5mm. layer of silica gel (Merck Kieselgel PF_{254}). The separated components, visualised under U.V. were isolated by scraping off the silica and extracting with methanol. The filtered methanol solution was evaporated to leave a residue which contained silica. The residue was dissolved in chloroform, filtered and evaporated.

Alumina for column chromatography was Woelm neutral grade and was deactivated by the addition of water. The activity values quoted refer to the Brockmann scale.

ATTEMPTED PREPARATION OF 2-QUINOLONE (163)

The preparation of this compound was attempted using the method of Tchichibabin[85] but gave only starting material.

PREPARATION OF O-NITROCINNAMIC ACID (164)

This compound was prepared by the method of De Tar[160].

ATTEMPTED PREPARATION OF 2-(2-AMINO) PHENYLPROPIONIC ACID (166)

Raney nickel catalyst (2.4g.) was added to a solution of o-nitrocinnamic acid (5g., 0.0259 moles) in 95% ethanol (150mls.) and hydrogenated at 60lb./squ. in. for 15 hours. The catalyst was filtered off and solvent evaporated to give a yellow solid (recrystallised from ethanol) m.p. 113° (lit. 115°[161]) which proved to be β-phenyl-(2-nitro) propionic acid (165). The N.M.R. spectrum showed absence of alkene protons and no $-NH_2$ protons. The I.R. spectrum showed the presence of a carboxylic acid group 3360cm.$^{-1}$ (broad) , and nitro group (1470cm.$^{-1}$ and 1380cm.$^{-1}$), and absence of an amine group.

PREPARATION OF β-CHLOROPROPIONIC ACID

This compound was prepared by the method of Moureu and Chaux[162].

PREPARATION OF β-CHLOROPROPIONYL CHLORIDE

A solution of thionyl chloride (12g., 0.1017 moles) in dry ether (40mls.) was added dropwise with stirring to a solution of β-chloropropionic acid (4.3g., 0.0398 moles) in dry ether (150mls.). The mixture was then refluxed for three hours, cooled and the ether and excess thionyl chloride was removed by evaporation under reduced pressure. The residue was distilled to give the acid chloride b.p. 111°/-46mms. (lit.[163] b.p. 82°/102mms.).

PREPARATION OF 2-CHLORO-N-PHENYLPROPIONAMIDE (167)

This compound was prepared by the method of Mayer and co-workers[86].

PREPARATION OF 3,4-DIHYDROCARBOSTYRIL (168)

This compound was prepared by the method of Mayer and co-workers[86].

ATTEMPTED PREPARATION OF 2-ETHOXY-3,4-DIHYDROQUINOLINE (169)

A modification of the procedure of Ayer and Niers[164] for the synthesis of 2-ethoxy-3,4,5,6-tetrahydropyridine. A solution of 3,4-dihydrocarbostyril (168) (6g., 0.0451 moles) in dry methylene chloride

(25mls.) was added to a stirred solution of triethyloxonium fluoroborate[165] (26g., 0.1368 moles) in dry methylene chloride (100mls.) under a nitrogen atmosphere. Stirring was continued for three days at room temperature. During this time aliquots of reaction mixture were scanned for lowering of I.R. absorption intensity at 1650cm.$^{-1}$ in 0.1mm. solution cells balanced with methylene chloride. No lowering of intensity was observed. Work up was achieved by pouring the reaction mixture into 5N potassium carbonate solution (100mls.), separating the organic layer and extracting the aqueous layer with methylene chloride (2 x 50mls.). The combined organic phase was dried (calcium chloride) and evaporated to give a light brown solid which on recrystallisation (water) gave a compound having the spectra and melting point of the starting material.

PREPARATION OF 2-BROMOETHYOXYETHANE (181)

This compound was prepared by a modified procedure to that used by Wood[87] whose method gave a neutral product but only in small yield. Phosphorus tribromide (280g. 1.045 moles) was added dropwise with stirring to 2-ethoxyethanol (240g., 0.375 moles), previously dried over calcium chloride, at a rate which kept the reaction mixture gently refluxing. The mixture was refluxed for a further 30 minutes after addition, cooled in an ice bath and poured into ice water (400 mls.). The lower light orange layer was separated, washed with cold aqueous sodium bicarbonate solution (10%) (200mls.), dried (calcium chloride). The product (169) was distilled to give a colourless sweet smelling neutral oil (338g., 72%) b.p. 42°/44mms. (lit.[87] 55°/50mms.). The bromide was acidic at room temperature but could be kept for long periods of time in a brown glass stoppered bottle at 0°C.

PREPARATION OF 2-CARBETHOXYCYCLOPENTANONE (180).

This compound was prepared by the method of Pinkney[166].

ALKYLATION OF 2-CARBETHOXYCYCLOPENTANONE (180)

a) Sodium (11.5g., 0.5 moles) chopped into small pieces was added to "super dry" ethanol (450mls.) with stirring. Stirring was continued until all the sodium had dissolved to form sodium ethoxide (about one and a half hours). To this solution was added dropwise with stirring 2-carbethoxycyclopentanone (180) (75g., 0.4807 moles) and the reaction mixture refluxed on a water bath for 30 minutes. This was

cooled to room temperature using an ice bath and 2-bromoethoxyethane (181) (75g., 0.4934 moles) added dropwise over a period of one hour with stirring. The reaction mixture was then refluxed with stirring on a water bath for seven hours during which time a large amount of solid material (sodium bromide) separated out. Most of the ethanol was distilled off to leave a reddish brown liquid residue which was filtered off from the solid present. The solid material was washed twice with ether (50mls.) and the combined organic material dried (calcium chloride), and evaporated. The residue was distilled to give a colourless oil (102g.) (b.p. 137° at 23mm. lit.[167] for diethyl adipate 138° at 20mm.) whose spectra and analysis corresponded to diethyl adipate.

Found: C-59.64%; H-8.91%

$C_{10}H_{18}O_4$ requires: C-59.41%; H-8.91%

b) Small pieces of sodium metal (11.5g., 0.5 moles) were added to dry toluene (400mls.) and the mixture heated gently with stirring until the solvent had started to reflux, at which point the sodium had melted and been dispersed as small spheres. The keto-ester (180) (75g., 0.4807 moles) was added dropwise with stirring and refluxing continued for one hour after the addition. The mixture was cooled to room temperature and 2-bromoethoxyethane (181) (75g., 0.4934 moles) added. The mixture was then refluxed for a further seven hours, cooled to room temperature and poured into ice cold 2N hydrochloric acid (400mls.). The toluene layer was separated, dried (calcium chloride) and evaporated to give a brown oil, distillation of which gave the product as a colourless oil (15.3g. 14%) b.p. 122° at 2.1mms. and a viscous oil (86.4g.) b.p. 130-186°/2.1-2.6mms. The latter compound was not further characterised.

Found: C-62.01%; H-8.64%

$C_{12}H_{20}O_4$ requires: C-62.16%; H-8.77%

N.M.R. ($CDCl_3$ solution) 2 proton quartet at 3.9-4.25 p.p.m. (ester methylene group).

4 proton multiplet at 3.2-3.85 p.p.m. (2 ether methylene groups).

8 proton multiplet at 1.6-2.9 p.p.m. (cyclopentane ring methylene groups). and side chain methylene group).

6 proton multiplet at 0.95-1.5 p.p.m. (ester methyl group and ether side chain methyl group).

ν_{max} 1750cm.$^{-1}$, 1725cm.$^{-1}$ (ester C=O and ketone C=O groups) and 1120cm.$^{-1}$ ($-CH_2-O-CH_2-$).

Mass Spectrum:

M/E 39(46%),43(43%),45(41%),46(36%),54(80%),55(94%),56(49%),73(77%), 82(54%),83(58%),84(50%),109(25%),110(100%),111(77%),128(98%),156(84%), 182(42%),183(69%),184(37%),228(10%)(M^+),229(4%).

Employing sodium hydride instead of sodium metal gave the same results. Changing the solvent to dimethoxyethane or dimethylformamide and using either sodium or sodium hydride also gave the same results. Employing 2-iodoethoxyethane (187) as alkylating agent gave an insignificantly higher yield (17%) using the method of Booth et al[90].

PREPARATION OF 2-IODOETHOXYETHANE (187)

This compound was prepared by a modified procedure of Ford-Moore[169] for the preparation of 2-iodoethylbenzoate. Anhydrous sodium iodide (60g., 0.4 moles) was added to dry butan-2-one (40mls.) and heated with stirring on a water bath for one hour, after which time 2-bromoethoxyethane (181) (54g., 0.3552 moles) was added over 30 minutes. Refluxing was continued for 24 hours. The reaction mixture was cooled to room temperature, filtered and the residue washed with more butan-2-one (2 x 50mls.). The combined organic material was evaporated until most of the solvent was removed, washed with water (500mls.), 10% sodium bisulphite solution (100mls.), 5% sodium bicarbonate (100mls.) and water (100mls.), dried (magnesium sulphate) and distilled to give a yellow oil (51.8g., 72%) b.p. 68°/41mm.

The product gave inconsistant analyses.

N.M.R. ($CDCl_3$ solution) 6 proton multiplet at 3.0-3.8 p.p.m. (the three methylene groups).

3 proton triplet at 1.0-1.4 p.p.m. (the methyl group)

ν_{max} (film) 1100cm.$^{-1}$ ($-CH_2-O-CH_2-$).

Mass spectrum;

M/E 45(77%),73(77%),89(56%),127(71%),155(100%),200(54%),(M^+),201(9%).

PREPARATION OF 2-(2-ETHOXYETHYL) CYCLOPENTANONE (184)

The procedure followed was that used by Prelog and Szpilfogel[92] for 1-(2-cyclopentanonyl)butan-3-one, giving a colourless oil b.p. 72°/4mm.

Found: C-68.13%; H-10.35%

$C_9H_{15}O_2$ requires: C-68.23%; H-10.26%

N.M.R.($CDCl_3$) 4 proton multiplet at 3.3-3.7 p.p.m. (2 methylene groups next to oxygen).

9 proton multiplet at 1.4-2.5 p.p.m. (methylene group α-to the ring, 3 cyclopentane ring methylene group, cyclopentane ring methine proton).

3 proton triplet at 1.0-1.3 p.p.m. (side chain methyl group).

ν_{max} 1730cm.$^{-1}$ (C=O), 1120cm.$^{-1}$ ($-CH_2-O-CH_2-$).

Mass spectrum:

M/E 39(68%),41(35%),42(36%), 43(27%),44(40%),45(69%),54(29%),55(32%), 56(26%),59(79%),72(48%),82(31%),83(94%),84(100%),85(61%),97(45%), 109(38%),111(33%),156(16%),(M^+),157(8%).

PREPARATION OF 2-(2-ETHOXYETHYL) CYCLOPENTANOL (183)

Sodium borohydride (2g., 0.0526 moles) was added to a solution of the ketone (184) (3.1g., 0.0199 moles) in absolute ethanol (40mls.). The reaction mixture was left for 16 hours at room temperature. Work up was achieved by the addition of the reaction mixture to water (300mls) and the organic material extracted with ether (2 x 100mls.), dried (magnesium sulphate) and evaporated. The residue was distilled to give a colourless oil b.p. 117°/2.1mms. (2.86g., 91%).

Found: C-66.95%; H-11.65%

$C_9H_{17}O_2$ requires: C-67.35%; H-11.39%

N.M.R.($CDCl_3$ solution) 2 proton broad singlet at 3.7-3.9 p.p.m. (-O-H and its adjacent proton which on treatment with D_2O reduced to a sharp 1 proton singlet).

4 proton multiplet at 3.2-3.7 p.p.m. (2 methylene groups next to oxygen).

9 proton multiplet at 1.3-2.0 p.p.m. (3 cyclopentane ring methylene groups, side chain methylene group and cyclopentane ring methine proton).

3 proton triplet at 1.0-1.3 p.p.m. (side chain methyl group).

ν_{max} 3400cm.$^{-1}$ (-OH), 1110cm.$^{-1}$ ($-CH_2-O-CH_2-$).

Mass spectrum:

M/E 39(77%),41(50%),42(53%),43(31%),44(32%),46(38%),55(61%),56(64%), 57(48%),66(47%),67(70%),68(69%),73(41%),79(39%),81(52%),83(61%), 84(100%),85(64%),94(43%),95(81%),96(57%),98(53%),111(71%),112(93%), 125(23%),129(27%),140(26%),141(17%),158(21%),(M^+),159(11%).

PREPARATION OF 2-(2-ETHOXYETHYL)-1-BROMOCYCLOPENTANE (147)

Phosphorus tribromide (30g., 0.1119 moles) was added with stirring to a solution of 2-(2-ethoxyethyl) cyclopentanol (183) (28g., 0.1772 moles) in dry benzene (150mls.) over a period of 30 minutes. After addition the mixture was heated at 40° for three hours, cooled and poured into ice cold 10% sodium bicarbonate solution (100mls.), dried (magnesium sulphate) and evaporated. The residue was distilled to give a colourless sweet smelling oil which rapidly decomposed in sunlight, b.p. 109°/2.2mms.

Found: C-49.60%; H-7.88%

$C_9H_{16}OBr$ requires: C-49.69%; H-7.73%

N.M.R.($CDCl_3$ solution) 1 proton singlet at 4.2 p.p.m. (proton adjacent to bromine).

4 proton multiplet at 3.2-3.75 p.p.m. (2 ether methylene groups).

9 proton multiplet at 1.3-2.0 p.p.m. (3 cyclopentane ring methylene groups, side chain methylene group and cyclopentane ring methine proton).

3 proton triplet at 0.95-1.3 p.p.m. (side chain methyl group).

ν max 1110cm.$^{-1}$ broad ($-CH_2-O-CH_2-$).

Mass spectrum;

M/E 39(41%),41(37%),55(39%),57(36%),67(61%),68(29%),69(46%),79(40%), 80(16%),81(35%),83(39%),85(36%),94(33%),95(100%),96(64%),110(28%), 112(26%),141(28%),146(22%),174(18%),176(16%),191(13%),193(14%),220(8%), (M^+),(222(7%).

ATTEMPTED PREPARATION OF 2-QUINOLYL CYCLOPENTANE (188) USING QUINOLINE

A crystal of iodine was added to a suspension of magnesium (dried) in dry ether (20mls.). To this was added dropwise bromocyclopentane (12.5g., 0.0845 moles) in dry ether (120mls.) over 45 minutes. The mixture was then refluxed for a further 30 minutes, cooled, decanted and the solvent changed from ether to benzene. A solution of quinoline (7g., 0.0534 moles) in dry benzene (70mls.) was added over a 20 minute period and the reaction mixture refluxed with stirring. After 24 and 48 hours aliquots were removed, distilled water added, benzene layer separated, dried (magnesium sulphate) and subjected to G.L.C. Both extracts showed peaks corresponding to quinoline and cyclopentane but none corresponding to any product.

PREPARATION OF 2-QUINOLYL CYCLOPENTANE (188) USING QUINOLINE-1-OXIDE

A solution of bromocyclopentane (17.5g., 0.1182 moles) in dry ether (30mls.) was added dropwise to a suspension of magnesium (3.5g., 0.1521 moles) (dried) in dry ether (100mls.). The mixture was refluxed for a further 30 minutes, cooled, decanted and added dropwise over nitrogen to a stirred solution of quinoline-1-oxide (5g., 0.034 moles) in dry ether (60mls.) with ice cooling. The brown reaction mixture was then refluxed with stirring for four hours, cooled to room temperature and added to ice cold ammonia solution (880) saturated with ammonium chloride (150mls.). The organic layer was separated and the aqueous layer extracted with chloroform (100mls.). The combined organic phases were dried (magnesium sulphate) and evaporated. The residue was distilled to give cyclopentane b.p. 44°/15mms. (3.1g., 36.5%), quinoline b.p. 112°/15mms. (3.2g., 32%) and 2-cyclopentyl quinoline (188) b.p. 164°/15mms. (2.1g., 31.3%) (lit.[169] 163°/14mms.).

Use of dry tetrahydrofuran as solvent gave lower yields of product (14%).

a) Attempted preparation of 2-(2-ethoxyethyl) quinolyl cyclopentane (160) via the Grignard reagent

The attempted preparation of this compound was by the method above using quinoline-1-oxide and the same relative molar quantities. Work up gave a red viscous oil which on distillation gave 2-ethoxyethylcyclopentane (b.p. 42°/0.35mms.), quinoline (b.p. 98°/0.35mms.) and quinoline-1-oxide (b.p. 128°/0.35mms.).

b) Attempted preparation of 2-(2-ethoxyethyl) quinolyl cyclopentane (160) via the Lithium reagent.

A solution of 2-ethoxyethyl-1-bromocyclopentane (159) (10g., 0.05 moles) in dry ether (25mls.) was added over 30 minutes to a suspension of lithium (1g., 0.1428 moles) in dry ether (100mls.). The reaction mixture was refluxed for 45 minutes, then a solution of dry quinoline (7.6g., 0.058 moles) in dry ether (40mls.) was added dropwise to the cooled reaction mixture over 30 minutes under a nitrogen atmosphere. Refluxing was continued for 6½ hours, allowed to cool to room temperature, then added to ice cold water (200mls.). The ether layer was separated and extracted with 2N hydrochloric acid (100mls.). The acid layer was basified with 2N sodium hydroxide

solution which was then extracted with ether (2 x 50mls.), the ether phases dried (magnesium sulphate) and evaporated. Distillation of the residue gave 2-ethoxyethylcyclopentane and quinoline.

c) Attempted preparation of 2-(2-ethoxyethyl) quinolylcyclopentane (160) via the lithium reagent using tetramethylethylenediamine

The lithium reagent of 2-(2-ethoxyethyl)-1-bromocyclopentane (190) (8g., 0.04 moles) was prepared as in the previous reaction (b) using dry pentane (125mls.) as solvent. This was added dropwise over 20 minutes to a stirred solution of quinoline (5.9g., 0.045 moles) in purified tetramethylethylenediamine (75mls.) at a reaction temperature of -78° (dry ice/acetone). The mixture was stirred at this temperature for 2½ hours and then allowed to warm to room temperature overnight. It was then heated to 50° on a water bath for 2 hours and worked up as in the previous reaction (b) to give quinoline and 2-(2-ethoxyethyl) cyclopentane.

PURIFICATION OF TETRAMETHYLETHYLENEDIAMINE

Tetramethylethylenediamine (100mls.) was heated for two hours on a water bath with benzoyl chloride (20mls.). The primary and secondary amine impurities separated out as their benzamides. The whole mixture was filtered and distilled and the fraction boiling at 120-124°/760mms. was left over freshly prepared sodium wire (2.3g.) overnight, decanted, redistilled and the fraction boiling at 122°/760mms. taken.

PREPARATION OF BROMOCYCLOPENTANE

This compound was prepared by the same procedure as that used in the preparation of 2-(2-ethoxyethyl-1-bromocyclopentane to give a colourless sweet smelling oil. (b.p. 148°/758mm., lit.[170] b.p. 137-9).

PREPARATION OF CYANOCYLOPENTANE

A slurry of sodium cyanide (3.8g., 0.0745 moles) in dimethylsulphoxide (40mls.) was heated to 90° and bromocyclopentane (7.9g., 0.0534 moles) was added dropwise at such a rate that the temperature did not rise above 110°. After a few minutes a white solid separated out and stirring was continued for a further 30 minutes. The reaction mixture was poured into water (200mls.),,extracted with ether 3 x 50mls.) and the combined organic phases washed with saturated

sodium chloride solution (100mls.). The organic layer was separated, dried (sodium sulphate), filtered and the ether evaporated. Distillation of the residue gave cyanocyclopentane (3.95g., 75.5%) as a yellow liquid b.p. 57°/46mms. (lit.[171] 170-1/760mms.).

PREPARATION OF CYCLOPENTANECARBOXYLIC ACID

A solution of cyanocyclopentane (3.3g., 0.0337 moles) in 95% ethanol (30mls.) and 20% sodium hydroxide (45mls.) was refluxed for eight hours. Distillation at atmospheric pressure removed most of the solvent (40mls.). The residue was extracted with ether (3 x 50mls.) and the combined ether extracts washed with water (3 x 100mls.). The combined aqueous layer was acidified with 2N hydrochloric acid followed by saturation with solid sodium chloride. The supernatant liquid was decanted, extracted with ether (3 x 100mls.) and the combined organic phase dried (magnesium sulphate) and evaporated. Distillation gave cyclopentanecarboxylic acid (2.16g., 55.8%) as a foul smelling liquid (b.p. 123°/42mms., lit.[172] 210-15(atm).

PREPARATION OF CYCLOPENTANECARBOXYLIC ACID CHLORIDE (200)

A solution of thionyl chloride (3.7g., 0.0276 moles) in dry ether (20mls.) was added dropwise to a solution of cyclopentanecarboxylic acid (2g., 0.0175 moles) in dry ether (30mls.). The mixture was refluxed for three hours then the ether and excess thionyl chloride were removed by distillation under reduced pressure. The residue was distilled to give cyclopentanecarboxylic acid chloride (200) (1.7g., 73%) as a colourless oil b.p. 70°/46mms. (lit.[173] b.p. 72-74°/50mms.).

PREPARATION OF CYCLOPENTANECARBOXYLIC ACID METHYL ESTER (202)

A solution of cyclopentanecarboxylic acid (10g., 0.0877 moles) and concentrated sulphuric acid (3mls.) in methanol (25mls.) were refluxed gently on a steam bath for one hour. The reaction mixture was cooled to room temperature and extracted with ether (2 x 25mls.). The combined organic phase was washed with water (25mls.), 5% sodium bicarbonate solution (25mls.) and saturated sodium chloride solution (25mls.). The organic phase was dried (magnesium sulphate), evaporated and the ester distilled to give a colourless oil (202) (8.2g., 73%) b.p. 44°/51mms. lit.[174] 156-7°(atm.)

ATTEMPTED PREPARATION OF CYCLOPENTANECARBOXANILIDE (201) VIA THE METHYL ESTER (202)

A solution of cyclopentanecarboxylic acid methyl ester (202) (13g., 0.1016 moles) in dry ether (50mls.) was added dropwise with stirring to a solution of freshly distilled aniline (19g., 0.2043 moles) in dry ether (100mls.). After the addition the reaction mixture was refluxed for three hours, poured into 2N hydrochloric acid (100mls.), separated, washed further with 2N hydrochloric acid (100mls.) then 5% sodium bicarbonate solution (100mls.). The organic layer was separated, dried (magnesium sulphate) and evaporated. The residue was found to be the unchanged methyl ester (202).

PREPARATION OF CYCLOPENTANECARBOXANILIDE (201) VIA THE ACID CHLORIDE (200)

A solution of cyclopentane carboxylic acid chloride (200) (13g., 0.0985 moles) in dry ether (50mls.) was added dropwise with stirring to freshly distilled aniline (19g., 0.2043 moles) in dry ether (100mls.). A white solid precipitated out immediately. Stirring was continued for a further one hour. Work up was as in the previous reaction, the white solid filtered off and recrystallised (aqueous ethanol) to give colourless plates of anilide (201) (15.1g., 81%). (m.p. 162.5°, lit.[175] 160.1°).

ATTEMPTED PREPARATION OF 2-(2-ETHOXYETHYL)-1-CYANOCYCLOPENTANE (196)

The method used for the attempted preparation was the same as that used for the preparation of cyanocyclopentane, but only starting material was recovered.

PREPARATION OF CYCLOPENTANECARBOXANILIDE (201) VIA PHENYL ISOCYANATE (203)

A solution of phenyl isocyanate (203) (8.25g., 0.0705 moles) in dry ether (30mls.) was added dropwise with stirring to an ethereal solution (125mls.) of the Grignard reagent of bromocyclopentane (previously prepared in the usual way from bromocyclopentane) (11.5g., 0.0777 moles) and magnesium (2.25g., 0.0938 moles). Stirring was continued for a further 45 minutes. Work up was achieved by addition of 1N hydrochloric acid (30mls.) and the ether layer was separated, dried (magnesium sulphate) and evaporated to give a white solid. Recrystallisation (aqueous ethanol) gave the anilide (201) (9.7g., 73%)

ATTEMPTED PREPARATION OF 2-(2-ETHOXYETHYL) CYCLOPENTANECARBOXANILIDE (191) VIA PHENYL ISOCYANATE

The procedure followed was the same as for the preparation of cyclopentanecarboxanilide (201) employing phenyl isocyanate (203) and the Grignard reagent of 2-(2-ethoxyethyl)-1-bromocyclopentane (159). Work up gave diphenyl urea (37%) (m.p. 189°, lit.[176] 189°) and 2-(2-ethoxyethyl cyclopentanecarboxanilide (3%).

Found: C-73.41%; H-8.75%; N-5.14%

$C_{16}H_{23}NO_2$ requires: C-73.56%; H-8.81%; N-5.36%

N.M.R. ($CDCl_3$ solution): 6 proton multiplet at 6.9-7.7 p.p.m. (5 aromatic protons and N-H proton which was not exchangeable in D_2O).
4 proton quartet at 3.2-3.75 p.p.m. (2 ether methylene groups).
1 proton multiplet at 2.0-2.4 p.p.m. (cyclopentane ring methine proton α-to C = O group).
9 proton multiplet at 1.3-2.0 p.p.m. (3 cyclopentane ring methylene groups, side chain methylene group and cyclopentane ring methine proton).
3 proton multiplet at (0.95-1.3 p.p.m. (side chain methyl group).
νmax 3540cm.$^{-1}$ (N-H), 1725cm.$^{-1}$ (C=O), 1110cm.$^{-1}$ (CH_2-O-CH_2).
λmax 206, 245 n.m.
Mass spectrum:
M/E 39(28%),41(39%),43(20%),55(54%),57(30%),59(38%),64(24%),65(32%), 66(23%),67(39%),68(20%),69(20%),77(44%),79(29%),81(51%),83(20%), 85(20%),92(44%),93(31%),94(100%),95(58%),96(100%),97(27%),107(24%), 112(27%),120(76%),121(30%),124(56%),126(24%),136(28%),140(44%),170(51%), 199(20%),216(24%),232(47%),261(M^+)(13%),262(3%).

ATTEMPTED PREPARATION OF 2-(2-ETHOXYETHYL)-1,3-CYCLOHEXANEDIONE (209)

a) A solution of cyclohexane-1,3-dione (205) (11g., 0.0983 moles) in "super dry" ethanol (25mls.) was added with stirring to a solution of sodium (2.5g., 0.1087 moles) in "super dry" ethanol (250mls.). Refluxing was maintained for a further 30 minutes. A solution of 2-bromoethoxyethane (181) (15g., 0.0987 moles) in "super dry" ethanol (25mls.) was then added over a ten minute period. Refluxing was continued for 16 hours. Work up was achieved by distilling off most of the ethanol and pouring the residue into 1N sodium hydroxide solution (100mls.) followed by extraction with ether (2 x 50mls.). The combined ether layer was dried (magnesium sulphate) and evaporated to give only starting material (181).

b) The same procedure as (a) was used but dimethoxyethane was used as solvent and sodium hydride to form the carbanion. Work up was achieved by washing the solution with ether, then making just acid with 2N hydrochloric acid and saturating with solid sodium chloride. The released organic material was extracted with chloroform, dried (magnesium sulphate) and evaporated. A fraction of the residue was separated by P.L.C. to give the two starting materials and a product whose spectra was as below.

N.M.R. ($CDCl_3$ solution) 1 proton singlet at 5.35 p.p.m. (not exchangeable in D_2O).

2 proton quartet at 3.75-4.08 p.p.m.

6 proton multiplet at 1.37-2.52 p.p.m.

3 proton triplet at 1.25-1.48 p.p.m.

Mass spectrum:

M/E 39(56%),41(84%),55(71%),68(32%),69(43%),72(62%),73(57%),84(81%), 85(40%),112(35%),113(31%),132(23%),149(18%),155(12%),156(9%),176(12%), 177(10%),190(7%),217(100%),(M^+),218(37%).

PREPARATION OF MONOMETHYLSUCCINYL CHLORIDE (226)

This compound was prepared by the method of Cason[177].

ATTEMPTED PREPARATION OF METHYL 4-KETO-7-ETHOXY HEPTANOATE (221)

The attempted preparation of this compound followed the procedure used by Cason and Prout[97] using monomethyl succinyl chloride and 3-bromopropoxyethane. Work up gave a product other than that expected. The N.M.R. and I.R. spectra are included in the discussion.

Mass spectrum:

M/E 41(82%),42(53%),43(67%),44(26%),45(77%),55(81%),56(82%),57(74%), 58(63%),59(42%),67(34%),69(35%),72(23%),73(57%),81(13%),82(44%), 83(43%),85(39%),87(79%),88(53%),98(48%),101(82%),114(47%),115(72%), 116(63%),129(43%),130(56%),131(42%),188(23%),(M^+),189(12%).

Using the method of Yura and Ide[95] a cyclisation was attempted on the product of this reaction. The N.M.R. spectrum of the product is included in the discussion.

Mass spectrum:

M/E 50(51%),51(64%),57(47%),65(40%),77(81%),78(30%),93(59%),123(100%); 124(6%),125(5%),161(9%),162(6%),164(8%),(M^+).

ATTEMPTED PREPARATION OF ETHYL 4-KETO-7-ETHOXY HEPTANOATE

This preparation was attempted following the procedure used by Cason and Prout[96] using monoethyl succinyl chloride. Work up only gave monoethyl succinic acid and the acid anhydride.

PREPARATION OF MONOETHYL SUCCINIC ACID

This compound was prepared by the method of Fourneau[178].

PREPARATION OF MONOETHYL SUCCINIC ACID CHLORIDE

This compound was prepared by the method of Cason[177] for the monomethyl succinyl chloride..

PREPARATION OF MONO-METHYL MALONIC ACID

This compound was prepared by the method used by Breslow et al[179] but using methyl alcohol (72%).

PREPARATION OF MONO-METHYLMALONYL CHLORIDE (249)

This compound was prepared by the method used by Breslow et al[179] for the preparation of mono-ethyl malonyl chloride (61%).

PREPARATION OF PHTHALOYL CHLORIDE

This compound was prepared by the method of Ott[180].

ATTEMPTED PREPARATION OF METHYL 2-THIENYL GLYOXYLATE (251)

A mixture of monomethylmalonic acid chloride (5.7g., 0.0419 moles) and anhydrous stannic chloride (12g., 0.046 moles) was added dropwise to a stirred solution of thiophen (3.5g., 0.0419 moles) in carbon disulphide (75mls.) (distilled from phosphorus pentoxide). The reaction was cooled in an ice/salt bath. As the addition progressed a

tarry black solid started to precipitate out of solution. Work up was achieved by allowing the temperature of the reaction mixture to reach room temperature and then pouring into ice cold 2N hydrochloric acid (100mls.). The organic layer was separated and the aqueous layer washed twice with ether (2 x 50mls.). The combined organic phases were dried (magnesium sulphate) and evaporated to give a deep red viscous oil. Separation by column chromatography on Woelm alumina (activity V) gave monomethylmalonic acid anhydride (1.64g., 18%) and 2-acetyl thiophen (1.65g., 31%).

PREPARATION OF β-(2-THIENYL) ACRYLIC ACID (256)

This compound was prepared by the method of Ferrando and Sy[181].

PREPARATION OF β-(2-THIENYL) PROPIONIC ACID (254)

This compound was prepared by the method of Sam and Thompson[114].

PREPARATION OF β-(2-THIENYL) PROPIONYL CHLORIDE (253)

A solution of purified thionyl chloride (redistilled from triphenyl phosphite) (62g., 0.525 moles) in dry ether (100mls.) was added dropwise to a stirred solution of β-(2-thienyl) propionic acid (254) (30g., 0.192 moles) in dry ether (450mls.) over a 45 minute period. The reaction mixture was then refluxed for a further hour. Work up was achieved by removal of the ether and excess thionyl chloride under reduced pressure followed by distillation to give a colourless liquid b.p. 114°/36mm. (lit.[182] 116°/42mm.).

PREPARATION OF 5,6-DIHYDRO-4H-CYCLOPENTA (b) THIOPHEN-4-ONE (216)

a) Following the method of Sam and Thompson[114] cyclisation was attempted heating polyphosphoric acid alone with the acid (254) or with the acid in a solution of methylene chloride for 15 minutes. These methods gave only a mixture of starting material and black tar. Extending the heating to 30 minutes only gave a greater proportion of black tar to starting material.

b) Following the method of Poirier et al[119] again using polyphosphoric acid, the only product was unchanged starting material.

c) The compound was prepared by an adaption of the method of Poirier et al[119]. A solution of β-(2-thienyl) propionyl chloride (253) (23g., 0.132 moles) in dry carbon disulphide (100mls.), and anhydrous stannic chloride (38.3g., 0.147 moles) were added separately and simultaneously to stirred dry carbon disulphide (500mls.) over a period

of one hour. During the addition the reaction mixture was cooled in an ice/salt bath. After the addition the reaction mixture was refluxed on a water bath for 30 minutes during which time the orange-red solution turned deep red and a large amount of insoluble material was observed. The reaction mixture was then cooled in an ice/salt bath and work up was achieved by addition to ice cold dilute hydrochloric acid (500mls.). The carbon disulphide layer was separated and the aqueous layer was extracted with chloroform (2 x 250mls.). The combined organic layers were dried (magnesium sulphate) and evaporated to give a pink solid which on recrystallisation (hexane) gave white platelets of 5,6-dihydro-4H-cyclopenta (b) thiophen-4-one (216) (3.1g., 17%) m.p. 118° (lit.[119] 118°).

Carbon disulphide was dried by distillation from phosphorus pentoxide.. Altering the reaction conditions by stirring at room temperature instead of refluxing for 1 hour after the addition gave no product but only β-(2-thienyl) propionic acid (254). Use of aluminium chloride instead of stannic chloride as the catalyst gave a similar yield (18%). Use of the acid chloride (253) without distillation also did not alter the yield.

ATTEMPTED PREPARATION OF 4,5-DIHYDRO-6H-CYCLOPENTA (b) THIOPHEN -4-OL (270)

A procedure similar to that used by Meth-Cohn and Gronowitz[120] for the reduction of 4,5-dihydro-6H-cyclopenta (b) 2-methyl-thiophen -4-one (263) to the corresponding alcohol (274) was used. Lithium aluminium hydride (0.7g., 0.0184 moles) was added to dry tetrahydrofuran (100mls.) and to this suspension a solution of 4,5-dihydro-6H-cyclopenta (b) thiophen-4-one (216) in dry tetrahydrofuran (100mls.) was added dropwise over one hour. The addition took place at 0°C. with stirring. Stirring was continued for a further hour at 0°C. Work up was achieved by dropwise addition of methanol (100mls.) followed by cold water (200mls.). The organic material was extracted with chloroform (3 x 100mls.), dried (magnesium sulphate) and evaporated to give a deep red gum that was only slightly soluble in chloroform and failed to give a significant N.M.R. spectrum.

PREPARATION OF 1-(2-PYRIDYL) CYCLOPENTANOL (266)

A solution of 2-bromopyridine (6.4g., 0.0408 moles) in dry ether (10mls.) was added dropwise to a solution of butyl lithium in hexane (30mls.) with stirring, the temperature being maintained at -35°

(dry ice/acetone). Stirring of the brown solution was continued for a further 30 minutes. A solution of cyclopentanone (3.4g., 0.0405 moles) in dry ether (10mls.) was added dropwise with stirring at -35°. During this addition the brown solution became more viscous and stirring was continued for 20 minutes at -35° and then for a further two hours at room temperature. The reaction mixture was poured onto ice cold water (30mls.) and then glacial acetic acid added until the aqueous layer was acidic. The aqueous layer was separated, washed with ether and then treated with aqueous ammonia solution (880) and extracted with chloroform (2 x 25mls.). The organic phase was washed with water (30mls.), dried (magnesium sulphate) and evaporated to give a brown semi-solid. This was boiled with petrol ether (b.p. 60-80°) (4 x 20mls.). The combined supernatant liquid, was decanted and evaporated to give a deep brown solid. This was recrystallised (carbon tetrachloride) to give white needles m.p. 83° (lit.[183] m.p. 84°).

Found: C-73.48%; H-7.97%, N-8.49%

$C_{10}H_{13}NO$ requires: C-73.6%; H-7.93%; N-8.39%

λmax 208, 262 n.m.

γmax (nujol mull) 3240-3300cm.$^{-1}$ (broad-OH)

N.M.R. ($CDCl_3$) 1 proton doublet at 8.35-8.55 p.p.m. (aromatic proton α-to nitrogen)

3 proton multiplet at 7.0-7.8 p.p.m. (3 aromatic protons)

1 proton singlet at 4.85 p.p.m. (-O-H proton - exchangeable in D_2O)

8 proton singlet at 1.85 p.p.m. (cyclopentanol ring methylene groups)

Mass spectrum:

M/E 51(24%),78(48%),70(82%),106(100%),107(37%),122(58%),130(16%), 134(40%),135(23%),144(68%),145(41%),146(15%),162(10%),163(M^+),(19%), 164(7%).

PREPARATION OF 4-(2-PYRIDYL)-4,5-DIHYDRO-6H-CYCLOPENTA (b) THIOPHEN-4-OL (267)

This compound was prepared following the same reaction conditions as those used for the preparation of 1-(2-pyridyl) cyclopentanol (266) except that tetrahydrofuran instead of ether was used as solvent. The crude product was separated by column chromatography on Woelm alumina (activity III) to give the alcohol (267) (27%), 2-2'dipyridyl (42%) (m.p. 68.5°, lit.[184] 69.5°) and ketone starting material (216). The alcohol (267) was further purified by recrystallisation from hexane

to give white crystals (m.p. 142-4° - decomp.).

The alcohol (267) gave inconsistent analyses and decomposed on standing to a brown gum but was identified by its mass spectrum. N.M.R.($CDCl_3$) 1 proton doublet at 8.308.5 p.p.m. (aromatic proton a- to nitrogen)
5 proton multiplet at 6.9-7.8 p.p.m. (5 aromatic protons)
1 proton broad singlet at 3.6 p.p.m. (-O-H - exchangeable in D_2O
2 proton triplet at 3.3-3.5 p.p.m. (methylene group α-to -OH group)
2 proton triplet at 2.65-3.1 p.p.m. (methylene group α-to thiophen ring)
Mass spectrum:
M/E 39(48%),50(65%),51(82%),57(63%),65(69%),74(57%),77(62%),78(41%), 93(82%),123(100%),124(22%),161(14%),163(10%),217(7%),(M^+)

PREPARATION OF 2-BROMOQUINOLINE

This compound was prepared by the method of Eisch[185].

PREPARATION OF CARBOSTYRIL

This compound was prepared by the method of Colonge and Chambard[186].

ATTEMPTED PREPARATION OF 4-(2-QUINOLYL)5,6-DIHYDRO-4H-CYCLOPENTA (b) THIOPHEN-4-OL (218)

A solution of 2-bromoquinoline (3g., 0.0145 moles) in dry tetrahydrofuran (15mls.) was added dropwise with stirring to a solution of n-butyl lithium in hexane (11mls.). The temperature was kept at -35° (dry ice/acetone) and stirring at this temperature was continued for a further 30 minutes. A solution of the ketone (216) (4.1g., 0.0297 moles) in dry tetrahydrofuran (30mls.) was added dropwise, the temperature still being maintained at -35°. Stirring of the brown viscous solution was continued for 30 minutes at -35° and then for two hours at -35°. Work up was by the same procedure as that used in the preparation of compound (266). Separation of the crude red mixture was by column chromatography on Woelm alumina (activity $\overline{IV}$) to give 2,2'-biquinolyl (2.8g.) recrystallised from hexane m.p. 194° (lit.[187] m.p. 196°) and the ketone (216) (0.36g.).

b) The reaction was repeated using an adaptation of the method of Gilman and Soddy[188] for the preparation of 2-quinolyl lithium. A solution of 2-bromoquinoline (3g., 0.0145 moles) was added quickly to a stirred solution of n-butyl lithium in hexane (11mls.) at -50° and

kept at this temperature for ten minutes. A solution of the ketone (216) (4g., 0.029 moles) in dry tetrahydrofuran (30mls.) was added quickly with stirring at -50° and the stirring maintained at this temperature for 30 minutes after the addition. Work up as in (a) gave the same products.

PREPARATION OF CYCLOPENTANE-1,3-DIONE (278)

This compound was prepared by the method of Merenzi and Nilsson[121,122] and by the method of Rasmusson et al[125], Korach et al[124], and McIntosh and Beaumier[123].

PREPARATION OF 2-CHLOROETHYL TOSYLATE (282)

P-tosyl chloride (95g., 0.461 moles) and 2-chloroethanol (40g., 0.506 moles) were heated together in an oil bath at 140° for 7 hours. During this time hydrogen chloride gas was evolved. The crude yellow mixture was then separated by distillation to give 2-chloroethanol (8g.) p-tosyl chloride (23g.) and 2-chloroethyl tosylate (284) (56g., 51.9%). Redistillation gave a colourless oil (b.p. 143°/1.5mm.) (lit.[189] b.p. 210°/21mms.)

ATTEMPTED PREPARATION OF 2-(2-CHLOROETHYL)1,3-CYCLOPENTANEDIONE(285)

A solution of cyclopentane-1,3-dione (5g., 0.0510 moles) in dry dimethoxy ethane (100mls.) was added dropwise to a suspension of sodium hydride (2.5g., 0.104 moles) in dry dimethoxyethane (50mls.) followed by two drops of methanol. The mixture was refluxed for one hour, cooled to room temperature and a solution of 2-chloroethyl tosylate (284) (11g., 0.04705 moles) in dry dimethoxyethane (20mls.) added. The mixture was refluxed for a further four hours. Work up was achieved by cooling the reaction mixture in an ice bath and adding glacial acetic acid until the solution was neutral. The organic material was extracted with ether (2 x 50mls.), dried (magnesium sulphate) and evaporated to give a yellow viscous oil whose T.L.C. R.f value and spectra indicated that it was only a mixture of the two reactants.

PREPARATION OF β-(2-FURYL) ACRYLIC ACID (286)

This compound was prepared by the method of Gardner, Rand and Hayes[126].

PREPARATION OF β-(2-FURYL) PROPIONIC ACID (288)

This compound was prepared by an adaptation of the method of Plisov and Bykovets[135]. A solution of β-(2-furyl) acrylic acid (286)

(30g., 0.1948 moles) in 95% ethanol (200mls.) was hydrogenated over palladium on charcoal catalyst (10%) (2g.) at atmospheric pressure and room temperature. After 3½ hours uptake (4,421mls: theoretical uptake 4,353mls.) had ceased. The catalyst was filtered off and the solvent evaporated to give an oil which solidified on standing. The product could be purified either by distillation (158°/11mms.) or recrystallisation (petrol ether b.p. 40-60°) m.p. 57° (lit.[128] 57-58°).

ATTEMPTED PREPARATION OF β-(2-FURYL) PROPIONYL CHLORIDE (288)

A solution of thionyl chloride (7g., 0.0593 moles) in dry ether (20mls.) was added dropwise with stirring over a period of 30 minutes to a solution of β-(2-furyl) propionic acid (3.2g., 0.0205 moles) in dry ether (40mls.) in the presence of dry pyridine (1ml.). The reaction mixture was then refluxed for a further 30 minutes. Work up was achieved by the removal of solvents and excess thionyl chloride under reduced pressure during which time the pale red solution became brown and gave a brown viscous residue. Repeating the reaction by stirring at room temperature instead of refluxing after the addition of the thionyl chloride, changing the solvent to the higher boiling toluene, or using a molar amount of thionyl chloride all gave the same result.

ATTEMPTED PREPARATION OF ETHYL a-ACETYL-LAEVULATE (294)

The preparation of this compound was attempted using the method of Stevenson and Johnson[138]. A colourless liquid was obtained b.p. 152°/41mm. (for compound (294) lit.[138] 131-3/17-18mm.).
N.M.R. ($CDCl_3$ solution) 3 proton multiplet at 3.8-4.3 p.p.m.
2 proton multiplet at 2.85-3.1 p.p.m.
6 proton doublet at 2.05-2.35 p.p.m.
3 proton triplet at 1.1-1.4 p.p.m.

Mass spectrum:
M/E 43(82%),45(73%),55(71%),65(74%),69(100%),70(21%),73(94%),97(41%), 98(38%),99(30%),101(83%),140(37%),141(33%),144(44%),168(8%),(M^+), 169(2%).

PREPARATION OF 2,5-DIMETHYL FURAN (291)

This compound was prepared by the method of Scott and Naples[144].

PREPARATION OF 2,5-DIMETHYL-3-FUROIC ACID (289)

This compound was prepared by the method of Hurd and Wilkinson[145].

PREPARATION OF QUINALDINIC ACID

This compound was prepared by Taylor's modification[190] of the method of Reissert[191].

PREPARATION OF QUINALDINIC ACID CHLORIDE (292)

This compound was prepared by the method of Himmick and Dickinson[192] via the ethyl ester.

ATTEMPTED PREPARATION OF 3-(2-QUINOLYL)-2,5-DIMETHYLFURAN (290)

a) This preparation was attempted using a modification of the method followed by Badger and Christie[193] for the synthesis of 2,5-dimethyl-3,2'-napthoylfuran from naphthoyl chloride and 2,5-dimethylfuran. Because of the possibility of reaction between the nitrogen of the quinoline and stannic chloride, the relative molar quantities were the same as those used by Besthorn[194] for a similar type of reaction using quinaldinic acid chloride and aluminium chloride.

A solution of stannic chloride (30g., 0.1152 moles) in dry benzene (70mls.) was added dropwise with stirring to a solution of 2,5-dimethylfuran (291) (10.5g., 0.1094 moles) and quinaldinic acid chloride (22g., 0.1152 moles) in dry benzene (300mls.) at 0°C. During this addition a red semi-solid separated out of solution. The temperature was maintained at 0°C. for 30 minutes after the addition and at 35° for a further 15 minutes. The reaction mixture was cooled and poured into ice-cold water (300mls.)(adjusted to pH8 with 2N sodium hydroxide solution) and extracted with chloroform (2 x 100mls.). The organic layer was then washed with water (150mls.), dried (magnesium sulphate) and evaporated to give a red oil. A portion of this was separated by P.L.C. to give 2-quinaldinic acid recrystallised from petrol-ether b.p. 60-80 (m.p. 169° - lit.[191] 168°-168.5) and a compound that appeared to be the product of condensation between 2,5-dimethylfuran molecules and ring opened 2,5-dimethylfuran molecules, which was not further identified.

b) A solution of 2-bromoquinoline (15.2g., 0.0721 moles) was added with stirring to a solution of n-butyl lithium in hexane (56mls.) in a nitrogen atmosphere at -50° and the temperature maintained for 10 minutes. A solution of the acid (289) (5g., 0.0357 moles) in dry tetrahydrofuran (35mls.) was added with stirring at -50° and the stirring continued at this temperature for 30 minutes after the addition.

Work up was achieved by the same procedure as that used in the preparation of compound (266). Separation of a portion of the residue gave 2,2'-biquinolyl m.p. 195° (from hexane) (lit.[187] m.p. 196°).

2-(2-QUINOLYL) CYCLOPENTANONE (163)

The preparation followed an improved procedure to that used by Baty et al[66]. Freshly distilled benzoyl chloride (61g., 0.434 moles) were added dropwise with stirring over a period of 3½ hours to a solution of freshly distilled quinoline-1-oxide (40g., 0.276 moles) and freshly distilled morpholine enamine of cyclopentanone (110g., 0.719 moles) in dry chloroform (250mls.). The temperature of the slightly exothermic reaction was maintained between -5°C. and 0°C. by ice/salt mixture cooling and control of the addition rate of the acid chloride. After addition was completed the solution was kept overnight and then poured into 20% hydrochloric acid (300mls.). The two phases were then concentrated under reduced pressure until the hydrochloric separated out. The yellow solid material was then dissolved in the minimum amount of water and extracted three times with benzene (to remove benzoic acid). The aqueous phase was then cautiously basified with solid sodium carbonate to pH8 and extracted three times with benzene. Evaporation of the solvent left a black semi-solid which could not be successfully recrystallised using a variety of solvents. Continuous extraction using petroleum ether (b.p. 60-80°) also failed to give a solid product. A crystalline product could be obtained by adsorbing the crude material on the minimum amount of Woelm alumina (activity I) and column chromatography of this on Woelm alumina (activity $\overline{V}$) (using 1½ times the amount of alumina to that used to adsorb the crude material), eluting with petroleum ether (b.p. 60-80°) to give 61.4g., (82%). Alternatively the product could be obtained by mercury diffusion pump distillation to give an orange oil (12.2g., 16.3%) (131°/0.04mm.) and the product (47.4g., 63.3%) (162-191°/0.035mm.).

QUINOLINE-1-OXIDE

This compound was prepared by the method of Ochiai[195].

MORPHOLINE ENAMINE OF CYCLOPENTANONE

This compound was prepared by the method of Stork et al[196].

ATTEMPTED REDUCTION OF 2-(2-QUINOLYL) CYCLOPENTANONE (163)

a) To a solution of 2-(2-quinolyl) cyclopentanone (163) (2.3g., 0.0109 moles) in 95% ethanol (100mls.) was added 5% palladium on charcoal catalyst (0.5g.). The solution was hydrogenated at room

temperature and atmospheric pressure for six days after which time the hydrogen uptake was nil. The catalyst was filtered off and the solution evaporated to give only starting material.

b) The above procedure was repeated with 10% palladium on charcoal catalyst. After four days uptake of hydrogen was nil and only starting material was recovered.

c) A solution of 2-(2-quinolyl) cyclopentanone (163) (6.17g., 0.02924 moles) in 95% ethanol (150mls.) was hydrogenated in the presence of platinum oxide catalyst (60mgs.) for 18 hours at room temperature and atmospheric pressure. After this time uptake of hydrogen was only 80mls. (theoretical uptake = 1,965mls.). A further 60mgs. of catalyst were added and the uptake of hydrogen (60mls.) stopped after 6 hours. The catalyst was filtered off and the solvent evaporated to give only starting material.

d) A solution of 2-(2-quinolyl)cyclopentanone (163) (3g., 0.01422 moles) in 95% ethanol (60mls.) was hydrogenated in the presence of platinum oxide catalyst (30mgs.) at room temperature and 60lbs./squ.in. pressure. After 18 hours there was no reduction in hydrogen pressure. The catalyst was filtered off and the solvent evaporated to give only starting material.

e) A solution of 2-(2-quinolyl) cyclopentanone(163) (6g., 0.02844 moles) in 95% ethanol (150mls.) was made just acid by the dropwise addition of 2N hydrochloric acid and platinum oxide catalyst (60mgs.) was added. Hydrogenation at room temperature and atmospheric pressure for 18 hours gave rise to uptake of 74mls. (theoretical uptake = 1,911 mls.). The catalyst was filtered off and the solvent evaporated to give only starting material.

2-(2-QUINOLYL) CYCLOPENTANOL (296)

This compound was prepared by the method of Baty et al[66].

REDUCTION OF 2-(2-QUINOLYL) CYCLOPENTANOL (296)

a) The two racemates were hydrogenated separately. A solution of 2-(2-quinolyl) cyclopentanol (cis) (296) (2g., 0.009479 moles) in 95% ethanol (100mls.) was hydrogenated in the presence of 5% palladium on charcoal catalyst (0.5g.) at room temperature and atmospheric pressure. This was repeated for the trans racemate. After 18 hours there was found to be no hydrogen uptake in both cases. The catalyst was filtered off and the solvent evaporated to give only starting material.

b) The above procedure was repeated using 10% palladium on charcoal catalyst but only starting material was obtained.

c) Mixed racemates of 2-(2-quinolyl) cyclopentanol (296) (3g., 0.01422 moles) in 95% ethanol (100mls.) were hydrogenated at room temperature and atmospheric pressure in the presence of platinum oxide catalyst (70mgs.) until 2 moles of hydrogen (637 mls.) were taken up and hydrogenation had ceased (6¼ hours). The catalyst was filtered off and solvent evaporated to leave a yellow oil. The products, 2-2-(1,2,3,4 tetrahydro) quinolyl cyclopentanol (164) (1.11g., 36%) and 2-(1,2,3,4-tetrahydroquinolyl) cyclopentane (300) (1.2g., 42%) were separated by column chromatography on Woelm alumina (activity IV).

2-[2-(1,2,3,4-TETRAHYDRO) QUINOLYL] CYCLOPENTANOL (164)

The compound was analysed as its picrate prepared in an ethanol solution and recrystallised by benzene m.p. 164°.

Found: C-53.87%; H-5.00%; N-12.76%

$C_{20}H_{22}N_4O_8$ requires: C-53.81%; H-4.93% N-12.56%

λmax 238, 276, 326 n.m.

νmax ($CHCl_3$ solution) 3630cm.$^{-1}$ (N-H), 3605cm.$^{-1}$ (O-H free), 3410cm.$^{-1}$ (O-H bonded). On dilution by ½ absorption at 3605cm.$^{-1}$ increased and that at 3410cm.$^{-1}$ decreased.

N.M.R. ($CDCl_3$) 4 proton multiplet at 6.4-7.0 p.p.m. (4 aromatic protons)
2 proton broad singlet at 5.35-6.05 p.p.m. (N-H and O-H - both exchangeable in D_2O).
1 proton singlet at 4.35-4.6 p.p.m. (proton adjacent to hydroxyl proton).
3 proton multiplet at 2.45-3.1 p.p.m. (methylene group α-to aromatic ring and methine proton α-to nitrogen).
9 proton multiplet at 0.9-2.0 p.p.m. (7 cyclopentane methylene protons 1 cyclopentane methine proton and methylene group β to aromatic ring)

Mass spectrum:

M/E 62(24%),77(19%),91(24%),117(20%),130(21%),132(100%),133(25%), 156(21%),197(9%),199(16%),217(17%),(M^+),218(4%).

2-(1,2,3,4-TETRAHYDROQUINOLYL) CYCLOPENTANE (300)

The compound was analysed as its picrate prepared in an ethanol solution and recrystallised from benzene m.p. 160°.

Found: C-55.80%; H-5.17%; N-13.18%

$C_{20}H_{22}N_4O_7$ requires: C-55.81%; H-5.11%; N-13.02%

λmax 211, 251, 301 n.m.

νmax ($CHCl_3$ solution) 3405cm.$^{-1}$ (N-H)

N.M.R. ($CDCl_3$) 4 proton multiplet at 6.4-7.0 p.p.m. (4 aromatic protons).

1 proton multiplet at 3.3-3.8 p.p.m. (N-H - exchangeable in D_2O).

3 proton multiplet at 2.45-3.1 p.p.m. (methylene group α-to aromatic ring and methine α-to nitrogen).

11 proton multiplet at 1.1-2.1 p.p.m. (9 cyclopentane ring protons and methylene protons β-to aromatic ring).

Mass spectrum:

M/E 77(33%),117(34%),118(11%),130(68%),131(44%),132(100%),133(79%), 156(18%),201(M^+),(33%),202(11%).

d) Platinum oxide catalyst (70mgs.) were added to a solution of 2-(2-quinolyl) cyclopentanol (296) (3g., 0.01408 moles) in glacial acetic acid (100mls.) previously distilled from chromic anhydride. After hydrogenation for 3 hours at room temperature and pressure uptake ceased and was found to be 2½ times more than that expected. The catalyst was filtered off and the solvent evaporated. The residue was taken up in chloroform (50mls.), washed with 10% sodium carbonate solution (2 x 50mls.) and the organic layer separated and dried (Mg SO_4). The solvent was evaporated to give a yellow viscous oil which solidified on standing. Purification by sublimation gave a white solid (1.4g., 47%) of 2-(2-decahydroquinolyl) cyclopentanol (297) m.p. 131°.

Found: C-75.18%; H-11.33%; N-6.18%

$C_{14}H_{25}NO$ requires: C-75.34%; H-11.21%; N-6.28%

νmax ($CHCl_3$ solution) 3580cm.$^{-1}$ (N-H), 3300cm.$^{-1}$ (O-H bonded). On dilution by ½ relative absorption did not alter.

N.M.R. ($CDCl_3$) 2 proton multiplet at 3.6-4.2 p.p.m. [O-H or N-H (exchangeable in D_2O) proton adjacent to -O-H]

1 proton multiplet at 2.35-2.7 p.p.m. (methine proton α-to nitrogen and β-to hydroxyl group).

22 proton multiplet at 0.65-2.1 p.p.m. [remaining aliphatic protons O-H or -N-H (not exchangeable in D_2O)]

Mass spectrum:

M/E 79(70%),81(61%),82(50%),95(56%),96(31%),110(27%),114(26%),121(36%), 122(23%),136(51%),138(100%),139(87%),180(41%),203(24%),204(22%),205(14%), 222(28%),223(34%),(M^+).

2-(2-QUINOLYL) CYCLOHEXANONE (308)

This compound was prepared by the method of Hamana and Noda[154].

2-(2-QUINOLYL) CYCLOHEXANOL (309)

This compound was prepared by the method of Hamana and Noda[154].

Two racemates were obtained which were separated by P.L.C. to give two white crystalline solids recrystallised from benzene. One racemate m.p. 150° (28.13% of total) was intermolecularly hydrogen bonded and the other m.p. 132-133° (71.87% of total) was intramolecularly hydrogen bonded.

REDUCTION OF 2-(2-QUINOLYL) CYCLOHEXANOL (309)

a) A solution of 2-(2-quinolyl) cyclohexanol (309) (5g., 0.022 moles) in 95% ethanol (150mls.) was hydrogenated at room temperature and atmospheric pressure in the presence of platinum oxide catalyst (100mgs.). After 18 hours, uptake of hydrogen had ceased (718mls., theoretical uptake 987mls.). The catalyst was filtered off and solvent evaporated to give a pale yellow viscous oil. Separation by column chromatography on Woelm alumina (activity III) and P.L.C. gave the two reactant racemates (2.14g.), one racemate of 2-[2-(1,-2,3,4-tetrahydro) quinolyl] cyclohexanol (310a or b) showing intermolecular hydrogen bonding (1.32g., 25.88%) and one racemate of 2-[2-(1,2,3,4-tetrahydro) quinolyl] cyclohexanol (310c or d) showing intramolecular hydrogen bonding (0.92g., 18.04%). Both were white crystals, recrystallised from benzene m. p. 137°.

1st. racemate of compound (310)

Found: C-78.3%; H-8.95%; N-6.0%.

$C_{15}H_{21}NO$ requires: C-77.93%; H-9.09%; N-6.06%

λmax 210, 250, 302 n.m.

νmax ($CHCl_3$ solution) 3635cm.$^{-1}$ (N-H), 3600cm.$^{-1}$ (-O-H free), 3395cm.$^{-1}$ (-O-H bonded). On dilution by ½ absorption at 3395cm.$^{-1}$ decreased in intensity and absorption at 3600cm.$^{-1}$ increased.

N.M.R. ($CDCl_3$): 4 proton multiplet at 6.3-7.1 p.p.m. (4 aromatic protons).

1 proton doublet at 4.0-4.35 p.p.m. (proton adjacent to -OH).

2 proton multiplet at 3.5-3.95 p.p.m. (-N-H and -O-H - both exchangeable in D_2O).

1 proton multiplet at 3.1-3.5 p.p.m. (methine proton α-to nitrogen).

2 proton multiplet at 2.5-2.95 p.p.m. (methylene group α-to aromatic

ring).

11 proton multiplet at 1.1-2.15 p.p.m. (8 cyclohexanol methylene protons, 1 cyclohexanol methine proton a-to -OH, methylene group β-to aromatic ring).

Mass spectrum:

M/E. 41(10%),77(21%),106(21%),117(24%),130(30%),132(100%),133(47%), 157(16%),211(14%),212(4%),23(61%),(M+),232(17%),

m.p. 110°

Second racemate of compound (310)

Found: C-78.3%; H-9.06%; N-6.0%

$C_{15}H_{21}NO$ requires: C-77.93%; H-9.08%; N-6.06%

λ_{max} 2095, 2450, 2820 n.m.

ν_{max} ($CHCl_3$ solution) 3610cm.$^{-1}$ (-N-H), 3760 (-O-H bonded). On dilution by ½ the relative intensities of the absorption did not change and no free -OH absorption observed.

N.M.R. ($CDCl_3$): 4 proton multiplet at 6.4-7.1 p.p.m. (4 aromatic protons).

2 proton multiplet at 4.1-4.75 p.p.m. (-O-H and -N-H - exchangeable in D_2O).

2 proton multiplet at 3.1-3.95 p.p.m. (methine proton adjacent to -OH and methine proton α-to nitrogen)

2 proton quartet at 2.5-2.95 p.p.m. (methylene group α-to aromatic ring).

11 proton multiplet at 0.95-2.15 p.p.m. (8 cyclohexanol methylene protons, 1 cyclohexanol methine proton α-to -OH, methylene group β-to aromatic ring).

Mass spectrum:

M/E. 41(20%),77(43%),91(21%),106(45%),117(64%),130(91%),132(100%), 133(76%),231(78%),(M+),232(21%).

b) Platinum oxide catalyst (90mgs.) was added to a solution of 2-(2-quinolyl cyclohexanol) (309) (5g., 0.02203 moles) in glacial acetic acid (100mls.) (previously redistilled from chromic anhydride) and the mixture was hydrogenated at room temperature and atmospheric pressure. Uptake of hydrogen which ceased after 3½ hours was 1,062mls. (expected uptake 1,004mls.). The catalyst was filtered off, solvent evaporated, and the residue was dissolved in chloroform (100mls.) which was washed with 10% sodium carbonate solution (2 x 100mls.). The organic layer was dried (magnesium sulphate) and the chloroform evaporated

to give a yellow viscous oil. Separation by column chromatography on Woelm alumina (activity III and P.L.C. gave the two racemates formed in (a) (310a or b) (1.74g., 34.2%) and (310c or d) (1.2g., 23.8%) as well as one racemate of 2- 2-(6,7,8,9-tetrahydro) quinolyl cyclohexanol (311) (1.56g., 30.6%), white crystals recrystallised from benzene m.p. 103°.

Found: C-78.0%; H-9.2%; N-5.9%

$C_{15}H_{21}NO$ requires: C-77.93%; H-9.09%; N-6.06%

λmax 209, 273, 315 n.m.

νmax (CH_3Cl_3 solution) 3360cm.$^{-1}$ (-OH bonded). On dilution by ½ the relative intensity of the absorption did not alter and no free -OH absorption observed.

N.M.R. ($CDCl_3$); 1 proton doublet at 7.3-7.5 p.p.m. (aromatic proton to nitrogen).

1 proton doublet at 6.9-7.1 p.p.m. (aromatic proton β-to nitrogen).

1 proton multiplet at 4.95 p.p.m. (-O-H - exchangeable in D_2O).

4 proton multiplet at 2.55-3.05 p.p.m. (methylene groups α-to the aromatic ring).

1 proton multiplet at 4.05-4.6 p.p.m. (methine proton adjacent to -OH).

13 proton multiplet at 1.1-2.3 p.p.m. (8 cyclohexanol methylene protons, 1 cyclohexanol methine proton α-to -OH, 2 methylene groups β-to the aromatic ring).

Mass spectrum:

M/E 77(36%),91(30%),120(49%),145(62%),146(21%),147)15%),160(100%), 161(71%),172(38%),174(51%),176(31%),202(40%),203(73%),213(57%),214(42%), 230(24%),23;(42%),(M+), 232(23%).

ALKYLATION OF 2-[2-(1,2,3,4-TETRAHYDRO) QUINOLYL] CYCLOPENTANOL (164)

2-[2-(1,2,3,4-tetrahydro) quinolyl] cyclopentanol (164) (2.5g., 0.0117 moles) was dissolved in ethyl β-bromopropionate (4.2g., 0.0233 moles) and finely powdered anhydrous potassium carbonate (2.2g., 0.0222 moles) and potassium iodide (0.2g.,0.0012 moles) were added. The mixture was heated with stirring at 140° under a stream of nitrogen for 3 hours. Initially vigorous effervescence occurred and the mixture turned grey in colour after fifteen minutes. At the end of the reaction time cold water (40mls.) were added to the now brown mixture and the organic material extracted with chloroform (2 x 50mls.). The combined chloroform extracts were washed with water (50mls.), dried (magnesium sulphate) and evaporated. Separation of the residual red viscous oil by column chromatography on Woelm alumina (activity-

IV) gave ethyl β-bromopropionate (1.1g.), ethyl acrylate (0.4g.), 2-[2-(1,2,3,4-tetrahydro) quinolyl] cyclopentanol (164) (0.8g., 32%) and 2-[2-(1,2,3,4-tetrahydro) quinolyl] cyclopentanol, 1-(β) propionate (298) (1.72g., 46.24%). The ester (298) was further purified by P.L.C. and gave the following data:

Found: C-75.86%; H-9.07%; N-4.81%

$C_{19}H_{27}NO_3$ requires: C-75.74%; H-8.97%; N-4.65%

λmax 210, 260, 308 n.m.

νmax (film) 1730-45 (broad C=O)

N.M.R. ($CDCl_3$ solution): 4 proton multiplet at 6.45-7.3 p.p.m. (4 aromatic protons)

2 proton quartet at 3.9-4.35 p.p.m. (ester methylene group)

2 proton multiplet at 3.303.9 p.p.m. (-O-H - exchangeable in D_2O, and methine adjacent to -OH)

5 proton multiplet at 2.4-3.05 p.p.m. (methylene group α-to aromatic ring, side chain methylene group α-to nitrogen, and methine proton α-to nitrogen)

11 proton multiplet at 1.4-2.2 p.p.m. (6 cyclopentanol methylene protons, 1 cyclopentanol methine proton α-to -OH, methylene group β-to the aromatic ring, side chain methylene group β-to nitrogen)

3 proton triplet at 1.1-1.4 p.p.m. (ester methyl group)

Mass spectrum:

M/E 41(76%),55(44%),69(46%),77(65%),78(34%),87(62%),88(34%),91(87%), 105(80%),106(51%),117(91%),118(86%),130(91%),132(100%),133(96%), 144(98%),145(79%),146(94%),158(65%),160(21%),170(21%),218(80%),232(94%), 233(97%),317(62%),(M^+),318(6%).

ALKYLATION OF 2-(1,2,3,4-TETRAHYDROQUINOLYL) CYCLOPENTANE (290)

This compound was prepared by the same method as that used for the alkylation of 2-[2-(1,2,3,4-tetrahydro)quinolyl] cyclopentanol. The crude product was separated by column chromatography on Woelm alumina (activity III) to give ethyl β-bromopropionate, ethyl acrylate, 2-(1,2,3,4-tetrahydro quinolyl) cyclopentane (290) (26.4%) and 2-(1,2,3,4-tetrahydroquinolyl) cyclopentane, 1-(β) propionate (289) (48.2%). The ester (9) was further purified by P.L.C. and gave the following data:

Found: C-75.86%; H-9.07%; N-4.81%

$C_{19}H_{27}NO_2$ requires: C-75.75%; H-8.97%; N-4.65%

λmax 211, 260, 309 n.m.
ϑmax (film) 1735cm.$^{-1}$ (ester C=O)
N.M.R. ($CDCl_3$ solution): 4 proton multiplet at 6.4-7.1 p.p.m. (4 aromatic protons)
2 proton quartet at 3.9-4.3 p.p.m. (ester methylene group)
2 proton multiplet at 3.3-3.9 p.p.m. (side chain methylene group β-to nitrogen)
1 proton multiplet at 2.9-3.25 p.p.m. (methine proton α-to nitrogen)
4 proton multiplet at 2.35-2.85 p.p.m. (side chain methylene group α-to nitrogen and methylene group α-to the aromatic ring)
14 proton multiplet at 0.9-2.2 p.p.m. (cyclopentane ring protons, methylene group β-to the aromatic ring, and ester methyl group)
Mass spectum:
M/E. 65(59%),74(60%),102(33%),113(57%),115(43%),116(40%),131(36%), 132(73%),133(48%),144(71%),145(60%),146(41%),156(50%),157(53%), 203(24%),205(31%),216(73%),217(23%),233(100%),234(61%),301(57%), (M^+),302(7%).

ETHYL β-BROMOPROPIONATE

This compound was prepared by the method decribed by Mozingo and Patterson[197] for the methyl ester. The oil was distilled b.p. 76-72°/-18mm., washed with cold aqueous sodium bicarbonate solution (to remove traces of hydrogen bromide), then water, dried (magnesium sulphate) and redistilled b.p. 41°/2mm. as a colourless oil (83%).

OXIDATION OF 2-(2-QUINOLYL) CYCLOPENTANOL (296)

a) A modified procedure to that used by Eastham and Taranishi[198] for the oxidation of cholesterol was followed. A solution of 2-(2-quinolyl) cyclopentanol (296) (1g., 0.0047 moles) in dry toluene (20mls.) was added to a solution of dried distilled cyclohexanone (8mls., 0.0837 moles) in dry toluene (30mls.). The combined solutions were distilled with the use of a take off condenser in order to dry the apparatus until 10mls. of toluene had been collected. A solution of aluminium isopropoxide (3g., 0.0147 moles) in dry toluene (250mls.) was added dropwise at the same rate that toluene was distilled off from the reaction vessel. The reaction mixture was allowed to cool to room temperature and then a saturated solution of potassium sodium tartrate (30mls.) was added during which time the organic layer became orange. The mixture was steam distilled to remove cyclohexanone and

cyclohexanol. The residue was extracted twice with chloroform (2 x 50-mls.) and the combined organic phase washed with water, dried (magnesium sulphate) and evaporated to give a light orange solid. The N.M.R. and G.L.C. spectra both indicated the product contained 2-(2-quinolyl) cyclopentanol (296) (38%) and 2-(2-quinolyl)cyclopentanone (163) (62%).

b) A modified procedure of a general improved Sarett oxidation used by Ratcliffe and Rodehurst[153] was followed. Powdered chromium trioxide (6g., 0.06 mole) was added with stirring to a solution of anhydrous pyridine (9.5g., 0.122 moles) in dry methylene chloride (150mls.). Stirring was continued for 20 minutes until a deep red solution formed. A solution of 2-(2-quinolyl) cyclopentanol (296) (2.3g., 0.0108 moles) in the minimum amount of anhydrous pyridine (20mls.) was added with stirring which was continued for a further 15 minutes after the addition at room temperature. During this time a dark brown precipitate was formed which was separated from the solution by decantation and then washed with diethyl ether (200mls.). The combined organic material was washed with 2N sodium hydroxide solution(3 x 100mls.), saturated sodium chloride solution (100mls.), water (100mls.), dried (magnesium sulphate) and the solvent evaporated. The N.M.R. and G.L.C. spectra both indicated the crude product contained 2-(2-quinolyl) cyclopentanol (296) (55%) and 2-(2-quinolyl) cyclopentanone (163) (45%).

The reagents for this reaction were purified as follows. Pyridine was refluxed over barium oxide for 1 hour, and then distilled, the fraction boiling at 115°/754mm. being collected. It was then stored over dried 4A molecular sieves. Chromium trioxide was powdered and stored over phosphorus pentoxide in a vacuum desiccator. The methylene chloride was dried over calcium chloride.

OXIDATION OF 2-[2-(1,2,3,4-TETRAHYDRO) QUINOLYL] CYCLOPENTANOL,1-(B) PROPIONATE (298)

a) The reaction was performed using the Oppenauer procedure for the oxidation of 2-(2-quinolyl) cyclopentanol (296). The N.M.R. and G.L.C. spectra of the crude product indicated that only reactants were present.

b) The reaction was performed using the improved Sarett procedure for the oxidation of 2-(2-quinolyl) cyclopentanol (296). The crude product was separated by column chromatrography on Woelm alumina (activity V) to give 2-[2-(1,2,3,4-tetrahydro) quinolyl] cyclopentanol,

1-(β) propionate (298) (32%) and 2-[2-(1,2,3,4-tetrahydro) quinolyl] cyclopentanone, 1-(β) propionate (166) (55%). A sample was further purified for analysis by P.L.C. to give a pale yellow oil.

Found: C-72.19%; H-7.82%; N-4.16%

$C_{19}H_{25}NO_3$ requires: C-72.38%; H-7.935%; N-4.444%

λmax 210, 260, 307 n.m.

ν̄max (film) broad 1730-1740cm.$^{-1}$ (ester C=O and ketone C=O)

N.M.R. ($CDCl_3$) 4 proton multiplet at 6.4-7.2 p.p.m. (4 aromatic protons)

2 proton quartet at 3.8-4.3 p.p.m. (ester methylene group)

2 proton multiplet at 3.4-3.8 p.p.m. (side chain methylene group β-to nitrogen)

2 proton multiplet at 2.8-3.25 p.p.m. (methine proton α-to nitrogen, and methine proton α-to ketone group)

4 proton multiplet at 2.3-2.8 p.p.m. (methylene group α-to aromatic ring, and side chain methylene group α-to nitrogen)

8 proton multiplet at 1.3-2.2 p.p.m. (6 cyclopentanone ring methylene protons, and methylene group β-to the aromatic ring)

3 proton triplet at 0.9-1.3 p.p.m. (ester methyl group)

Mass spectrum:

M/E 41(46%),51(27%),55(18%),67(29%),69(41%),77(57%),78(42%),79(36%), 87(51%),88(43%),89(40%),91(79%),105(61%),106(38%),117(79%0,118(60%), 130(61%),133(100%),134(44%),144(92%),146(59%),158(80%),159(34%),218 (48%),219(19%),232(49%),233(97%),299(36%),301(28%),315(M+),(33%), 316(10%).

ATTEMPTED CONDENSATION OF 2-(2-QUINOLYL) CYCLOPENTANONE,1-β PROPIONATE (298)

a) A solution of 2-(2-quinolyl) cyclopentanone 1-β propionate (2g., 0.00635 moles) (298) in "super dry" ethanol was added to a solution of sodium ethoxide in ethanol (20mls.) (made by dissolving sodium metal (0.16g., 0.0068 moles) in "super dry" ethanol (20mls.). The reaction mixture was stirred at room temperature for 24 hours. Work up was achieved by addition of 2N hydrochloric acid until just neutral. The aqueous layer was extracted with ether, the ether layer dried (magnesium sulphate) and evaporated. The N.M.R. and G.L.C. spectra and mass spectrum molecular ion were identical to the reactant.

b) The reaction was conducted as above (a) but sodium tertiary

butanol in "super dry" tertiary butanol was used instead of ethanol. The N.M.R. and G.L.C. spectra and mass spectrum molecular ion were again identical to the reactant.

PREPARATION OF 2-(2-CHLOROCYCLOPENTYL)-1,2,3,4-TETRAHYDROQUINOLINE (315)

a) A solution of thionyl chloride (12.4g., 0.104 moles) (redistilled from triphenyl phosphite) in dry ether (50mls.) was added dropwise with stirring to a solution of 2-[2-(1,2,3,4-tetrahydro) quinolyl] cyclopentanol (164) (9g., 0.0415 moles) and pyridine (4g., 0.0513 moles) in dry ether (200mls.). After the addition, the mixture was refluxed for 1½ hours and the ether and thionyl chloride distilled off under reduced pressure to give a viscous black residue, the N.M.R. spectrum of which revealed an absence of cyclopentane protons.

b) The procedure used was as above (a) but dry toluene instead of dry ether was used as solvent. After addition of the thionyl chloride, the mixture was stirred at room temperature for 1½ hours. Work up was achieved by addition of 10% sodium bicarbonate solution until neutral. The organic layer was separated, dried (magnesium sulphate) and evaporated to give a brown oil. The product was purified by column chromatography on Woelm alumina (activity III) protected from the sunlight to give a light yellow viscous oil (4.6g., 47%).

Found: C-71.03%; H-7.71%; N-5.60%

$C_{14}H_{18}NCl$ requires: C-71.34%; H-7.64%; N-5.95%

λmax 201, 251, 299 n.m.

νmax (film) 3410cm.$^{-1}$ (-N-H), 750cm.$^{-1}$ (C-Cl)

N.M.R. ($CDCl_3$ solution): 4 proton multiplet at 6.35-7.2 p.p.m. (4 aromatic protons)

1 proton broad multiplet at 4.35-4.75 p.p.m. (proton adjacent to chlorine)

1 proton broad singlet at 3.7-3.9 p.p.m. (-N-H proton - exchangeable in D_2O)

1 proton broad multiplet at 3.1-3.55 p.p.m. (methine proton α-to nitrogen)

2 proton multiplet at 2.6-3.0 p.p.m. (methylene group α-to aromatic ring)

9 proton multiplet at 1.4-2.5 p.p.m. (3 cyclopentane ring methylene groups, methine proton α-to chlorine, methylene group β-to aromatic ring)

Mass spectrum:

M/E. 41(43%),51(26%),65(25%),77(79%),91(31%),103(24%),105(27%),106 (20%),116(31%),117(80%),118(19%),130(83%),131(49%),132(100%),133(90%), 149(28%),156(36%),158(30%),200(18%),201(94%),202(30%),235(10%),236(1%), 237(6%),(M^+)238(1%).

ATTEMPTED PREPARATION OF 2-(2-QUINOLYL) CHLOROCYCLOPENTANE (314)

The same procedure was used as for the preparation of 2-(2-chlorocyclopentyl)-1,2,3,4-tetrahydroquinoline, employing toluene as solvent to give 2-quinolyl cyclopentane (306) (52%) (b.p. lit.[199] 76-80°/0.05-mm.).

Found: C-84.11%; H-7.70%; N-6.97%

$C_{14}H_{15}N$ requires: C-84.28%; H-7.61%; N-7.12%

λmax 210, 230, 234 n.m.

N.M.R. ($CDCl_3$ solution): 6 proton multiplet at 7.15-8.1 p.p.m. (6 aromatic protons)

1 proton multiplet at 3.1-3.7 p.p.m. (cyclopentane methine proton)

8 proton multiplet at 1.45-2.4 p.p.m. (4 cyclopentane ring methylene groups)

Mass spectrum:

M/E. 44(23%),77(18%),112(20%),128(54%),129(31%),156(100%),157(49%), 167(58%),168(96%),169(77%),197(64%),(M^+),198(55%).

REDUCTION OF 2-QUINOLYL CYCLOPENTANE (306)

A solution of 2-quinolyl cyclopentane (306) (4g., 0.0203 moles) in 95% ethanol (100mls.) was hydrogenated in the presence of platinum oxide catalyst (100mgs.) at atmospheric pressure and room temperature. Uptake of hydrogen (942mls., theoretical uptake 929mls.) ceased after 4 hours. The catalyst was filtered off and the solvent evaporated to give a light yellow oil. Purification was by P.L.C. in chloroform to give 2-(1,2,3,4-tetrahydroquinolyl) cyclopentane (300) (72%)

Found: C-83.34%; H-9.36%; N-6.72%

$C_{14}H_{19}N$ requires: C-83.58%; H-9.45%; N-6.96%

λmax: 210, 250, 302 n.m.

νmax (film): 3410cm.$^{-1}$ (-N-H)

N.M.R. ($CDCl_3$ solution) 4 proton multiplet at 6.35-7.1 p.p.m. (4 aromatic protons)

1 proton broad multiplet at 3.6-4.15 p.p.m. (-N-H proton, - exchangeable in D_2O)

3 proton multiplet at 2.6-3.2 p.p.m. (methylene group α-to aromatic ring, methine proton α-to nitrogen)
11 proton multiplet at 1.0-2.15 p.p.m. (9 cyclopentane ring protons, methylene group β-to aromatic ring).

PREPARATION OF N-(ETHOXY CARBONYL ACETYL)-2-(2-CHLOROCYCLOPENTYL) 1,2,3,4-TETRAHYDROQUINOLINE (316)

A solution of freshly distilled mono-ethyl malonyl chloride (3g., 0.02 moles) in dry toluene (50mls.) was added dropwise with stirring to a solution of 2-(2-chlorocyclopentyl)-1,2,3,4-tetrahydroquinoline (315) (2g., 0.0085 moles) in dry toluene (150mls.) over a 30 minute period. Stirring at room temperature was continued for a further 3 hours. Work up was achieved by addition to ice cold 2N hydrochloric acid (400mls.) with stirring. The organic layer was separated, dried (magnesium sulphate) and evaporated. The product was separated from acid anhydride by-product by column chromatography on Woelm alumina (activity VI) to give a highly mobile light yellow oil (2.1g., 70.7%).

Found: C-65.67%; H-7.02%; N-4.16%

$C_{19}H_{24}NO_3Cl$ requires: C-65.24%; H-6.87%; N-4.01%

λmax 209, 239 n.m.

νmax (film) 1735cm.$^{-1}$ (broad ester C=O), 1660cm.$^{-1}$ (ketone C=O)

N.M.R. ($CDCl_3$ solution): 4 proton singlet at 7.13 p.p.m. (4 aromatic protons)
1 proton multiplet at 4.6-5.05 p.p.m. (methine proton adjacent to chlorine)
2 proton quartet at 3.8-4.3 p.p.m. (ester methylene group)
2 proton singlet at 3.48 p.p.m. (methylene group α-to ketone group)
2 proton quartet at 2.4-2.8 p.p.m. (methylene group α-to aromatic ring)
2 proton multiplet at 2.0-2.4 (methine proton α-to nitrogen, and cyclopentane ring methine proton α-to chlorine)
11 proton multiplet at 1.1-1.85 p.p.m. (3 cyclopentane ring methylene groups, methylene group β-to aromatic ring, and ester methyl group)

Mass spectrum:

M.S. 57(37%),77(30%),91(24%),114(27%),117(56%),118(24%),130(68%), 131(51%),132(100%),133(67%),141(28%),144(38%),166(25%),122(58%), 198(91%),199(43%),246(97%),247(21%),349(26%),(M),350(6%),351(11%), (M+),352(3%).

ATTEMPTED CYCLISATION OF THE AMIDE (316)

a) The amide (316) (1.6g., 0.00458 moles) in dry dimethoxyethane

(10mls.) was added dropwise with stirring to a suspension of sodium hydride (0.25g., 0.005 moles) in dry dimethoxyethane (50mls.) causing a slight exothermic reaction. After addition stirring was continued at room temperature for 1½ hours. The reaction mixture was cooled in ice and then poured slowly with stirring into ice cold 2N hydrochloric acid (100mls.). The organic material was extracted with ether (3 x 100 mls.), the combined organic phases washed with water (200mls.), dried magnesium sulphate) and evaporated to give a yellow oil.

b) The procedure used was as above (a) but the reaction mixture was refluxed and not stirred at room temperature for 1½ hours.

c) The procedure used was as above (a) but the reaction mixture was refluxed in dimethylformamide for 1½ hours.

d) The procedure was as above (a) but the reaction mixture was heated at 50° for 5 hours with stirring in pure hexanethylphosphoric acid triamide.

In reactions a-d the N.M.R. and G.L.C. spectra and mass spectral molecular ion were identical with those of the starting material.

PURIFICATION OF HEXANETHYLPHOSPHORIC ACID TRIAMIDE

The solvent was left over molecular sieves (4A) for 1 hour, filtered and then distilled under nitrogen from fresh molecular sieves (4A). The fraction boiling at 80°/1mm. was collected.

ATTEMPTED PREPARATION OF THE TETRAHYDROPYRAN DERIVATIVE OF 2-(2-QUINOLYL) CYCLOPENTANOL (296)

a) The method used was similar to that followed by Jones and Mann[200] for the preparation of 2-propargyloxytetrahydropyran from propargyl alcohol. 2-(2-quinolyl) cyclopentanol (296) (2g., 0.00939 moles) was added to 2,3-dihydropyran (freshly distilled) (1g., 0.0119 moles) under a nitrogen atmosphere. This was followed by the addition of 2 drops of concentrated hydrochloric acid. Stirring at 40° was maintained for 2 hours. The reaction was worked up by the addition of saturated sodium bicarbonate solution (40mls.) and the organic material extracted with chloroform (2 x 40mls.). The combined organic phase was washed with water (100mls.), dried (magnesium sulphate) and evaporated to give a yellow oil. The N.M.R. spectrum of this oil showed the presence of no dihydropyranyl nor tetrahydropyranyl protons. The I.R. spectrum showed the absence of any ether absorption.

b) 2-(2-quinolyl cyclpentanol (296) (2g., 0.00939 moles) was dissolved in dry toluene (30mls.) and dry hydrogen chloride gas passed through the solution to saturation. The white ppt. which was formed was filtered off, washed with more dry toluene (5mls.), dried and recrystallised (acetone) m.pt. 176°. The hydrochloride (1.8g., 0.00723 moles) was added to freshly distilled 2,3-dihydropyran (0.9g., 0.00833 moles) under a nitrogen atmosphere to form a slurry. Concentrated hydrochloric acid (2 drops) were added and the mixture stirred for 18 hours at 40°. Work up was as above (a) to give a yellow oil which showed the same spectral characteristics as the product in (a).

ATTEMPTED PREPARATION OF 2-[2-(1,2,3,4-TETRAHYDROQUINOLYL)] CYCLOPENTANONE (300)

Chromium trioxide (6g., 0.1154 moles) was added with stirring to a solution of anhydrous pyridine (9.5g., 0.1218 moles) in methylene chloride (150mls.) and stirring continued for 20 minutes until a deep red solution was formed. A solution of 2-[2-(1,2,3,4-tetrahydro) quinolyl] cyclopentanol (164) (2.4g., 0.01127 moles) in the minimum amount of anhydrous pyridine (20mls.) was added with stirring which was continued for a further 15 minutes. During this time a chocolate brown ppt. formed from which the organic solution was decanted. The ppt. was washed with ether (100mls.) and the combined organic solution was washed with 2N sodium hydroxide solution (3 x 100ms.), and once with saturated sodium chloride solution (100mls.). The organic phase was separated, dried (magnesium sulphate) and the solvent evaporated to give a red solid (2.1g., 86%) whose spectra were identical to those of 2-(2-quinolyl) cyclopentanone (163).

b) A solution of aluminium isopropoxide (12g., 0.0541 moles) in dry toluene (200mls.) was added dropwise with stirring to a solution of 2-[2-(1,2,3,4-tetrahydro)]quinolyl (164) (4g., 0.0188 moles) in dry toluene (50mls.) under a nitrogen atmosphere. The mixture was refluxed for three days. The solution was cooled to room temperature and added with stirring to 2N hydrochloric acid (200mls.). The aqueous layer was separated and extracted with ether (2 x 200mls.). The aqueous layer was separated, basified with 2N sodium hydroxide solution and extracted with chloroform. The organic layer was separated, dried (magnesium sulphate) and evaporated to give a yellow oil show-

ing identical spectra with those of the starting material.

ATTEMPTED PREPARATION OF N-(ETHOXY CARBONYL ACETYL)-2-(2-IODOCYCLOPENTYL 1,2,3,4-TETRAHYDROQUINOLINE

Sodium iodide (3g., 0.02 moles) was added to a solution of the amide (316) (1g., 0.00286 moles) in dry methyl ethyl ketone (40mls.). The mixture was refluxed for 18 hours. Work up was achieved by removal of the solvent and addition of water (50mls.). Organic material was extracted with ether (2 x 30mls.), the ether layer washed with water (50mls.), dried (magnesium sulphate) and evaporated. The crude material was separated by T.L.C. to give monoethyl malonic acid (0.104g., 14%), 2-(2-chlorocyclopentyl)-1,2,3,4-tetrahydroquinoline (315) (0.161g., 14.3%), N-(ethoxy carbonyl acetyl)-2-(2-chlorocyclopentyl)1,2,3,4-tetrahydroquinoline (316) (0.476g., 47.5%) and the malonic acid amide of 2- 2-(1,2,3,4-tetrahydro) quinolyl cyclopentane (0.081g., 6.6%).

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