SYNTHETIC APPROACHES TO 9-AZASTEROIDS

by

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SUMMARY

An account is given of total syntheses of azasteroids, syntheses of 4-piperidones, and also syntheses of 2-quinolizidones.

1,2,3,4,5,6-Hexahydro-3-oxo-4aH-benzo[c]quinolizine was prepared and methylation shown to occur in the 2-position which was of no further synthetic value. 4-Cyano-1,2,3,4,5,6-hexahydro-3-oxo-4aH-benzo[c]quinolizine was prepared and alkylated with bromo-acetone. Attempts to cyclise the product to produce the 9-azasteroid system were unsuccessful.

1-Phenyl-4-piperidone was synthesised by a method giving a higher yield than reported in the literature, and some alkylation reactions carried out on it.

Some reactions of compounds containing reactive hydrogens with quinoline-1-oxide in the presence of acetic anhydride are reported.

Some 2-cyclopentyl quinoline derivatives are prepared by the action of cyclopentanone derivatives containing active hydrogens on quinoline-1-oxide in the presence of acetic anhydride or quinoline in the presence of acid chlorides. Attempts to construct ring C of the 9-azasteroid system from the 2-cyclopentyl quinoline derivatives have been investigated.

ACKNOWLEDGMENTS

I wish to express my sincere thanks to Dr. G. Jones for his help and encouragement during this work. I would like to thank also, Dr. J. D. Baty for some enlightening discussions, and Mrs. J. A. Morrough for the typing of this thesis.

I am indebted to Professor H. D. Springall and the University of Keele for the provision of laboratory facilities, and to Smith, Kline and French Ltd., and the Science Research Council for financial support.

CONTENTS

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

NOMENCLATURE

The use of the name azasteroid will be restricted to steroids in which a nitrogen atom actually replaces one of the carbon atoms of the steroid skeleton, or is inserted as an additional atom in one of the rings. Whenever possible, compounds are named according to "Handbook for Chemical Authors", 1961, or "Chemical Abstracts". Arabic numerals will be used for the sake of simplicity.

TOTAL SYNTHESIS OF AZASTEROIDS

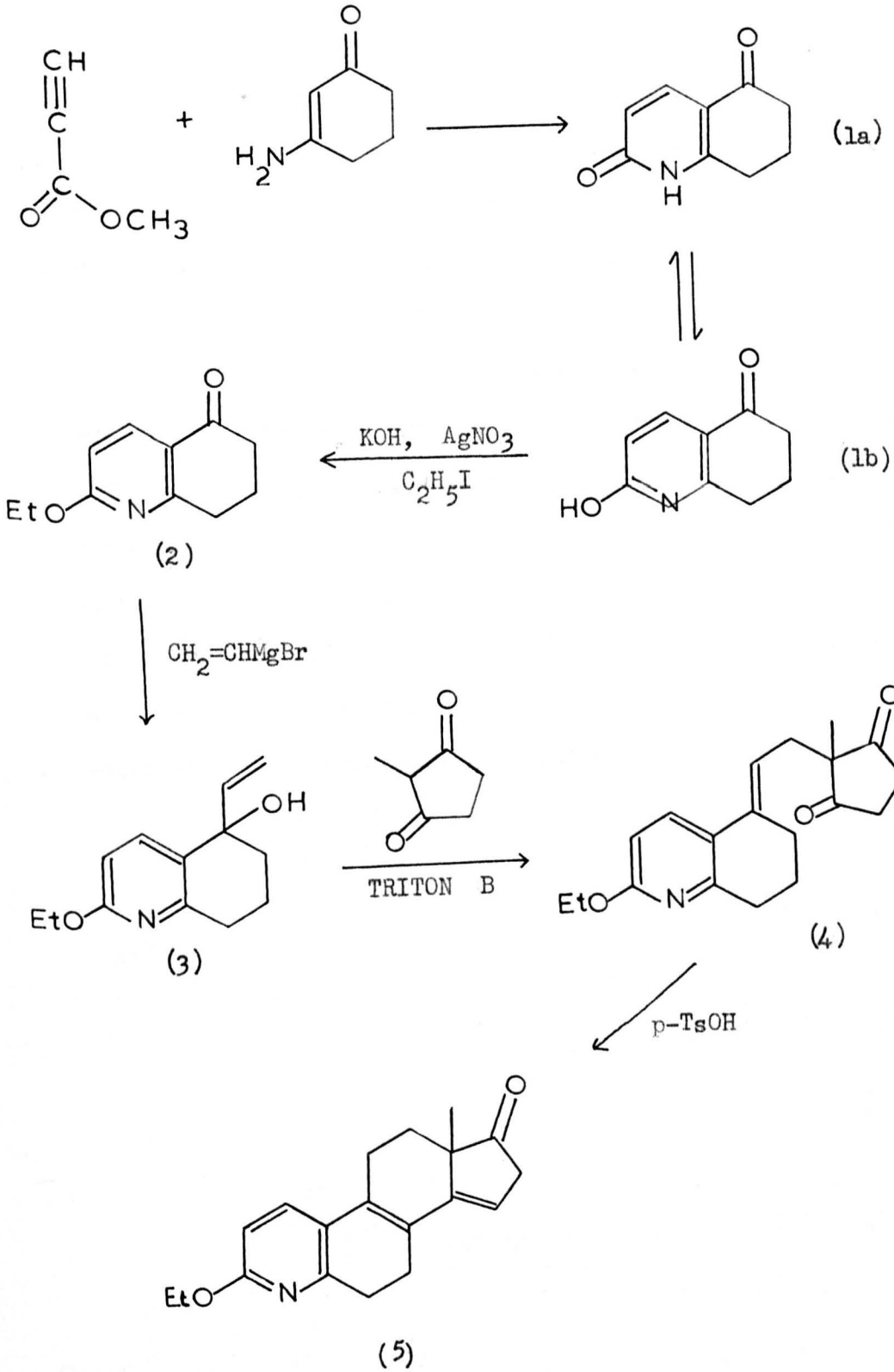
The modification of naturally occurring steroids causes enhancement or suppression of individual biological components of their range of activities. The activity of steroid hormones is, in general, specifically related to their structure, and it has been found that only a limited number of structural variations are possible with retention of biological activity.[1] Synthetic azasteroids are potentially of therapeutic value, since, replacement of trigonal sp^2-carbon by trigonal nitrogen or of tetrahedral sp^3-carbon by tetrahedral positively charged nitrogen,[2] and expansion of one of the rings from six- to seven-membered,[3] produces little modification to overall size or configuration of the steroid molecule. Havranek and Doorenbos proposed that a source of increased biological activity might be the increased electron density produced by the unshared electrons on nitrogen, particularly in ring A azasteroids.[4]

Large numbers of azasteroids have been prepared, but little attention appears to have been devoted to their biological properties. Knof has reported that certain 6-azasteroids have a cytotoxic effect on tumours,[5,6] and Meltzer that 8-azasteroids were useful in the treatment of shock and circulatory collapse in mammals.[7] Cross and his co-workers prepared some 6-azasteroid derivatives and found that they stimulate the action of the pituitary gland and show anti--estrogenic and antiprogestational activities.[8] Scribner found that 4-aza-3,5-cyclocholestane derivatives possessed fungistatic activity.[9]

Doorenbos prepared and tested a number of azasteroids,[4,10,11] showing that they have potentially useful biological activities such as antimicrobial, anti-inflammatory,[12] hypocholesterolemic,[13] central nervous system stimulant or depressant, and hypotensive properties.

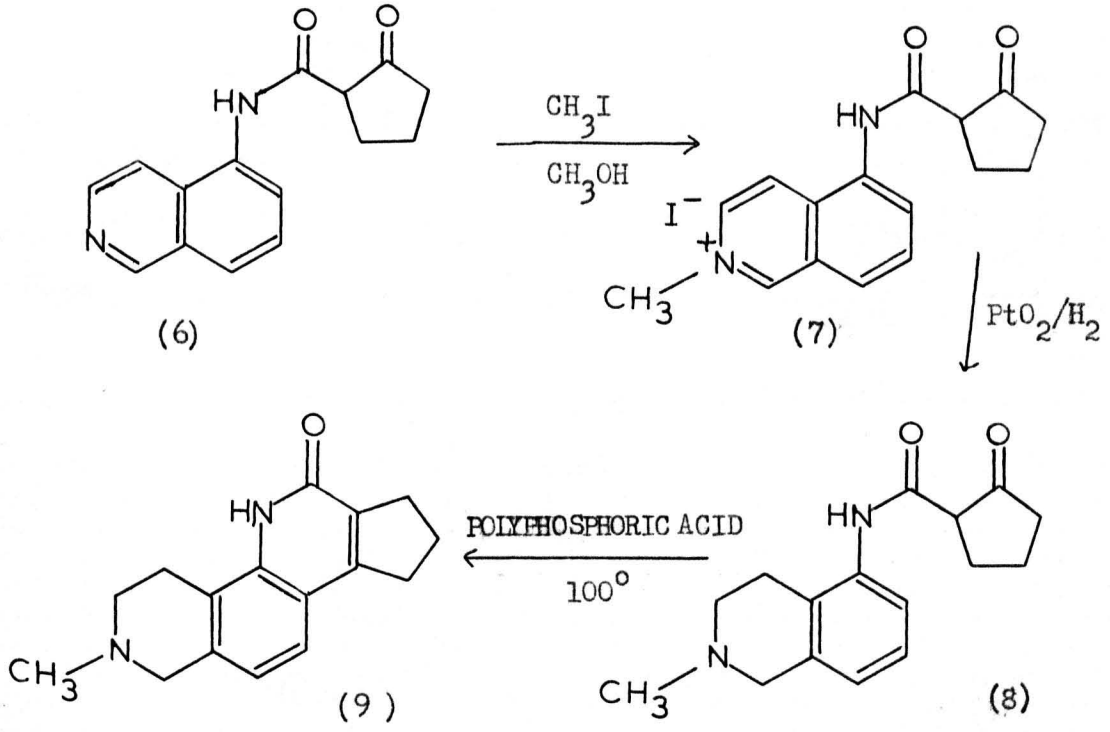
In contrast to the synthetic work on partial synthesis of azasteroids and azahomosteroids from natural steroids, very little work on the total syntheses of azasteroids has been described until recently. Up until 1962, no total synthesis had been accomplished, and no azasteroid with a nitrogen atom replacing one of the tertiary carbon atoms of the steroid nucleus were known. In 1963-68, several total syntheses of azasteroids were announced, including the preparation of some azasteroids incorporating a nitrogen atom at one of the bridgehead positions.

Huisman reported the synthesis of 4-aza-8,14-bisdehydro-estrone ethyl ether (5) which may be considered useful as a key intermediate for the preparation of 4-aza-19-norsteroids.[14] Methyl propiolate was condensed with 3-aminocyclohexenone-2 to give the di-quinolone (1). The silver salt of (1b) was refluxed with ethyl iodide to give the ketone (2). The latter was treated with a fivefold excess of vinyl magnesium bromide to afford the vinyl alcohol (3), which was isolated as an oil and utilised in the next step without further purification. The alcohol (3) was condensed with 2-methylcyclopentane-1,3-dione, in the presence of Triton B reagent, to give the crystalline tricyclic diketone (4) in good yield, which was cyclised to the 4-azasteroid skeleton


CH
C
C
O
OCH3
+
H2N
O
N
H
(1a)
(1b)
HO
KOH, AgNO3
C2H5I
EtO
(2)
CH2=CHMgBr
OH
(3)
TRITON B
(4)
p-TsOH
(5)

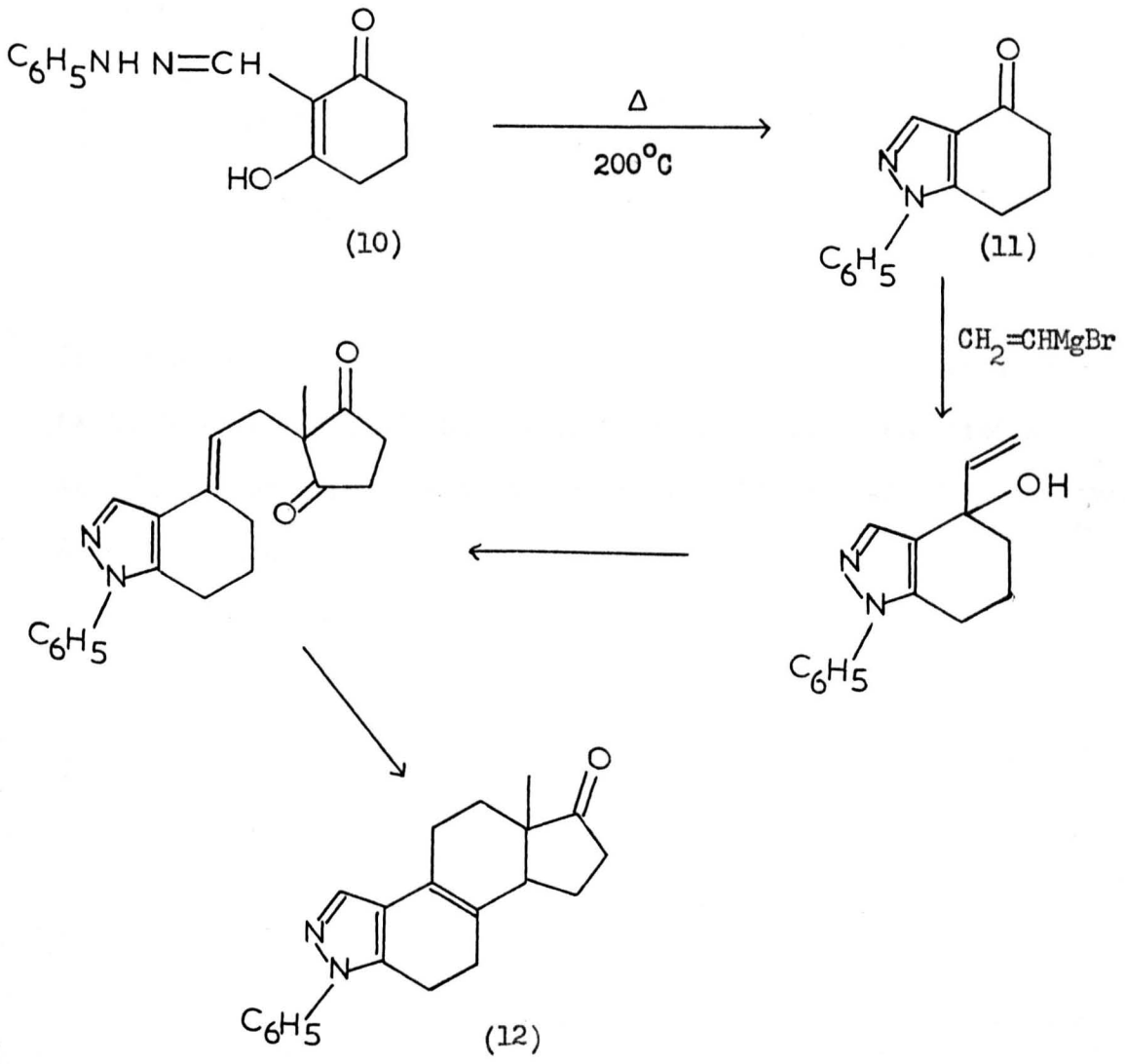
by boiling under reflux with toluene in the presence of slightly over one equivalent of p-toluenesulphonic acid.

A possible route to a 3,11-diazasteroid was reported by Popp and his co-workers by the reaction of aryl amines with 2-ethoxycarbonyl-cyclopentanone.[15,16] Bew and Clemo had previously attempted unsuccessfully to use this route to diazasteroids.[17] The amide (6) was prepared by heating 2-ethoxycarbonyl-cyclopentanone with 5-aminoisoquinoline and the methiodide (7) was obtained in 90% yield by boiling (6) under reflux with methyl iodide in methanol. The methiodide (7) was reduced catalytically in an aqueous ethanol solvent to give the tricyclic system (8) in good yield. The light brown oil (8) was cyclised without further purification by heating to 100° with polyphosphoric acid, giving 12-keto-1,2,3,4,11,12,15,16-octahydro-3-methyl-3,11--diazacyclopenta(a)phenanthrene (9) as a light yellow solid.

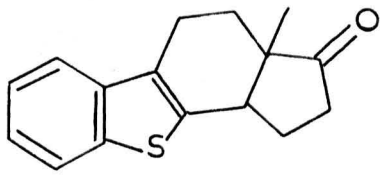


Similar reactions were being carried out with the amide formed from 2-ethoxycarbonylcyclopentanone and 5-aminoquinoline.

In 1967, Lehmann and co-workers synthesised an A-nor-2,3--diazasteroid ring system utilising the phenyl hydrazone (10), which was cyclised by heating to 200° to the 4-oxo-1-phenyl-4,5,6,7-tetrahydroindazole (11).[18] The A-nor-2,3-diazasteroid system (12) was then synthesised using the same reaction sequence used by Huisman to prepare the 4-azasteroid (5).[14]



Tilak successfully synthesised 3-desoxy-6-thia-B-norequilenin (13), and 6-oxa-B-norequilenin (14)[19] by Johnson's equilenin procedure, but the same procedure was unsuccessful in the attempted preparation of 6-aza-B-norequilenin. 7-Methoxy-9-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (15), prepared as shown from 2-hydroxy-methylene--cyclohexanone and m-methoxy-benzene-diazonium chloride, was converted



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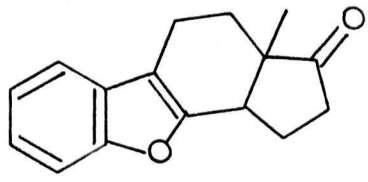
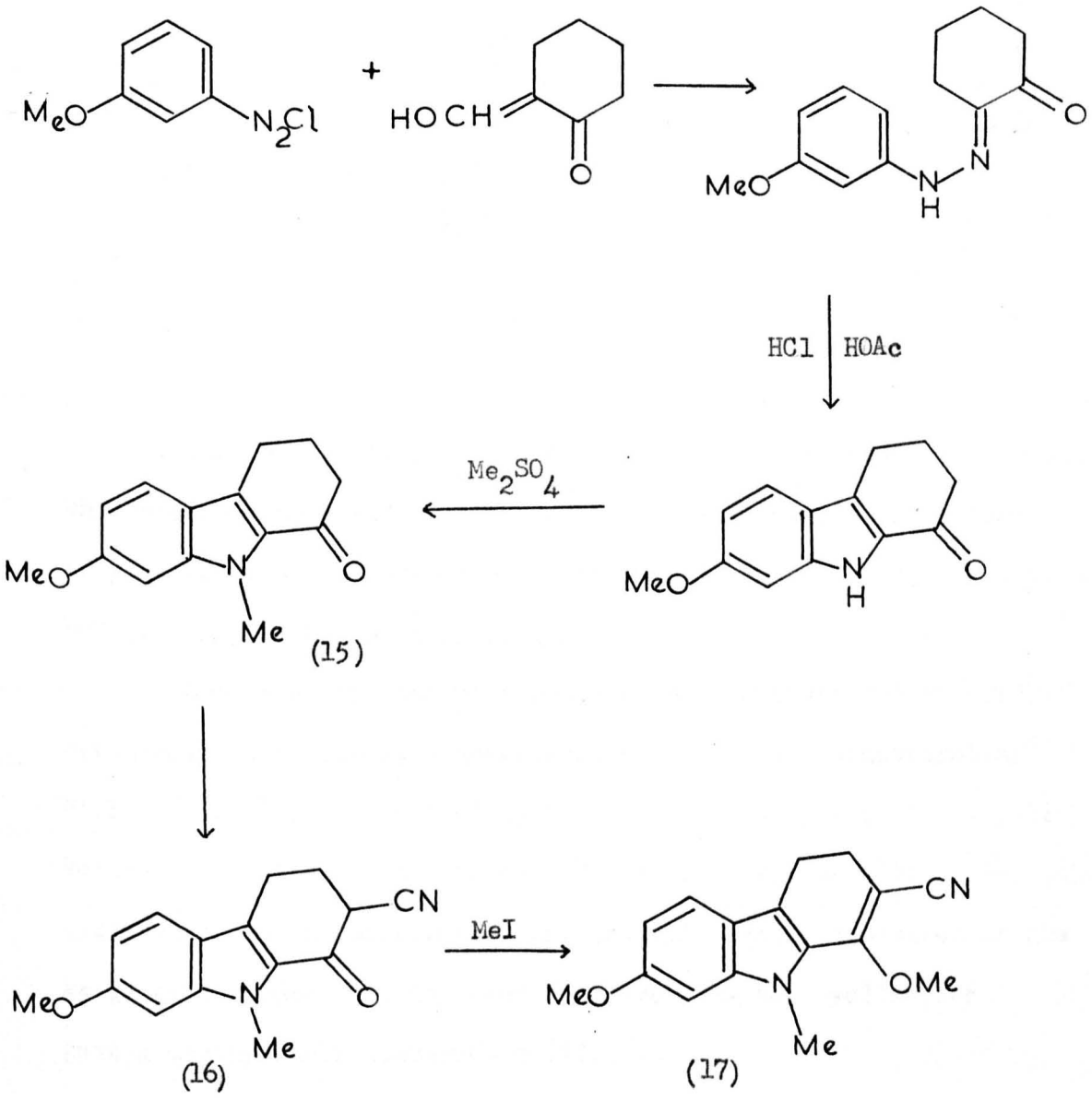
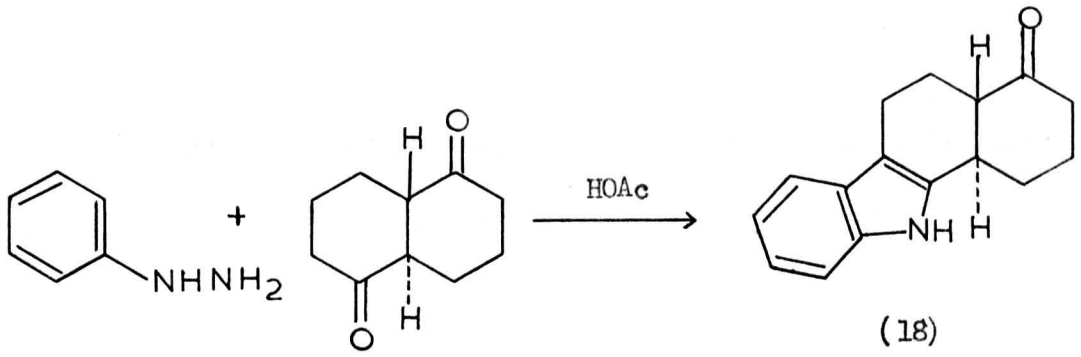


(14)

into 2-cyano-7-methoxy-9-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (16) as in Johnson's method, but further synthesis was prohibited as methylation gave the O-methyl derivative (17) instead of the desired 2-methyl compound.



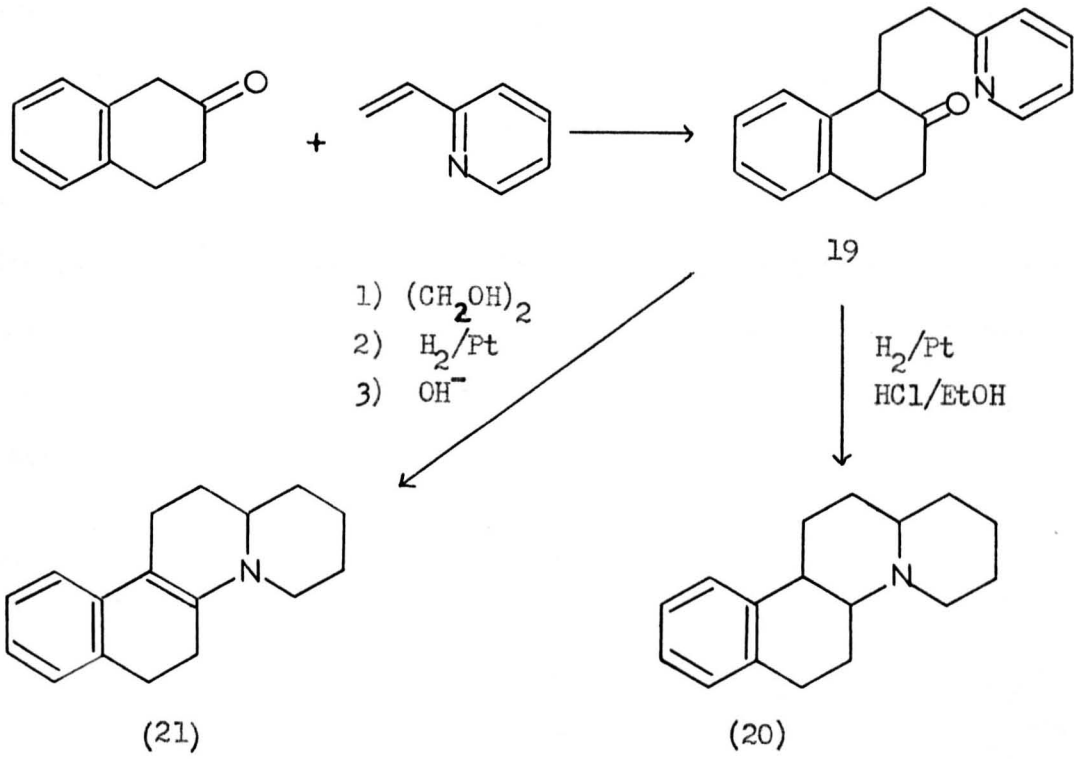
6-Aza-3-desoxy-D-homo-B,18-bisnorequilenin (18) was finally obtained from trans-decalin-1,5-dione and phenylhydrazine in a one-step synthesis by condensation in boiling acetic acid.



(18)

Another approach to 6-aza equilenin was reported by Burckhalter who condensed m-anisidine with several α-cyclopentyl derivatives of β-ketoesters thus preparing compounds with rings A, B, and D intact but this approach was abandoned.

Some azachrysenes were prepared by Lagothetis which may be considered to be 14-aza-D-homosteroids or 10-aza-D-homosteroids.[21] Michael addition of β-tetralone to 2-vinylpyridine gave a tricyclic ketone (19), which gave a $d_6$decahydro-4a-azachrysene (20) on reductive cyclisation in the presence of hydrochloric acid. Reduction of the ketal of compound (19) followed by hydrolysis and cyclisation gave a decahydro-4a-azachrysene (21).



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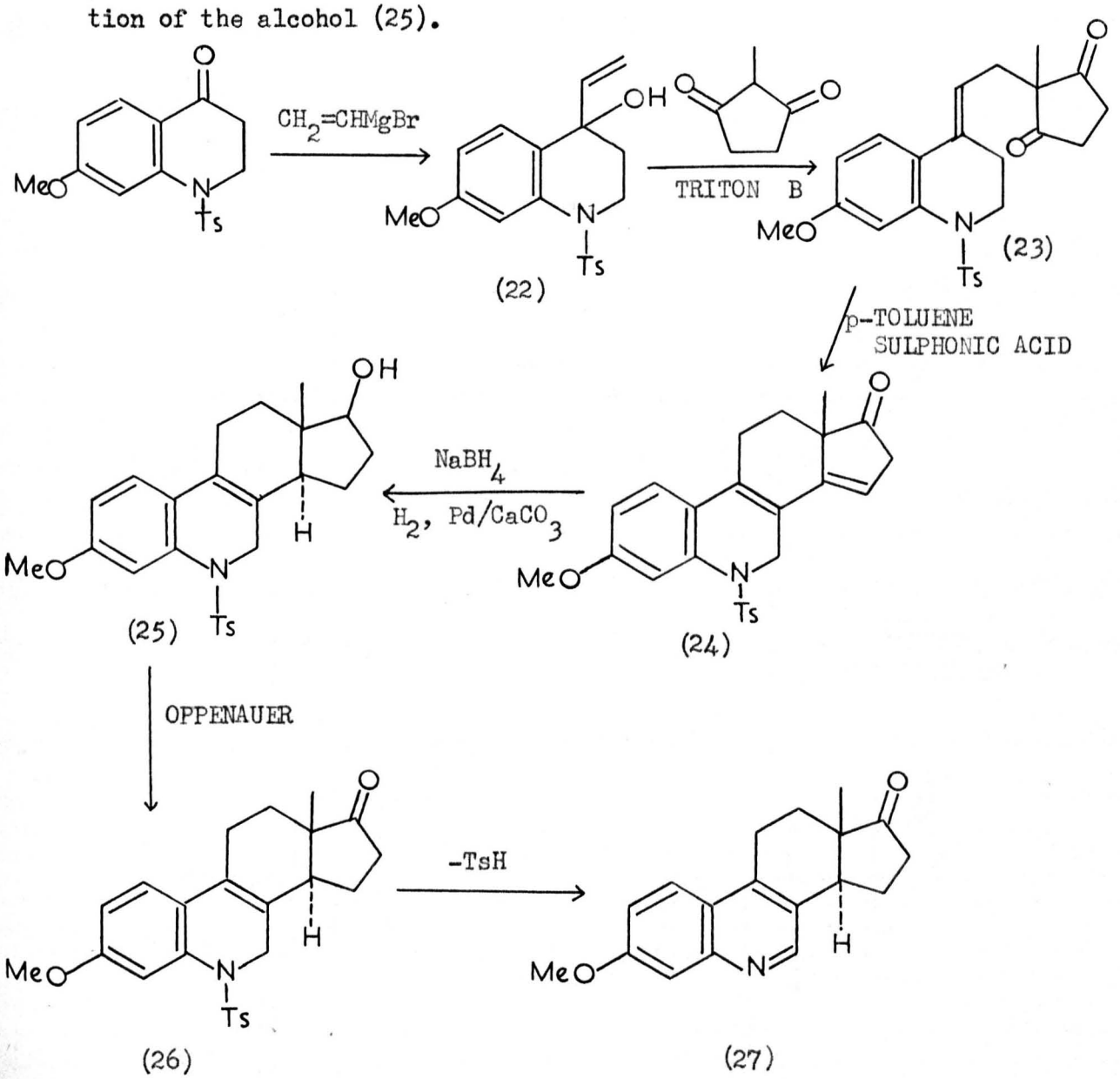
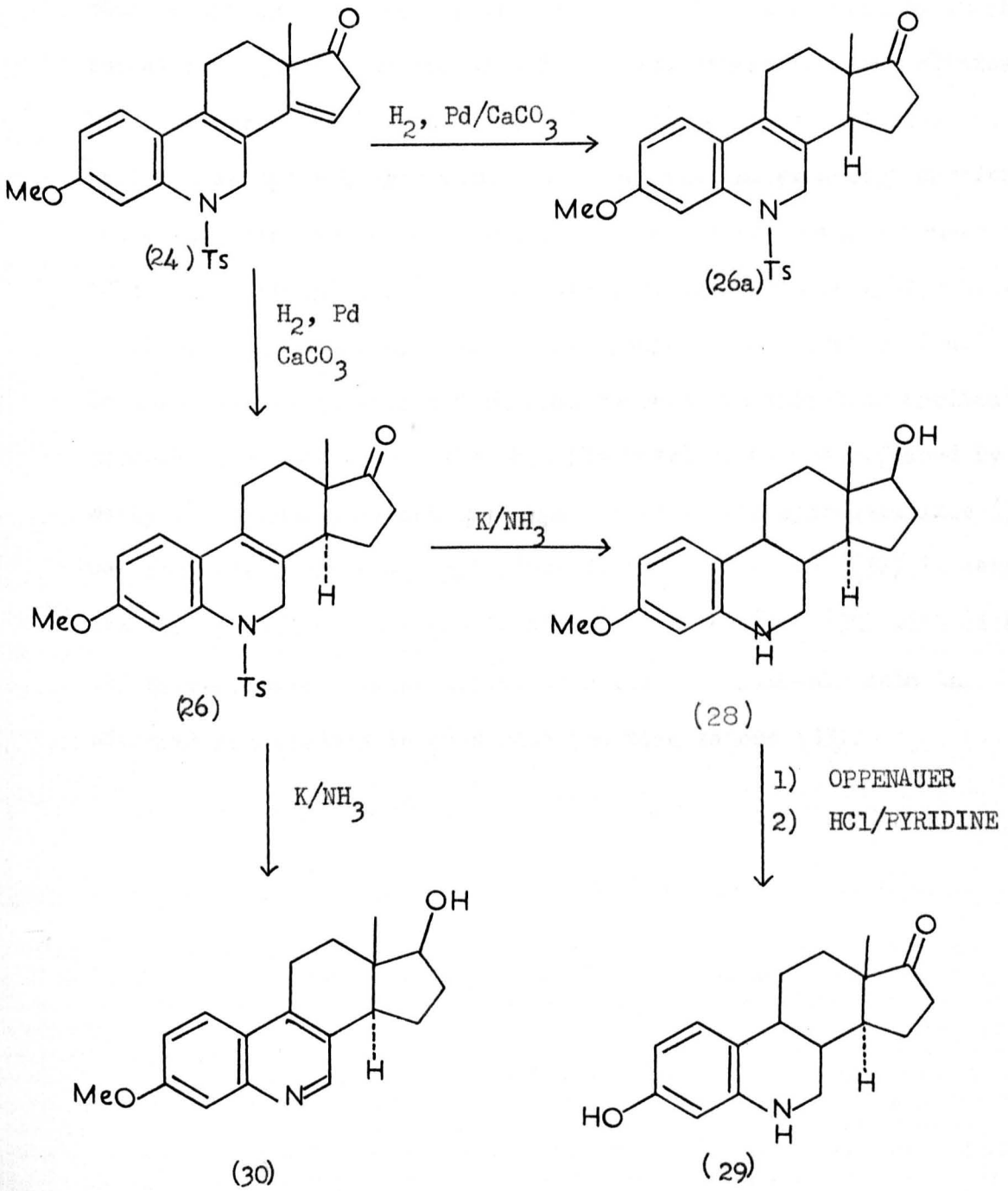
(21) (20)

Rather simple syntheses of 6-azaequilenin and 6-azaestrone derivatives were reported by Huisman[22,23,24] and Smith.[25] Huisman's synthesis involved the addition of vinylmagnesium bromide to 3-methoxy--1,2,3,4-tetrahydro-N-tosyl-4-quinolone giving crystalline allylic alcohol (22), which reacted with 2-methylcyclopentane-1,3-dione in the presence of Triton B to form the diketone (23). Cyclodehydration of (23) to racemic 6-aza-6-tosyl-8,14-bisdehydro-estrone methyl ether (24) was catalysed by p-toluene sulphonic acid. This sequence of reactions was similar to those used by Huisman to synthesise 4-azasteroids[14] and by Lehmann to synthesise ring A di-azasteroids.[18] The 6-aza-ketone (24) was the key intermediate for the synthesis of 6-aza-19-norsteroids.

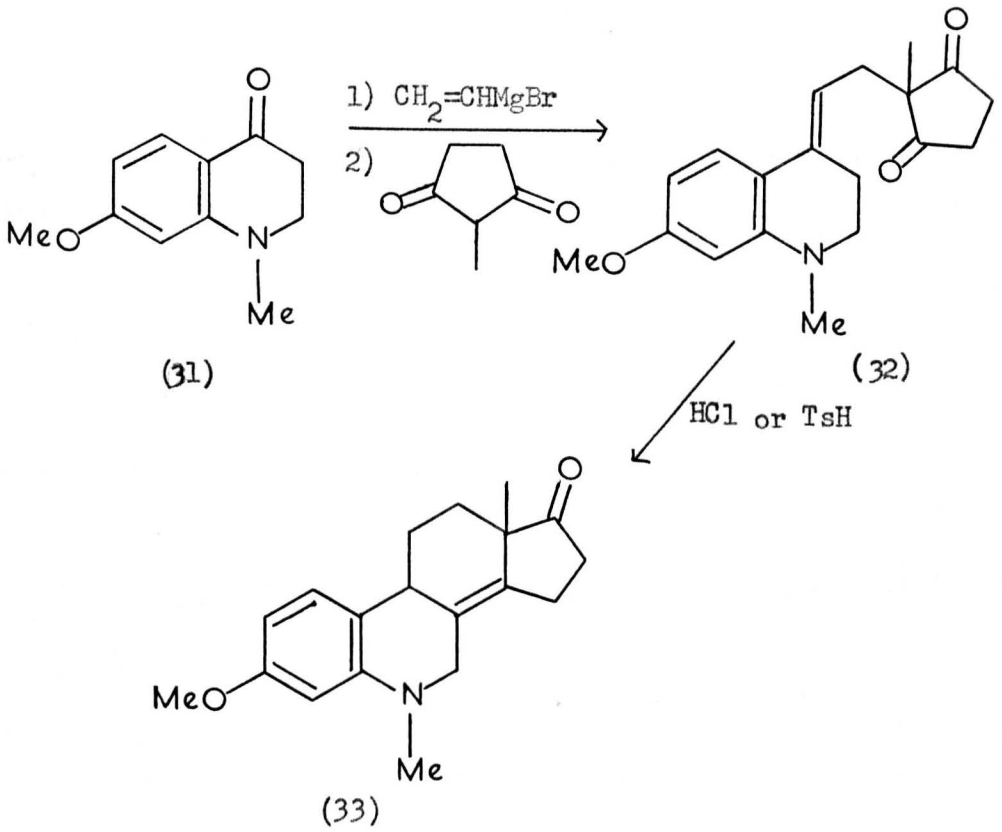
Sodium borohydride reduction of ketone (24) followed by catalytic hydrogenation of the resulting 17β-alcohol, proceeded more or less stereospecifically to the 6-azaestradiol derivative (25), which was oxidised by the Oppenauer method to the 8(9)-dehydro-17-ketone (26). The latter compound on detosylation gave 6-azaequilenin methyl ether (27), identical to that prepared by Burckhalter. 6-Azaequilenin methyl ether (27) was also obtained by detosylation, then chromic acid oxidation of the alcohol (25).



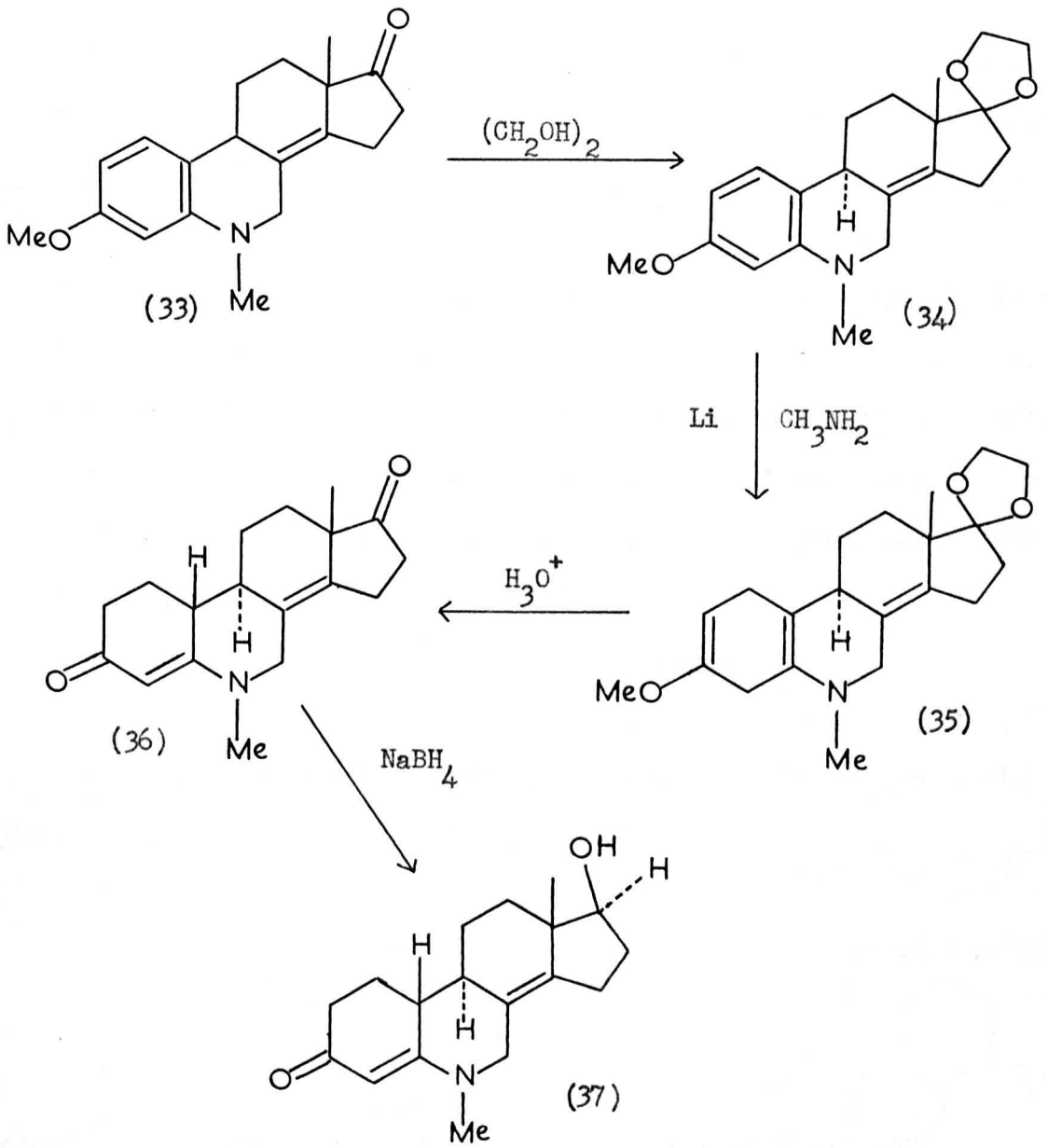
In later work, Huisman and co-workers catalytically reduced the 6-azaketone (24) to a mixture of two isomeric 14,15-dihydro-ketones, the 14α isomer (26) and 14β isomer (26a), which were separated by fractional crystallisation.[24]



When ketone (26) was treated with a calculated amount of potassium metal in liquid ammonia at -80°C, the predominant product was 6-azaequilenin methyl ether (27), with small quantities of the corresponding alcohol (30) and the 6-aza estradiol derivative (28). When an excess of potassium was used, a mixture was obtained which contained a higher portion of (28). 6-Azaestrone (29) was obtained by Oppenauer oxidation of alcohol (28) and then demethylation using pyridine in hydrochloric acid. Smith et al. independently carried out a very similar set of reactions.[25] Kessar reported a number of routes for obtaining N-protected derivatives of 3-methoxy-1,2,3,4--tetrahydro-4-quinolone used in the synthesis of 6-azasteroids.[26] In 1966, van Veltbuysen and Huisman reported an anomolous cyclisation product of the diketone (23) when the tosyl group was replaced by methyl.[27] N-Methyl-7-methoxy-4-oxo-1,2,3,4-tetrahydroquinoline (31) was converted, via the vinyl alcohol, to the diketone (32) in essentially the same procedure used previously.[22] Treatment of (32) with either 18% hydrochloric acid in T.H.F. or p-toluene sulphonic acid in nitromethane yielded in each case the same ketone (33).

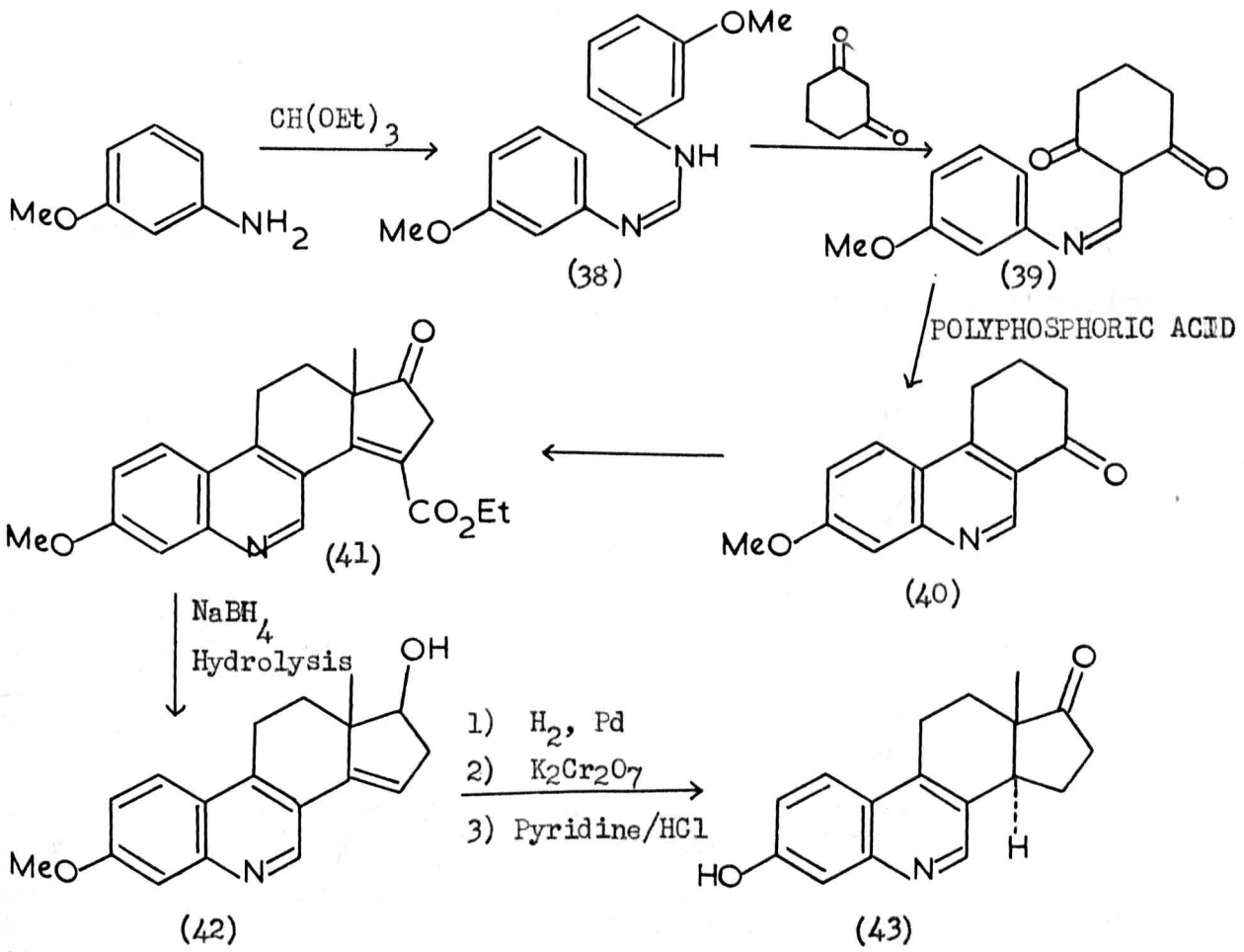


This anomolous cyclisation leading to (33) rather than the racemic 6-aza-6-methyl-8,14-bisdehydro-estrone methyl ether encountered in previous experiments,[22] involved a net reduction of the system, and was thought to proceed via a disproportionation of the reacting molecule, with hydride transfer at some stage of the cyclisation process. The ketone (33) was converted to its ketal derivative (34), reduction of the latter with lithium in methylamine gave the corresponding enol ether (35) which was directly hydrolysed to ketone (36). Synthesis of 6-aza-N-methyl-19-nor-testosterone system (37) was accomplished by reduction of ketone (36) with sodium borohydride.

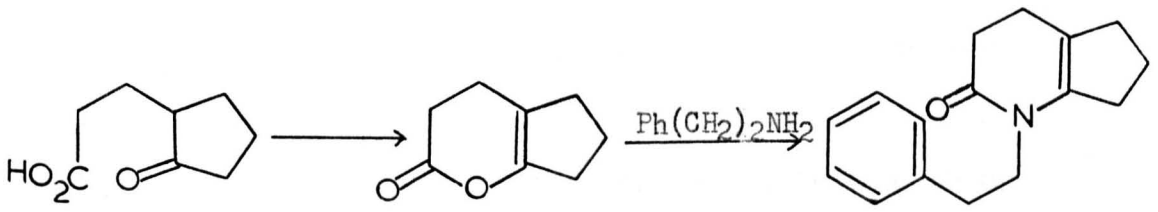


In 1963, Bunkhalter and Watanabe effected a total synthesis of 6-azaequilenin (43) from m-anisidine in fifteen stages.[28] m-Anisidine was condensed with ethyl orthoformate to give N,N'-bis-(3-methoxyphenyl) formamidine (38), which on heating with cyclohexane-1,3-dione gave N-(2,6-dioxohexahydro-benzylidine)-m-anisidine (39). This latter

compound was cyclised with polyphosphoric acid to 2-methoxy-5,6,7,8--tetrahydro-8-oxophenanthridine (40), which was converted by Johnson's Stobbe procedure into 6-aza-15-ethoxycarbonyl-3-methoxy-17-oxoestra--1,3,5(10),6,8(9),14(15)-hexaene (41). Stereo-specific sodiumborohydride reduction to the 17 β-hydroxy derivative, followed by hydrolysis and decarboxylation, gave 6-aza-17β-hydroxy-3-methoxyestra-1,3,5(10),6,8(9),14(15)--hexaene (42). The synthesis of dl-6-azaequilenin (43) was completed by stereospecific hydrogenation of the 14,15-double bond to give C/D-trans fusion, bichromate oxidation of the 17β-hydroxyl group and demethylation with pyridine in hydrochloric acid.

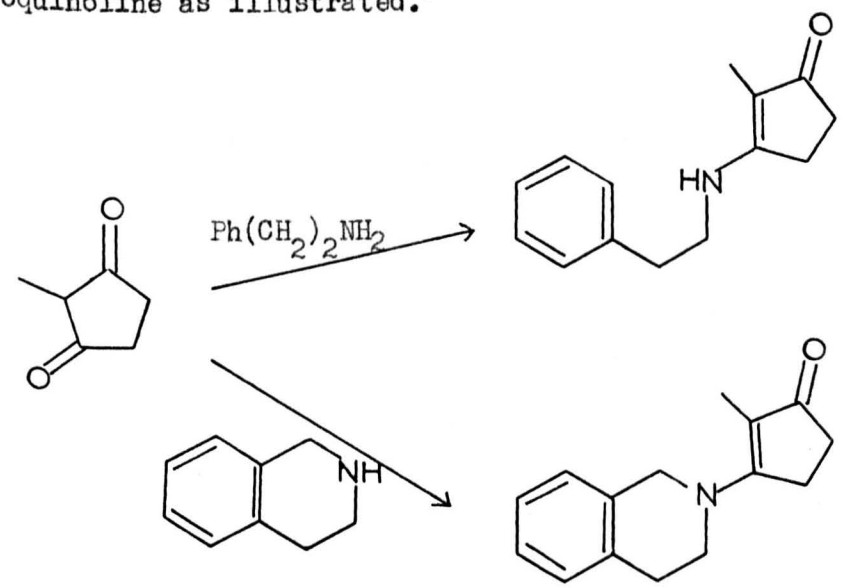


Recently, the synthesis of 8- and 9-azasteroids has been reported by several groups of workers. Kessar et al. have described approaches to 8-azasteroids.[29,30] One method was by the reaction of an amine such as β-phenylethylamine with a lactone such as that (44) obtained from 2-oxocylopentyl-3'-propionic acid, to give the lactam (45).[29]

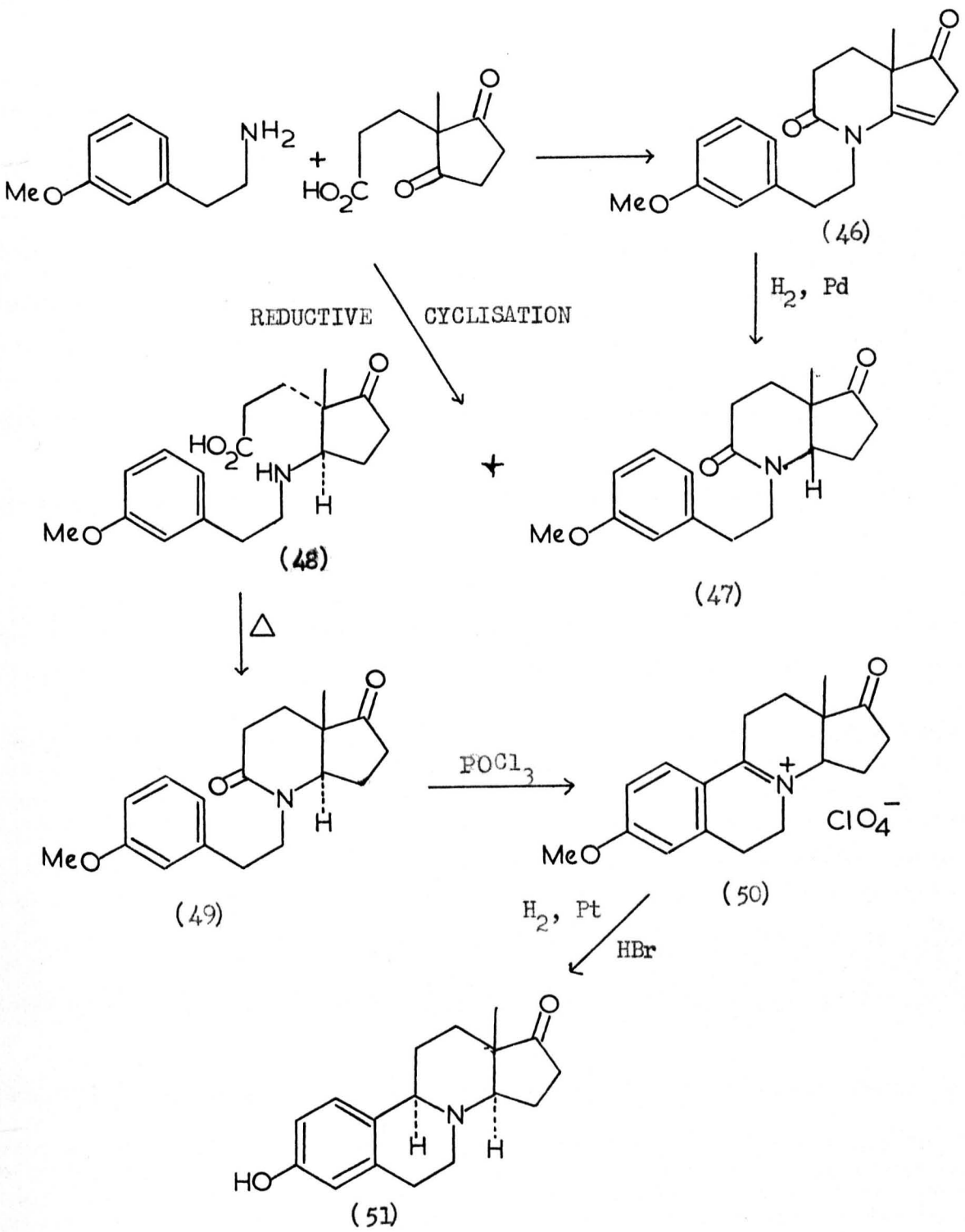


(44) (45)

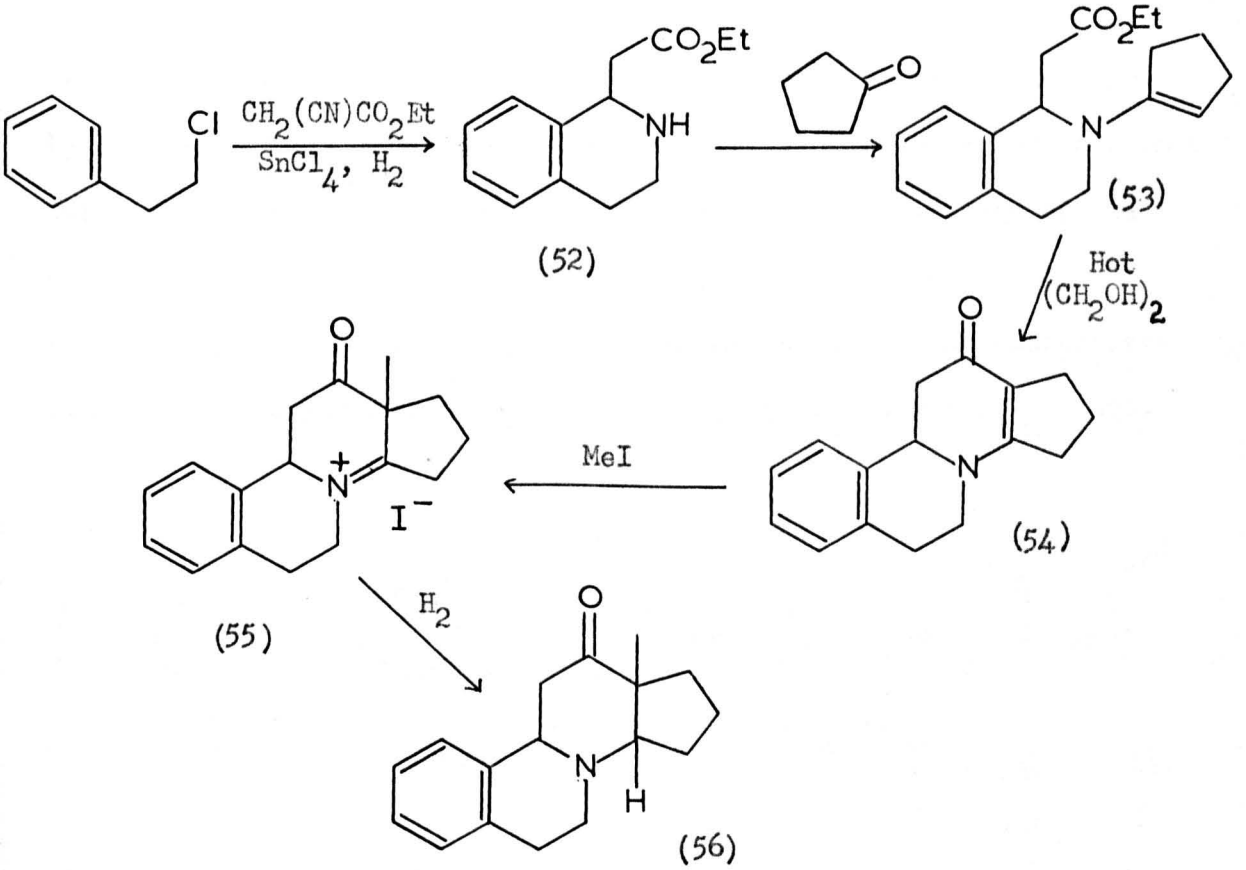
Another method was based on the formation of enamines from 2-methyl--cyclopentane-1,3-dione and β-phenylethylamine or 1,2,3,4-tetrahydroisoquinoline as illustrated.[30]



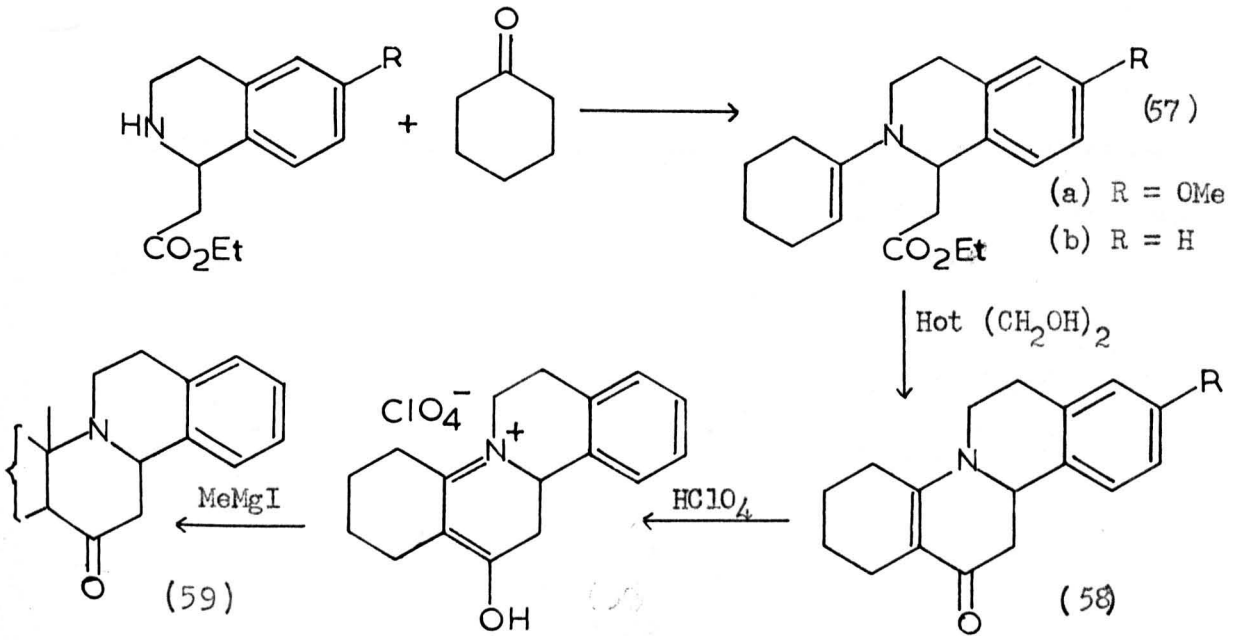
Meltzer and his co-workers made the first preparation of azasteroids with a bridgehead nitrogen and have prepared a variety of 8-azasteroids.[7,31,32,33,42] The methods used by Meltzer are illustrated by the preparation of 8-azaestrone.[32] β-(m-Methoxyphenyl) ethylamine was condensed with 2-β-carboxyethyl-2-methylcyclopentane--1,3-dione to give the unsaturated tricyclic lactam (46) which was stereospecifically reduced to the lactam (47) which had rings C and D cis fused. The C/D trans lactam (49) was obtained when condensation and reduction were carried out simultaneously, when the uncyclised trans-aminoacid (48) was obtained and cyclised by heating above its melting point to (49). Cyclodehydration of the trans lactam (49) gave the quarternary salt (50) which was stereospecifically hydrogenated giving a trans B/C ring fusion. Demethylation then gave dl-8-azaestrone (51). By using substituted β-phenylethylamines and 5- or 6-membered cycloketoacids, Meltzer was able to make a variety of 8-azasteroid systems.[7,31,33]


MeO
NH2
HO2C
O
N
(46)
H2, Pd
REDUCTIVE CYCLISATION
HO2C
HN
H
(48)
+
(47)
Δ
(49)
POCl3
ClO4−
(50)
H2, Pt
HBr
HO
(51)

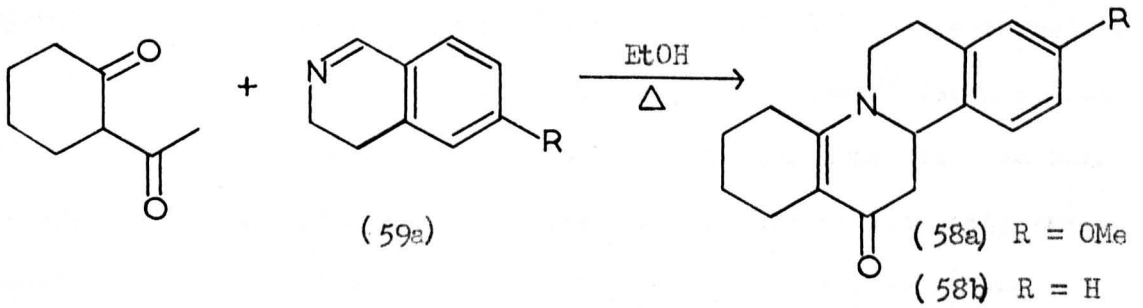
Meyers et al. reported a versatile approach to the 8- and 9--azasteroid system using a common synthetic intermediate (52), prepared by condensing ethyl cyanoacetate with phenylethyl chloride in the presence of stannic chloride, and reduction of the resulting dihydroisoquinoline derivative.[34] For the preparation of 8-azasteroids, the intermediate (52) was condensed with cyclopentanone to give the enamine (53), which was cyclised to the enamino-ketone (54). Methylation of compound (54) with excess methyl iodide gave only the angular methylated quarternary salt (55), which was catalytically reduced to the 8-aza-12-oxoestratriene (56). The ring junctions were originally thought to be B/C trans and C/D cis, but have since been shown to be B/C cis and C/D trans.[41] The 9-aza-D-homosteroid systems were derived



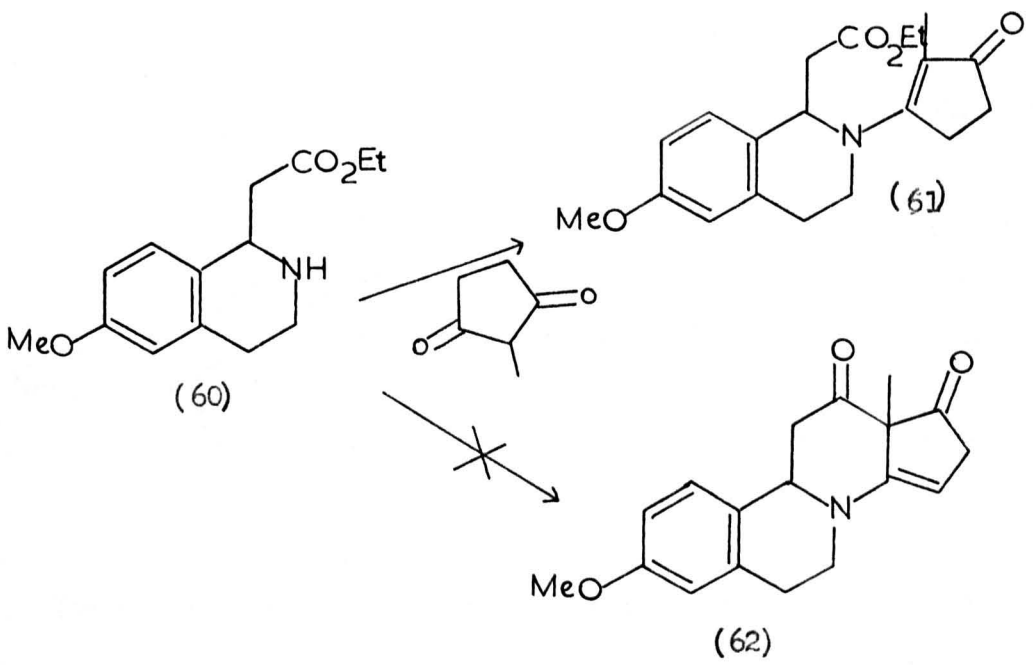
from (52) by a very similar route using cyclohexanone instead of cyclopentanone and outlined below.



The compound (58b) was converted into the methylated derivative (59) by reaction of its perchlorate salt with methyl magnesium iodide. In a later paper, Meyers reported that intramolecular cyclisation of the enamines did not require hot ethylene glycol as solvent.[35] The compound (58) was also synthesised by condensation of the appropriate 3,4-dihydro-isoquinoline (59a) with 2-acetylcyclohexanone in ethanol.[36]

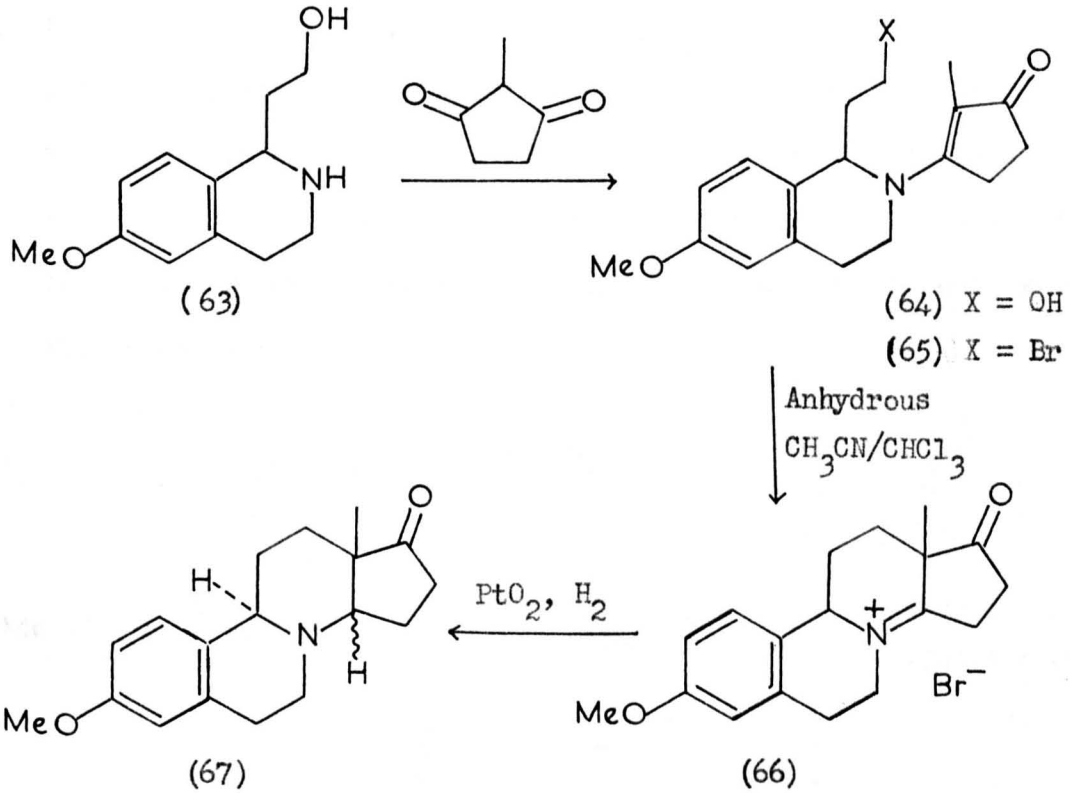


In a logical extension of their previous work on 8-azasteroids, Meyers et al. used cyclic diketones, in place of the monoketones, and the isoquinoline ester (60) in anticipation of obtaining the diketosteroid system (62).[37] When compound (60) was treated with 2-methyl-cyclopentane-1,3-dione, a poor yield of the enaminoketone (61) was obtained, with no trace of the desired diketosteroid system (62).



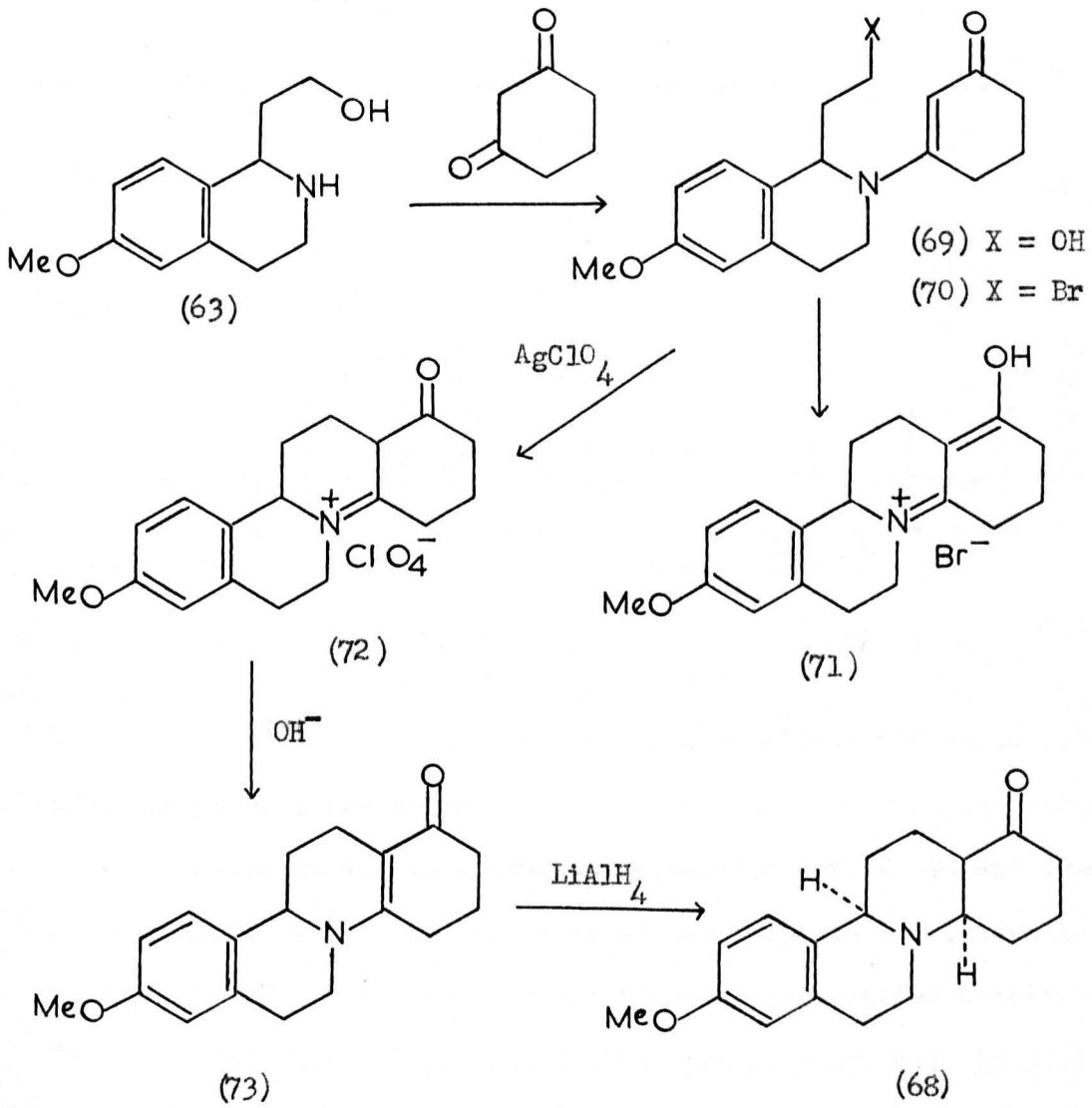
Similar results were obtained when 2-methyl-cyclohexane-1,3-dione and cyclohexane-1,3-dione were reacted with compound (60). An alternative approach to the 8-azasteroid system was from the known[38] isoquinoline alcohol (63), which was converted to the enamino-ketone (64), in high yield, using 2-methyl-cyclopentane-1,3-dione. The alcohol (64) was quantitatively transformed into the bromide (65) using phosphorus

tribromide in chloroform, and cyclised to the unstable iminium salt (66) by prolonged heating in anhydrous acetonitrile.

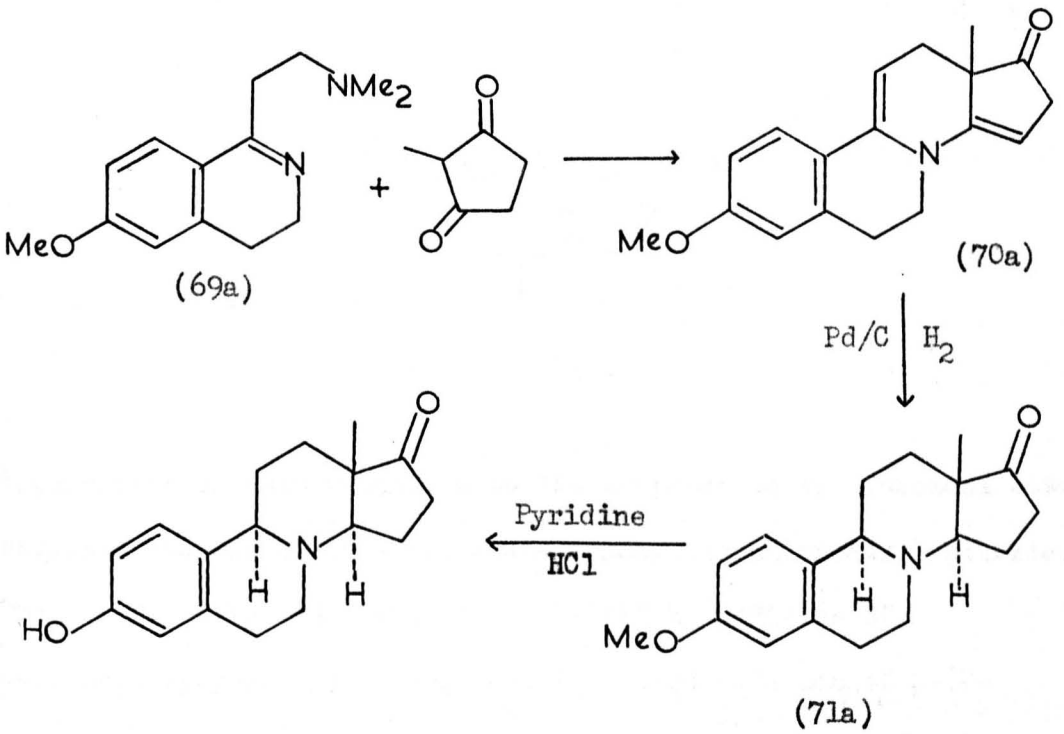


The unstable salt (66) was reduced without purification to the mixture of 14α-and 14β-isomers of 8-azaestrone methyl ether (67), which were separated by fractional crystallisation.[41] Recently, Meltzer et al. reported the total synthesis of 18-nor-D-homo-8-azaestrone (68),[39] using similar methods as for the synthesis of 8-azaestrone methyl ether (67).[37] Compound (68) had previously been synthesised by Nelson and Tamura.[40] The tetrahydroquinoline (63) was condensed with cyclohexane-1,3-dione to give the enamino-ketone (69) which on

treatment with phosphorus tribromide gave the bromide (70). The bromide (70) slowly crystallised to the ionic bromide (71) and hence the bromide (70) was treated immediately after preparation with silver perchlorate in acetonitrile to give the unstable iminium salt (72), which on cautious neutralisation with dilute base gave the ketone (73). Lithium aluminium hydride reduction of ketone (73) led to the 18-nor-D-homo-8-azaestrone (68) which was shown to have a trans-BC and trans-CD ring junction.[39,40]



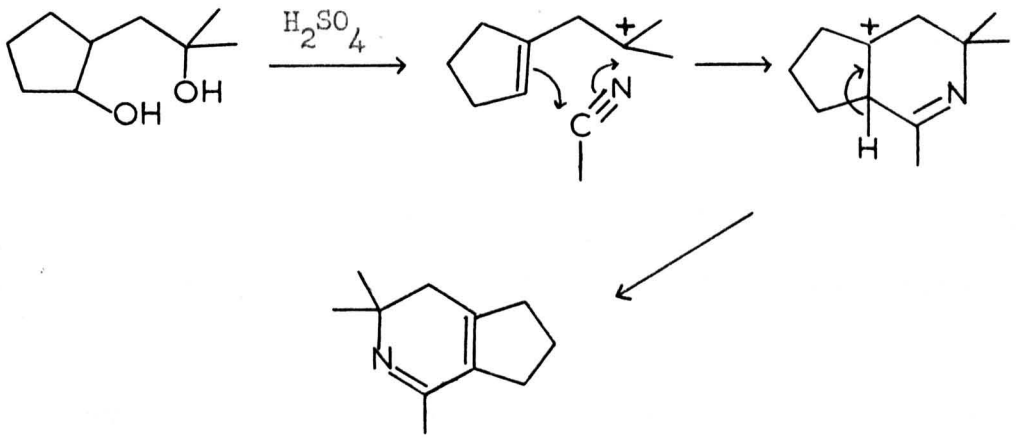
Clarkson described a convenient stereospecific synthesis of (±)-8-azaestrone, using, as the key step, a Michael reaction between 1-(β-dimethylaminoethyl)-3,4-dihydro-6-methoxyisoquinoline (69a) and 2-methyl-cyclopentane-1,3-dione, which gave the tetracyclic dienamine (70a).[43] Catalytic hydrogenation of this dienamine gave the methoxy-azaestrone (71a) which was demethylated using pyridine hydrochloride to 8-azaestrone.



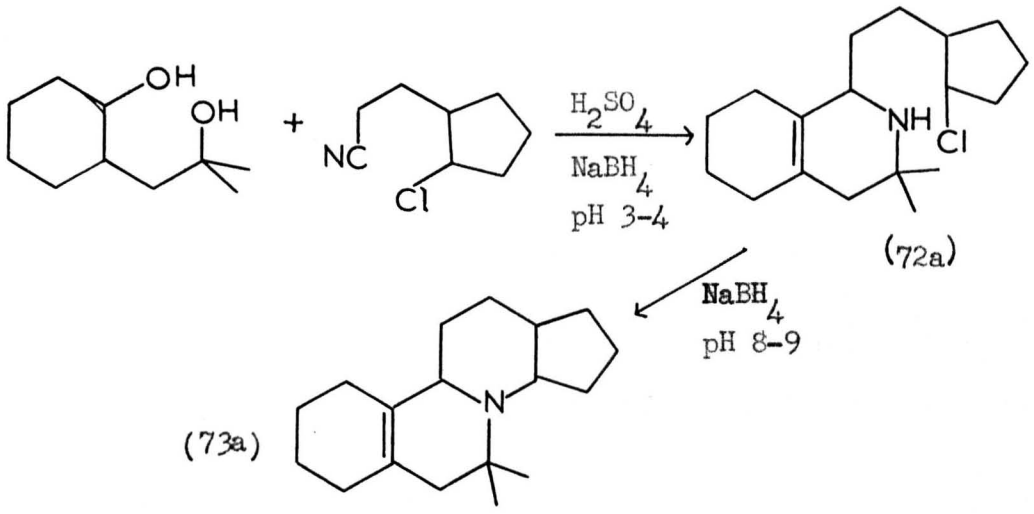
Similar reactions were carried out using 2-methylcyclohexane-1,3-dione producing D-homo compounds.

Meyers et al. reported the preparation of 8-, 9- and 13-aza-steroid systems,[44] as well as several new bicyclic and tricyclic bases,[45-47] by a novel method involving few preparative stages. The essential first stage of all these preparations was the condensation

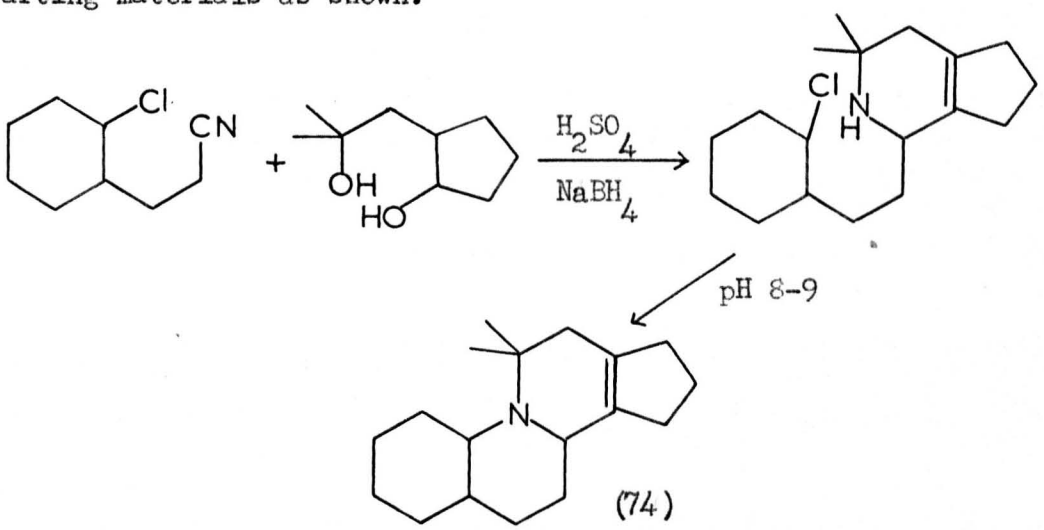
of a tertiary alcohol containing an additional nucleophilic substituent with a nitrile in cold concentrated sulphuric acid, illustrated by the following sequence.[45]

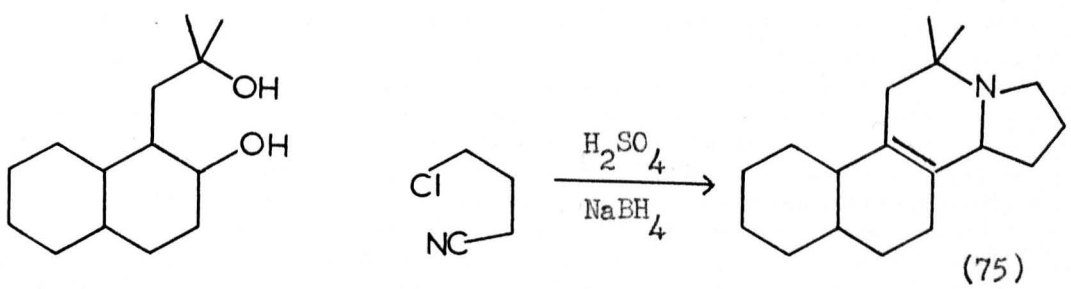


Application of this procedure to the preparation of steroidal bases required the use of an appropriate monocyclic chloroalkyl nitrile.[44] Thus an 8-azasteroid system was obtained by addition of α-(2-hydroxycyclohexyl)-t-butanol to a cold solution of β-(2--chlorocyclopentyl)-propionitrile in excess concentrated sulphuric acid, reduction of the resulting dihydropyridine under weakly acid conditions to the tetrahydropyridine (72a), and cyclisation of the latter under basic conditions to 8-aza-11,11-dimethyl-18,19-bisnorandrost--5(10)-ene (73a).



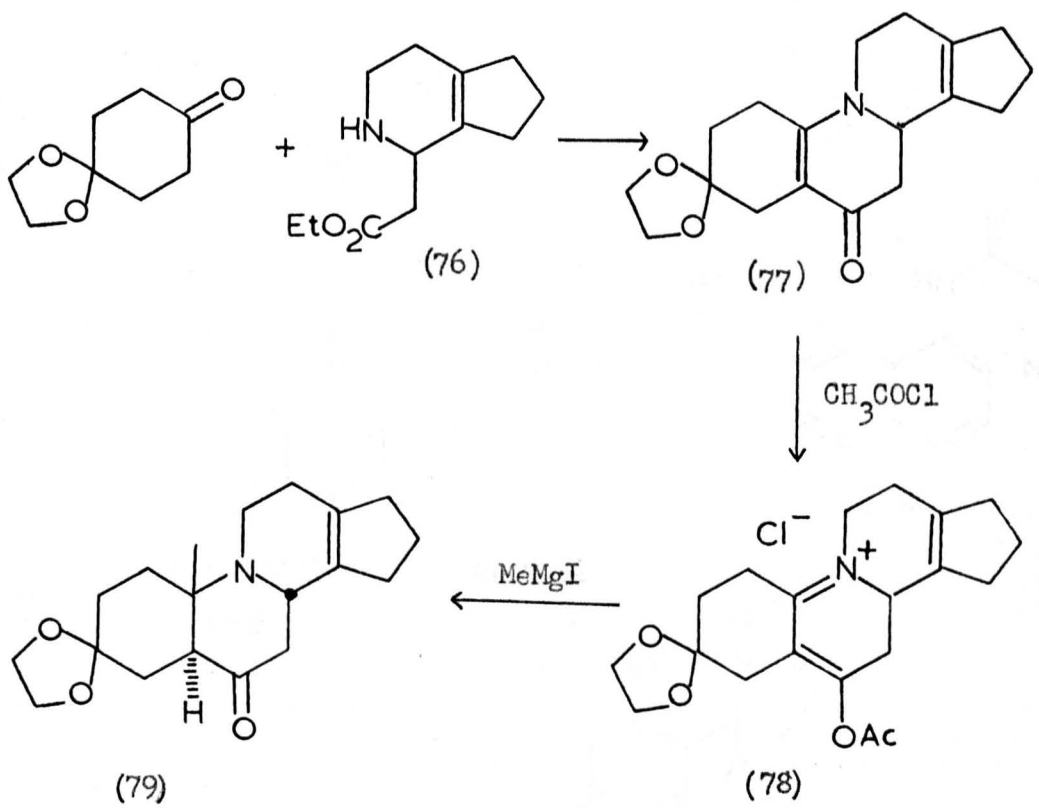
The isolation of the dihydro- and tetrahydropyridines was unnecessary, suitable conditions for the reduction and cyclisation stages being achieved simply by dilution with water and adjustment of the pH. 9-Aza(74)- and 13-aza(75)-steroids were prepared similarly by choice of starting materials as shown.





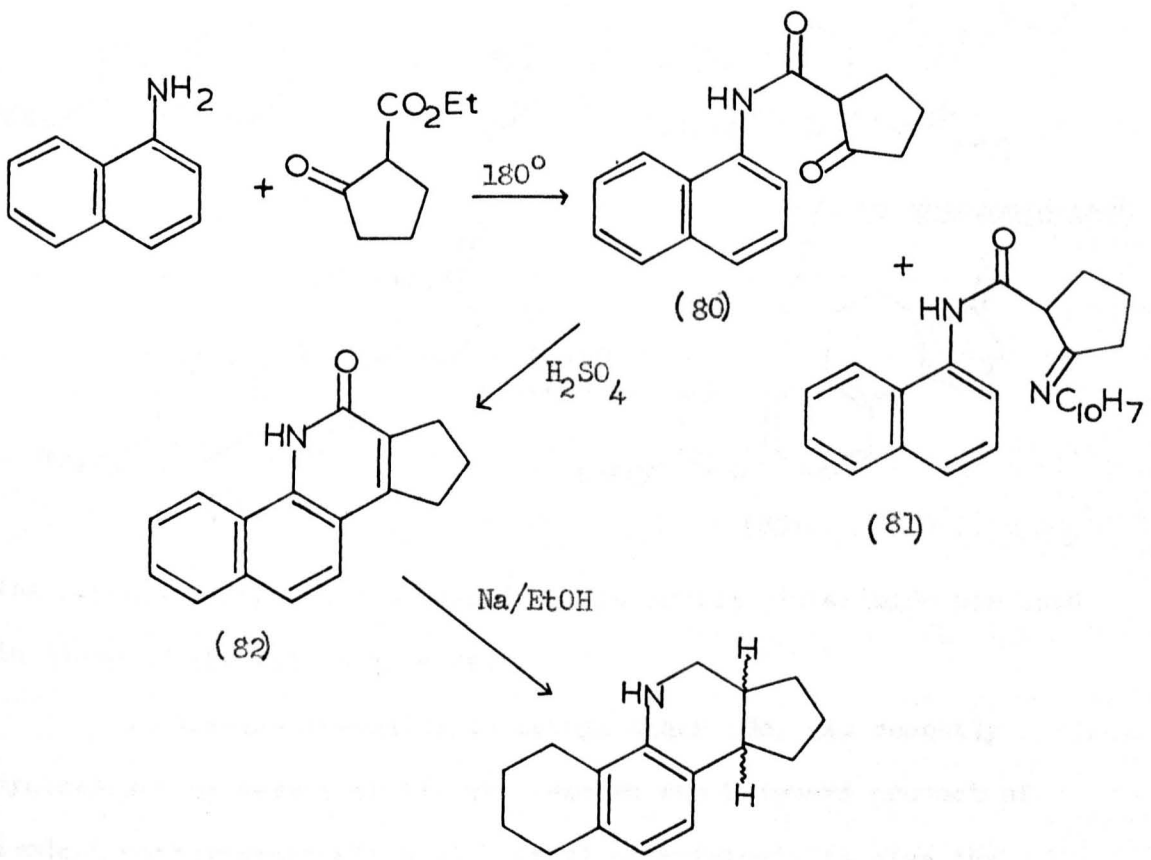
The steroid systems so far produced all possess a gem dimethyl group, as a tertiary alcohol centre was found to be necessary for the generation of carbonium ions.

Very recently, Meyers et al. have reported a facile approach to 3,3-ethylenedioxy-18-nor-9-azaandrost-13(14)-ene-6-one (79) and the related D-homoderivatives.[48] Treatment of the piperidine ester (76) with the monoketal of cyclohexane-1,4-dione in refluxing toluene produced the tetracyclic system (77). Reaction of ketone (77) with acetyl chloride produced the O-acetyl derivative (78) which was used in situ in the reaction with methyl magnesium iodide forming ketone (79).



Spectroscopic evidence supported AB-trans and BC-trans junctions. D-Homoderivatives were also prepared in a similar manner to the above.

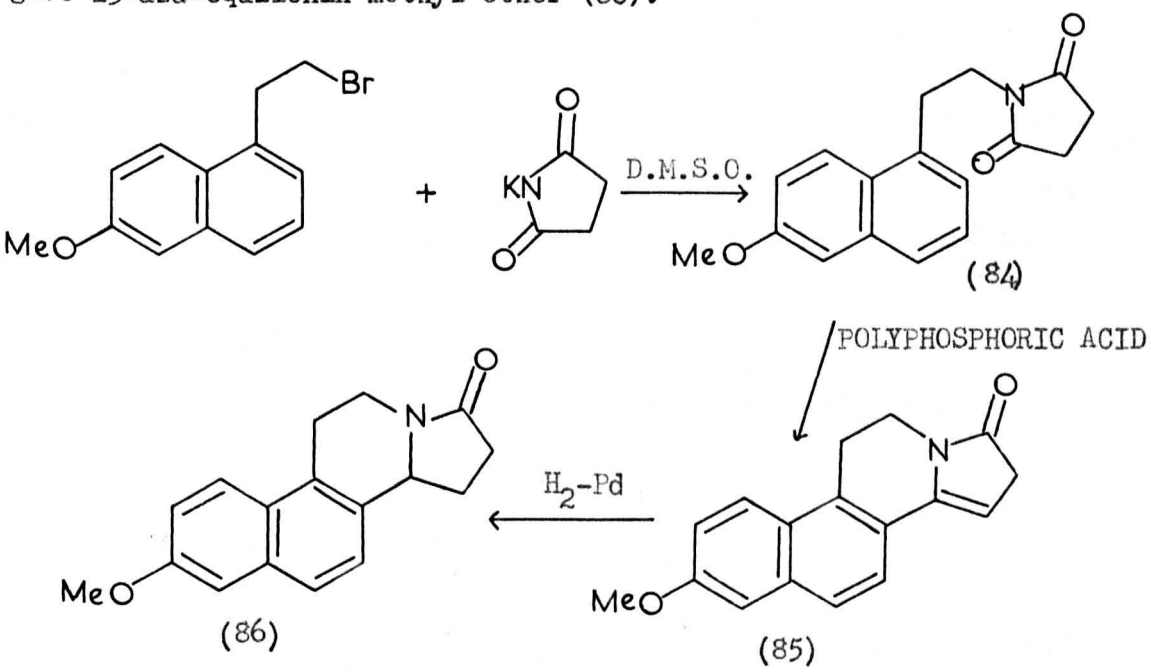
Clemo and Mishra succeeded in preparing compounds which may be considered as 11-aza-18,19-bisnorandrostanes with one or both of rings A and B aromatic.[49] α-Naphthylamine was condensed at 180° with 2-ethoxycarbonylcyclopentanone to give products containing one (80) and two (81) α-naphthylamine residues. The former was cyclised with concentrated sulphuric acid to an 11-aza-$\Delta^{13(14)}$-lactam (82), which on prolonged reduction with sodium in ethanol gave an 11-aza-18,19-bisnorandrosta-5(10),6,8-triene (83).



(83)

Similar reactions were carried out with 5,6,7,8-tetrahydro-1-naphthylamine, and 6-methoxynaphthylamine.

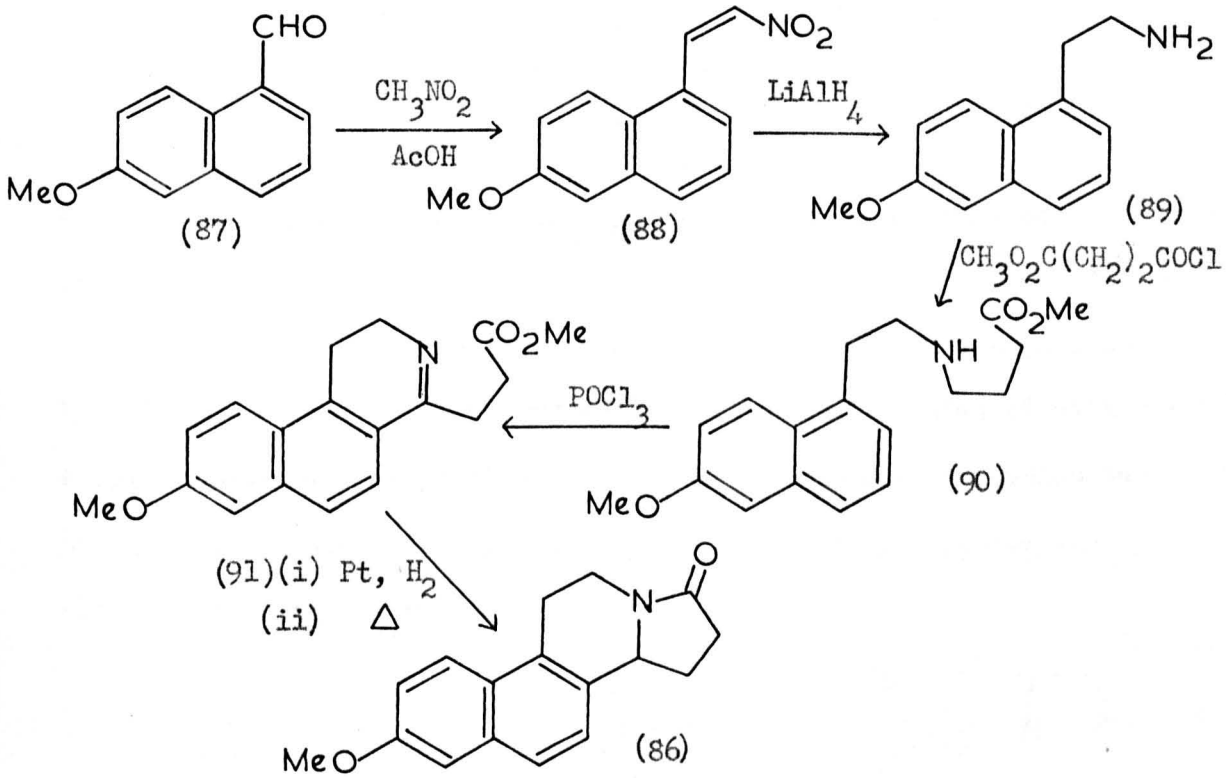
13-Aza- and 13-aza-D-homo-analogues of equilenin methyl ether were synthesised by Birch and Subba Rao.[50] 13-Aza-equilenin methyl ether was synthesised from 1-(2-bromoethyl)-6-methoxy naphthalene and the potassium salt of succinimide, using dimethyl sulphoxide as condensing solvent, to give compound (84) which was cyclodehydrated to the tetracyclic amine (85). Catalytic hydrogenation of amine (85) gave 13-aza-equilenin methyl ether (86).



The D-homo-analogue was obtained whenpotassium glutarimide was used in place of the succinimide salt.

13-Aza-18-nor-equilenin methyl ether (86) was recently synthesised by Kessar et al. who reacted the Grignard product of 1-iodo-6-methoxynaphthalene with ethyl orthoformate to give the aldehyde (87).[51] This aldehyde was condensed with nitromethane in

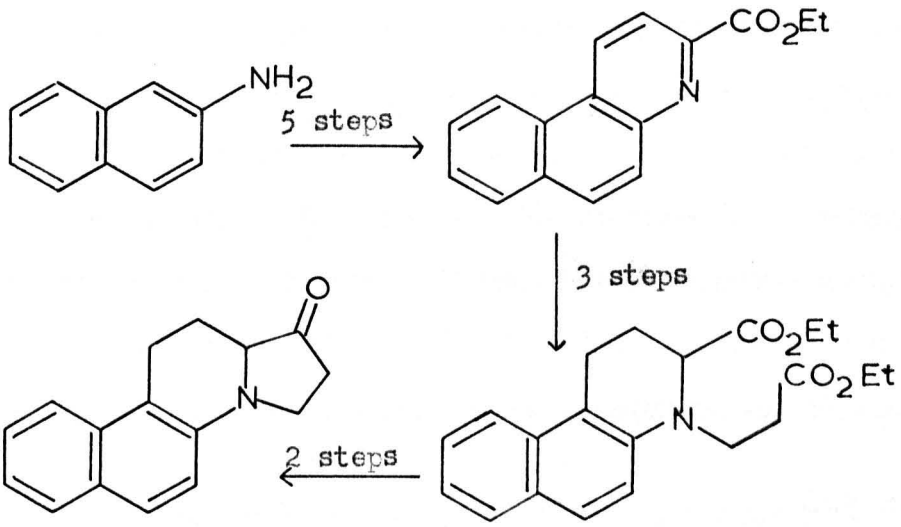
acetic acid and the product (88) reduced with lithium aluminium hydride to obtain the amine (89). The amine (89) was condensed with 3-methoxycarbonylpropionyl chloride to yield the amide (90) which was cyclised with phosphorus oxychloride to the tricyclic amino-ester (91). On hydrogenation, using platinum in acetic acid, the amino-ester (91), yielded a compound which was cyclised thermally to give (±) 13-aza--18-norequilenin methyl ether (86).



The amide (86) was also isolated in low yield from a single step condensation of amine (89) with 2-ketoglutaric acid in refluxing acetic acid.

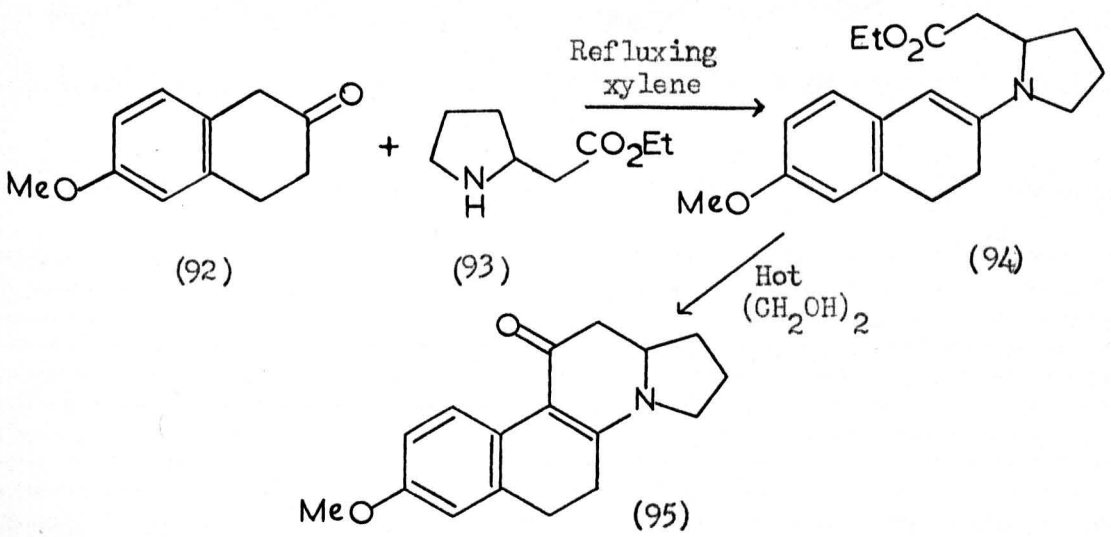
14-Aza-3-desoxy-18-nonequilenin was prepared by Poirier et al. through a sequence of reactions starting from 2-naphthylamine,[52]

as shown.

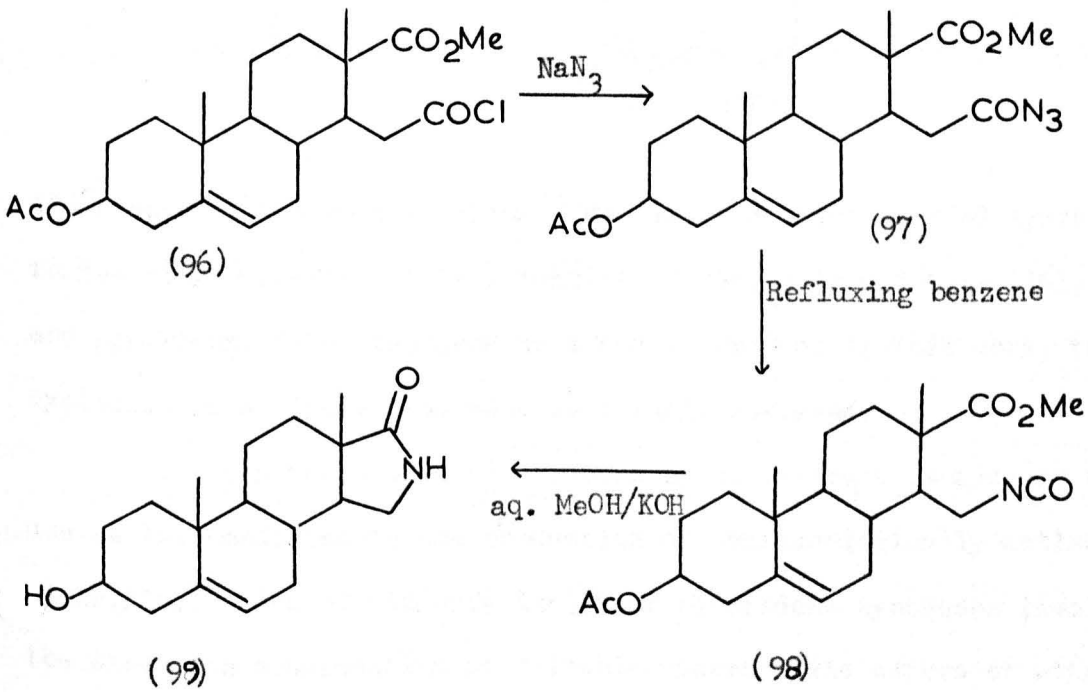


Popp and Schleigh used a similar approach to the synthesis of 14-azasteroids.[53]

Recently, a general approach to 14-azasteroids was published by Huisman et al.[54] 6-Methoxytetralone-2 (92) was condensed with ethyl 2-pyrrolidylacetate (93) to produce the enamine (94) which was heated for 19 hours in ethylene glycol to produce the 14-aza-11--keto-steroid system (95).



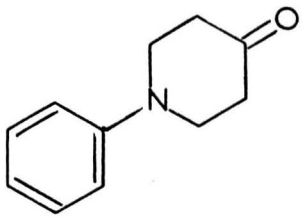
In 1968, Kierstead reported the synthesis of a 16-azasteroid system. 1,2,3,4,4a,4b,5,6,7,8,10,10a-dodecahydro-7-acetoxy-1-(chlorocarbonylmethyl)-2,4b-dimethyl-2-phenanthrene carboxylic acid methyl ester (96) was treated with sodium azide in aqueous acetone to give the corresponding 7-hydroxy-1-azidocarbonylmethyl compound (97). Refluxing azide (97) in benzene afforded the 1-isocyanatomethyl compound (98), which on hydrolysis and cyclisation in aqueous methanolic potassium hydroxide gave 3β-hydroxy-16-aza-androst-5-en-17-one (99).



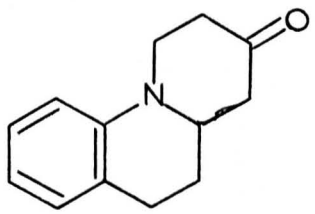
(96) (97) (98) (99)

SYNTHESIS OF 4-PIPERIDONES

The structures of N-phenyl-4-piperidone (100) and 1,2,3,4,5,6-hexahydro-3-oxo-4aH-benzo(c)quinolizine (101) are shown below. The two ring systems are essentially the same and



(100)

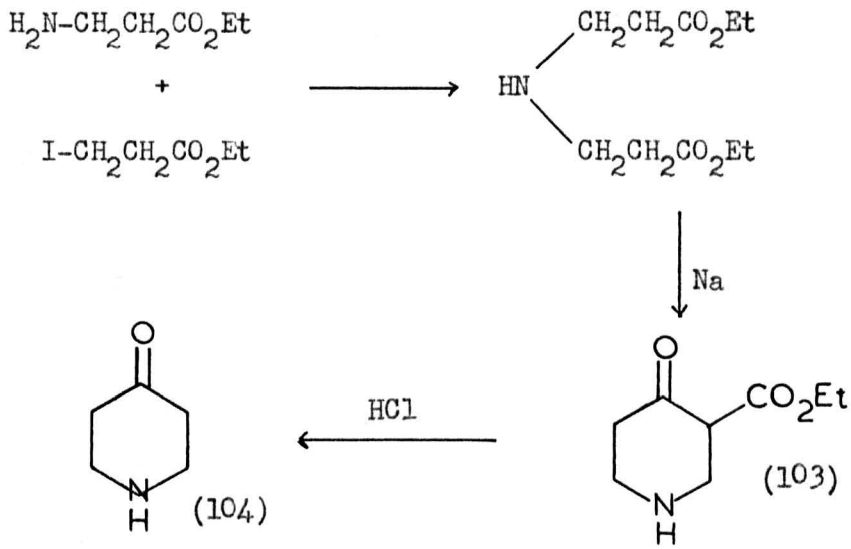


(101)

since some of the work in this thesis is an attempt to find synthetic routes to a 9-azasteroid by formation of ring D from ketone (101), and piperidone (100) was used as a model compound in this work, the syntheses of 4-piperidones will be briefly reviewed.

The synthesis of 4-piperidones is of interest because of their use as intermediates in the production of pharmacologically active materials.[56] One of the more important piperidone syntheses involves the Dieckmann condensation of suitable dicarboxylic esters or nitriles, in which the ring closure is completed between the carbon atoms in the β, ɣ positions. The first of such ring closures was reported by Ruzicka and Fournasir, who first sought to prepare 4-piperidone from 4-pyridone by catalytic hydrogenation but obtained 4-piperidinol.[57] They treated ethyl β-iodopropionate with ethyl β-aminopropionate to

to obtain di-(β-ethoxycarbonylethyl)amine (102). On treatment with sodium, this gave a poor yield of 3-ethoxycarbonyl-4-piperidone (103). The product was hydrolysed and decarboxylated to 4-piperidone (104).

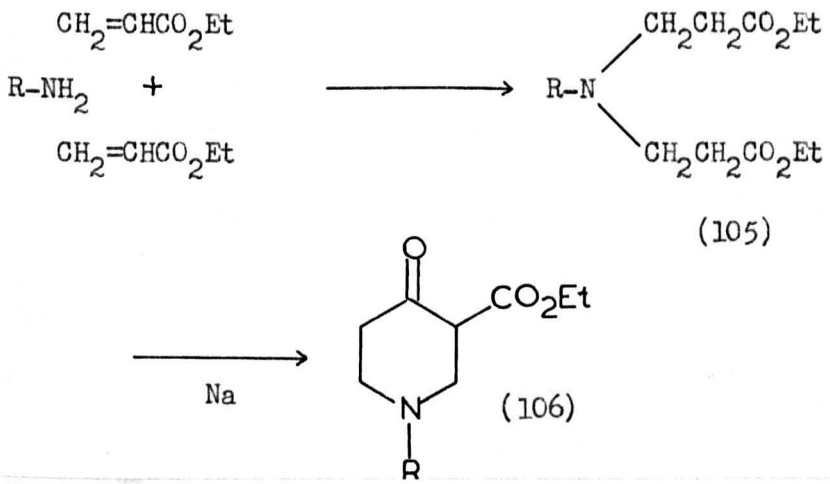


(102)

(103)

(104)

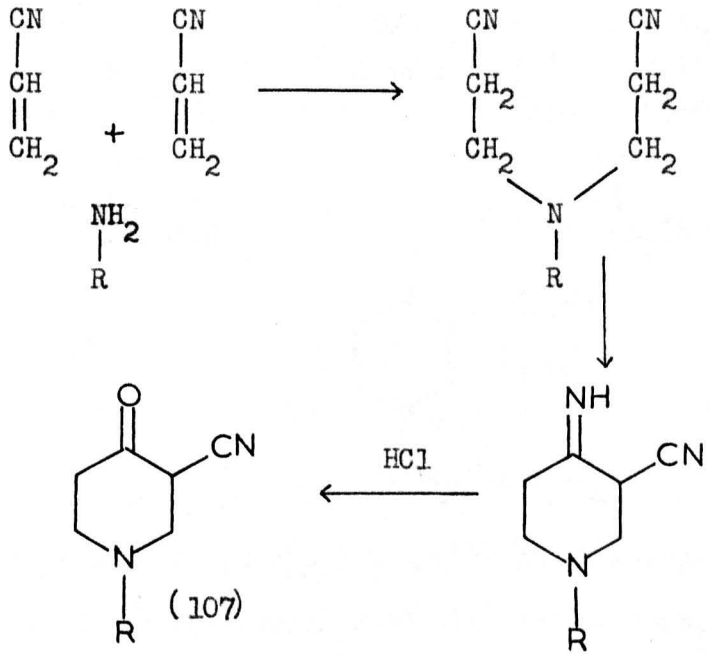
Further study of the Dieckmann reaction resulted in a slightly better procedure but still with low yields.[58] However, higher yields have been reported when a tertiary amine is employed.[59-67] In addition, the starting esters (105) were made in excellent yields by addition of primary amines to ethyl acrylate.[62]



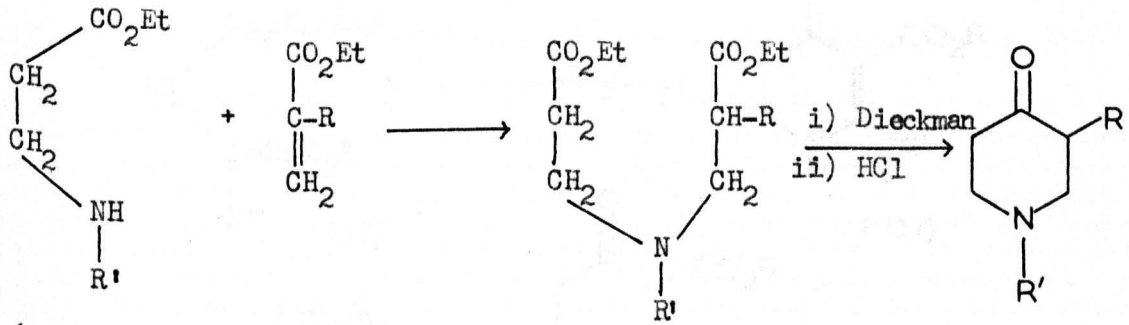
(105)

(106)

This reaction has been successfully conducted with compounds in which R was an alkyl group from methyl to pentyl, as well as phenyl, benzyl, β-phenylethyl, and benzoyl. The reaction was equally successful when acrylonitrile was substituted for ethyl acrylate, the product being a 3-cyanopiperidone (107).[68-71]

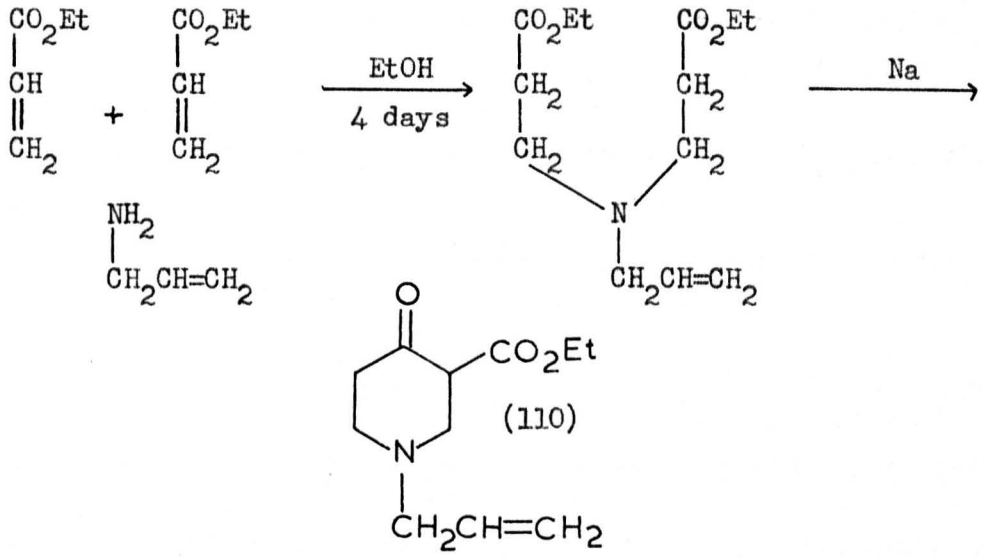


3-Alkyl-4-piperidones (109) were obtained by the addition of 3-ethoxycarbonylethylamines (108) to ethyl methacrylate or ethyl 2-alkyl acrylate.[72]



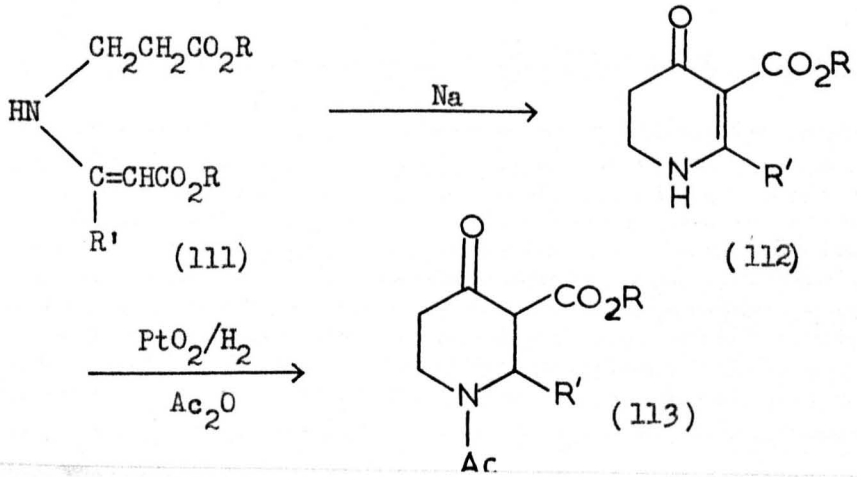
(108) (109)

Compounds of type (109) were also made by the alkylation of keto-ester (106) using alkyl halides.[56,73] Hoffmann added allylamine to ethyl acrylate and cyclised the product with sodium to produce an [illegible] 1-allyl-4-piperidone (110).[74]



(110)

Becker and Haufe reported a new synthesis of 4-piperidones which, in contrast to the Dieckmann-McElvain cyclisations, produces no isomers.[75] Dieckmann cyclisation of (111) gave the unsaturated 4-piperidone (112) which on catalytic reduction in acetic anhydride gave the N-acetyl-4-piperidone derivative (113).

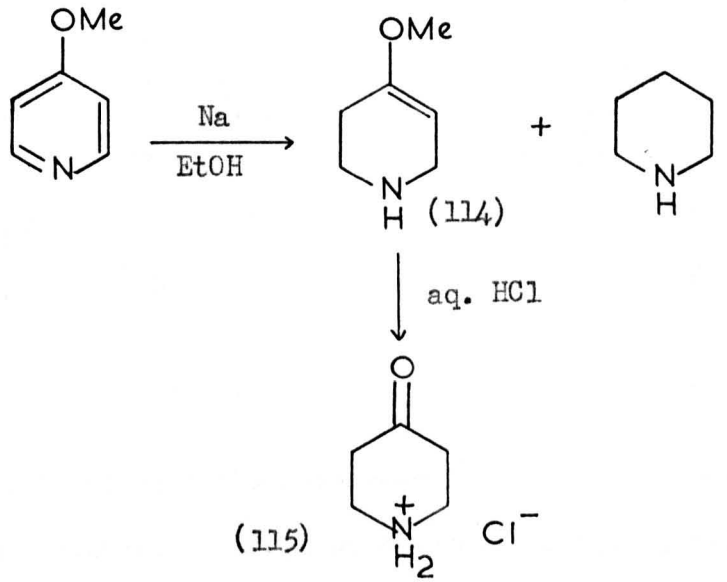


(111)

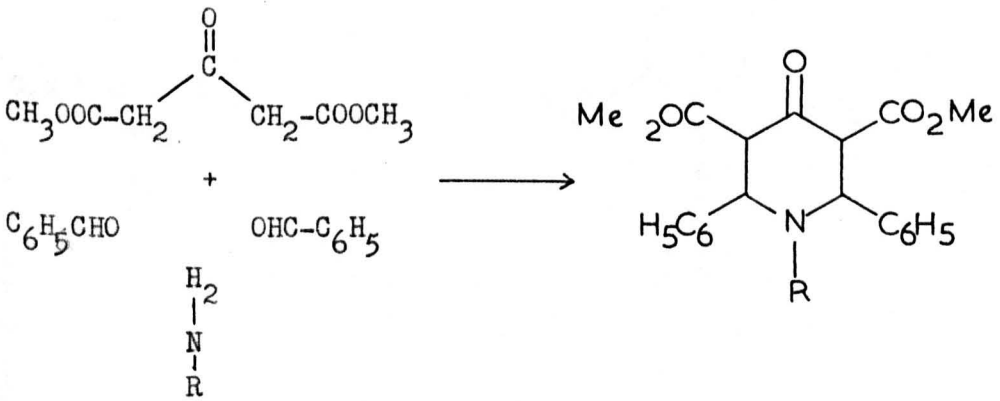
(112)

(113)

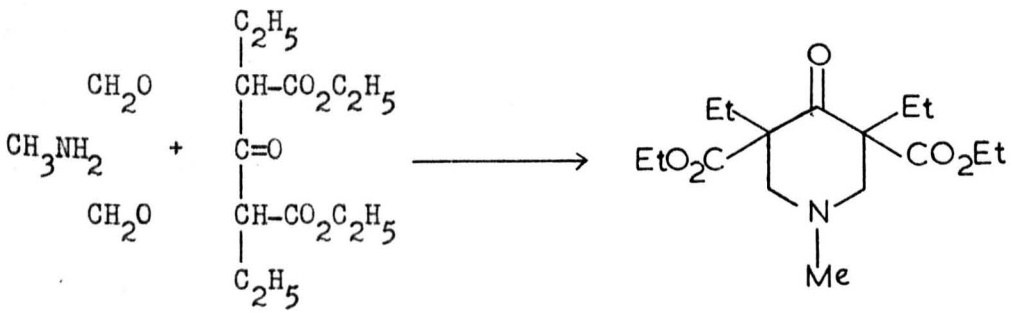
Reduction of 4-methoxy pyridine with sodium in ethanol gave a mixture of piperidine and 6-methoxy-1,2,5,6-tetrahydropyridine (114).[76] The latter was hydrolysed with aqueous hydrochloric acid to 4-piperidone hydrochloride (115).



An ingenious synthesis of 4-piperidones was developed by Petrenko-Kritshenko[77-84] in which two molecules of benzaldehyde were condensed with ammonia (or a primary aromatic or aliphatic amine) and an ester of acetonedicarboxylic acid, as shown below.

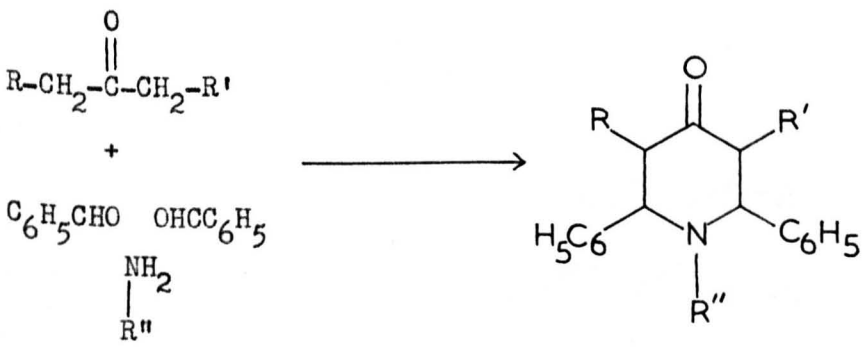


The reaction was successful when acetaldehyde was substituted for benzaldehyde,[85,86] although it was reported to fail with formaldehyde.[57] Ethyl α,α'-diethylacetonedicarboxylate (116) reacted with formaldehyde and methylamine, however, to give a 4-piperidone (117).[87]



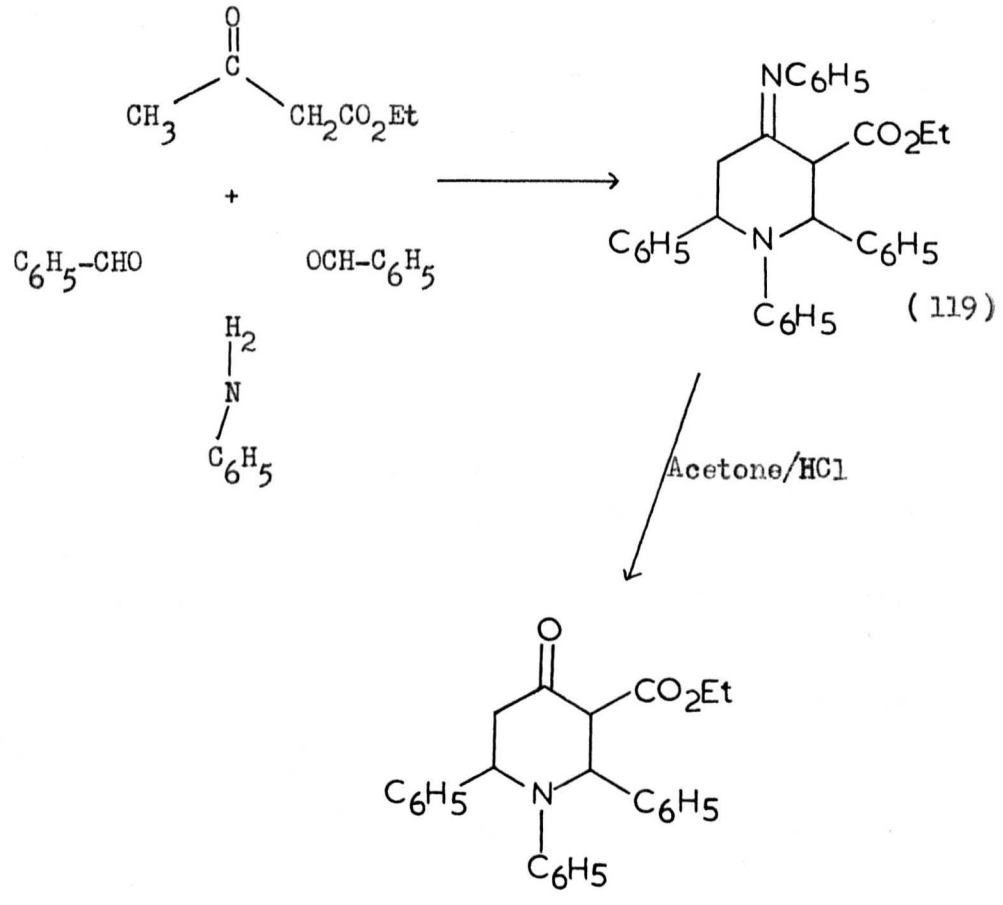
(116) (117)

Attempts to conduct the same reaction on simple ketones instead of acetonedicarboxylic esters were unsatisfactory until Baliah and Noller reported that the reaction proceeded with ease when acetic acid was the solvent,[88] as shown below.



(118)

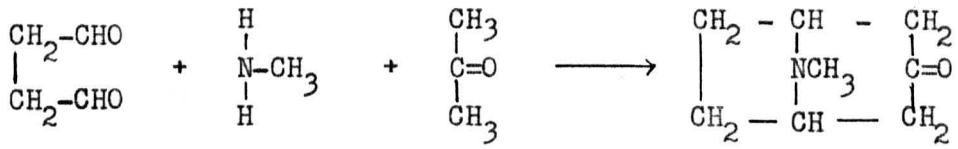
The yields were highest when ammonia was used (R" = H) and lowest when the size of the R group increases. The same fundamental reaction was employed by Böhm and Stöcker in which acetoacetic ester replaces the ketone in the above reaction.[89] Thus, aniline, benzaldehyde, and ethyl acetoacetate were heated in ethanol in the presence of malonic acid to give 3-ethoxycarbonyl-1,2,6-triphenyl-4-phenyliminopiperidine (119). Hydrolysis with dilute hydrochloric acid in acetone gave the 4-piperidone (120).



(119)

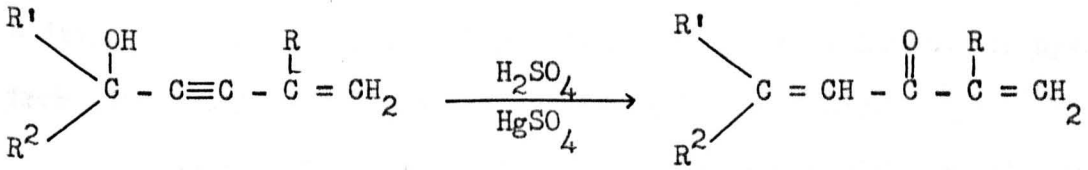
(120)

The Petrenko-Kritschenko reaction formed the basis for Robinson's classical synthesis of tropinone (121) from acetone, succindialdehyde, and methylamine in basic solution.[90]

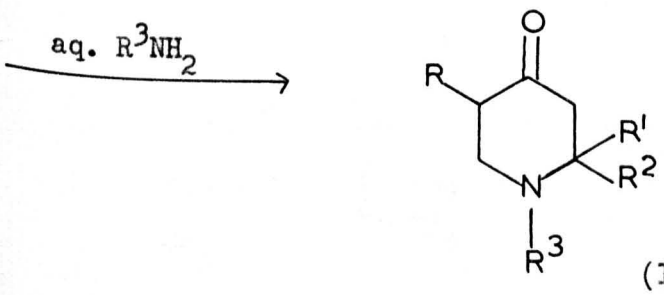


(121)

Several authors have recently prepared 4-piperidones by heating divinyl ketones with primary amines.[91-93] For example, the acetylene (122) was isomerised to the divinyl ketone (123) by means of hydration with mercuric sulphate in sulphuric acid and dehydration. The ketone (123) was heated with a primary amine to give the tetra-alkyl-4--piperidone (124).

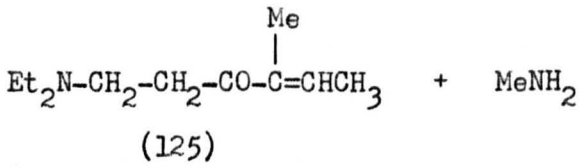


(122) (123)



(124)

The yields decreased with increased molecular size and branching of amines used.[91] Nazarov used a similar method in the action of primary amines on alkenyl-2-dialkylaminoethyl ketones (125) to give the 4-piperidone (126).[94]



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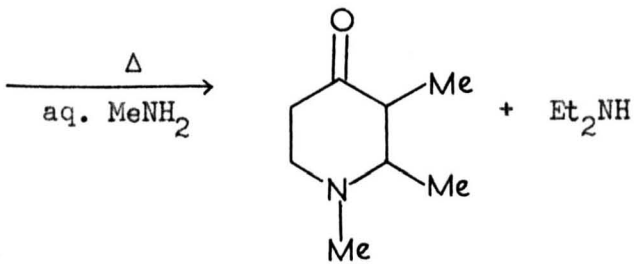
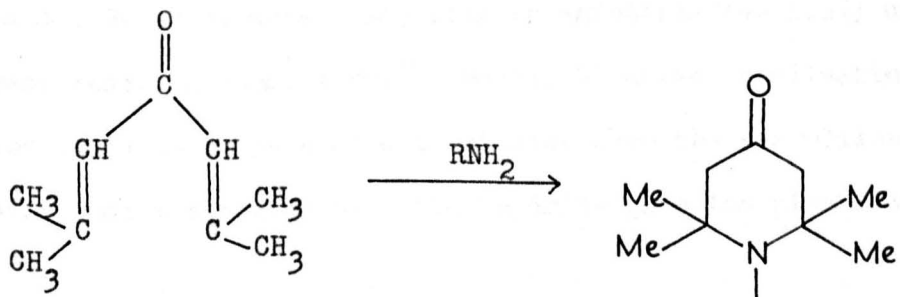


(126)

A divinyl ketone was presumably obtained by elimination of diethylamine from (125), which then reacted as in previous methods.

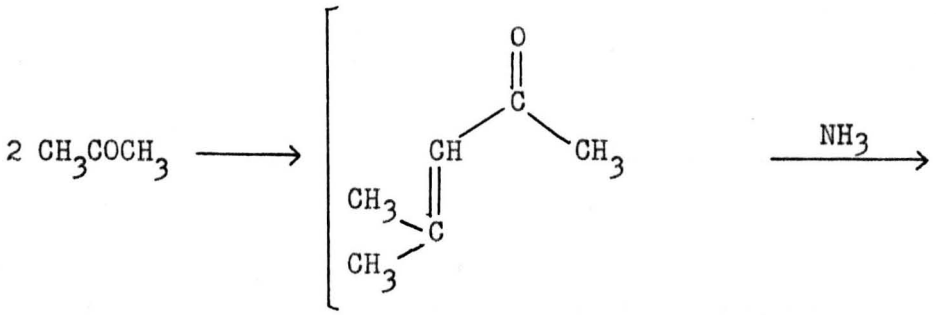
Phorone (127), or similar compounds, react with ammonia or primary amines to give 4-piperidone derivatives.[95,96]



(127)

(128)

Ammonia reacts with acetone under the right conditions to give a very small yield of triacetonamine (128), the condensation taking place through the intermediates, mesityl oxide (129) and diacetonamine (130).[97]



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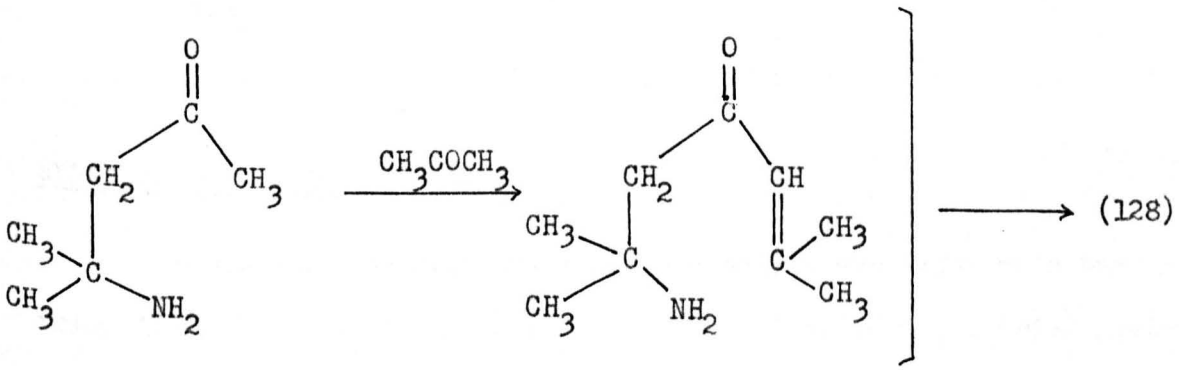
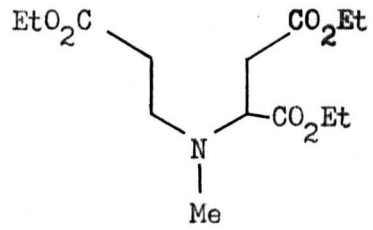
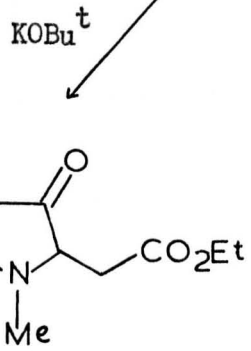


(130)

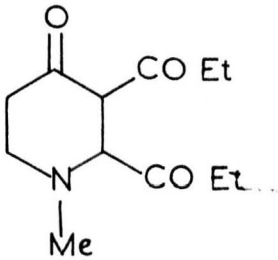
In 1967, Augustine and co-workers reported the synthesis of a 4-piperidone (133) and a 3-pyrrolidone (132) from an aminotriester (131) using different reaction conditions.[98] Hence, Dieckmann cyclisation of triester (131) using potassium t-butoxide gave the pyrrolidone (132) and using sodium ethoxide or sodium hydride gave the piperidone (133).



(131)



(132)

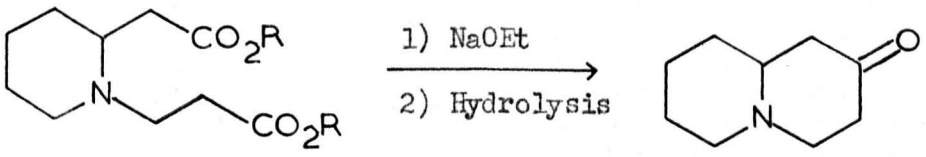


(133)

SYNTHESES OF 2-QUINOLIZIDONES

Because of the similarity of 2-quinolizidone (135) with the tricyclic ketone (101), and N-substituted 4-piperidones, a brief review of the syntheses of 2-quinolizidone will be included in this thesis.

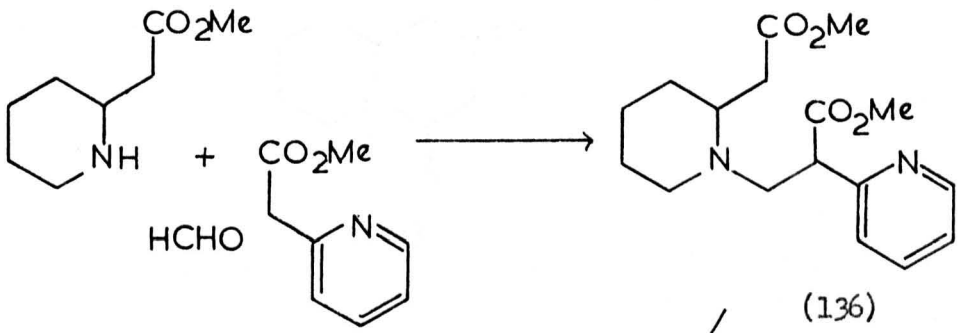
The earliest syntheses of 2-quinolizidone involved the Dieckmann cyclisation of the diester (134).[99-101]



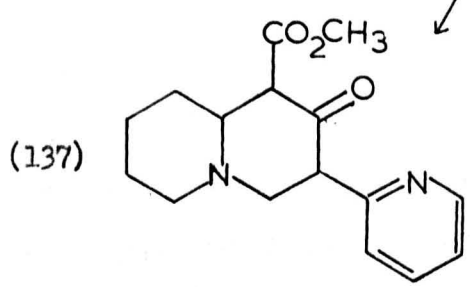
(134) (135)

Oxidation of 2-hydroxyquinolizidine with chromic anhydride has also been used to prepare 2-quinolizidone.[102]

In the course of study into the structure of retamine, Bohlmann et al. synthesised a 2-quinolizidone derivative (137) from the di-ester (136), which was obtained from the Mannich condensation of methyl 2-pyridyl acetate, methyl 2-piperidyl acetate, and formaldehyde.[103]

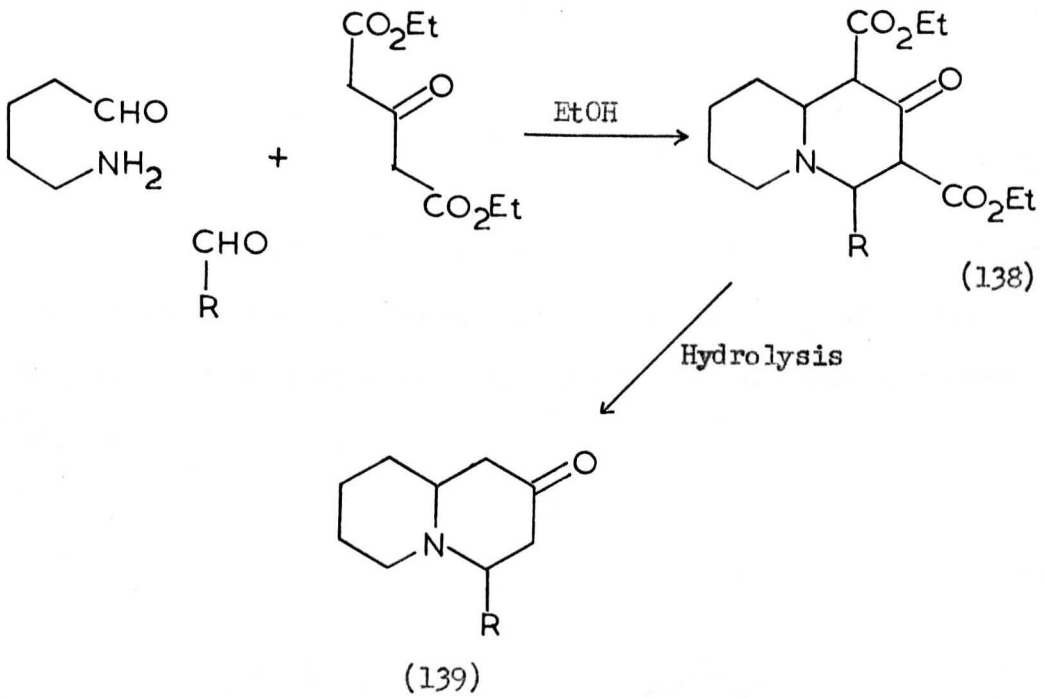


(136)



(137)

Anet and co-workers synthesised some 4-substituted 2-quinolizidones (139) by condensing δ-aminovaleraldehyde with diethyl acetonedicarboxylate and various aldehydes in buffered ethanolic solution.[104] Hydrolysis and decarboxylation of the keto diester (138) led to the 2-quinolizidones (139).


CHO
NH2
+
CHO
R
CO2Et
O
CO2Et
EtOH
CO2Et
O
N
CO2Et
R
Hydrolysis
O
N
R

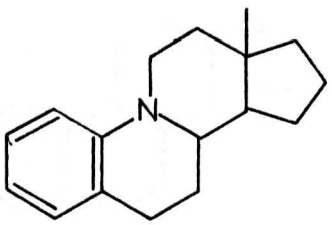
(138)

(139)

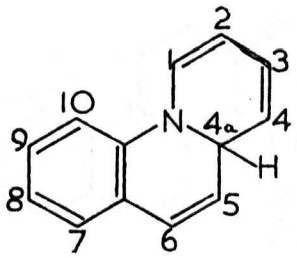
DISCUSSION

GENERAL SYNTHETIC APPROACH

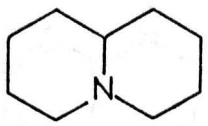
It was decided that the initial synthetic work should centre on a 9-azaestra-1,3,5(10)-triene nucleus (140). Such a structure would be stereochemically less complex than the corresponding androstane derivative.



(140)



(141)

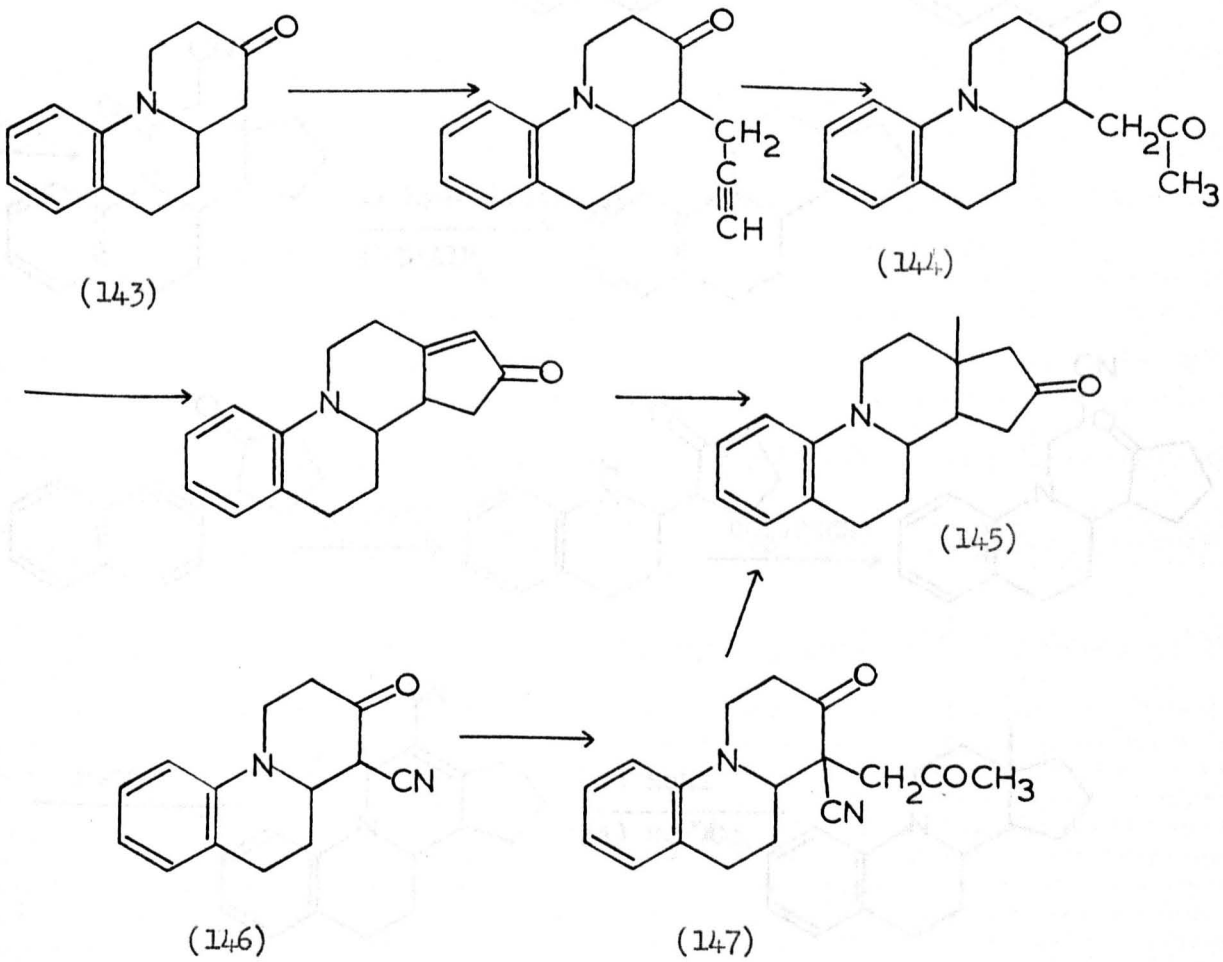


(142)

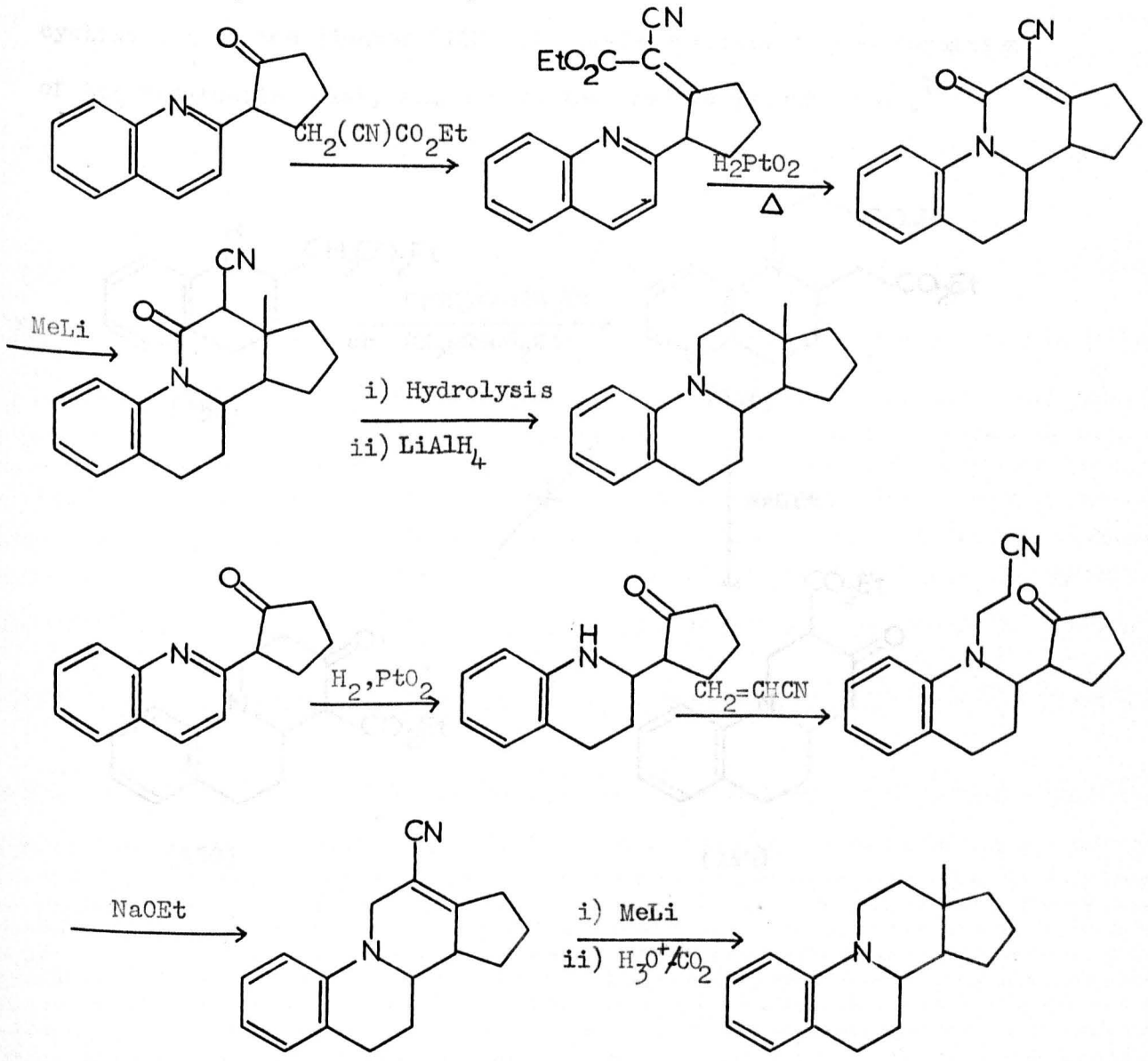
The more immediate aim was to prepare tricyclic derivatives of 4aH-benzo[c]quinolizine (141) suitably substituted for the addition of ring D. The older nomenclature for these compounds based on benzpyridocoline will not be used and the perhydro derivative (142) of quinolizine (formerly pyridocoline) will be referred to as quinolizidine and not as norlupinane or piperidocoline.

Initial experiments involved the preparation of derivatives of 1,2,3,4,5,6-hexahydro-3-oxo-4aH[c]quinolizine prepared by Jones and Wood,[105] and also derivatives suitably substituted in the

8-position for conversion to 3-hydroxyl group in the 9-azasteroid system. The 9-azasteroid structure (145) could be obtained from the ketone (143) by introduction of a three-carbon unit by alkylation of ketone (143) with propargyl bromide, hydration to the diketone (144), base catalysed condensation, and methylation leading to the 9-aza-16-oxosteroid (145). Alternatively, the 9-azasteroid structure (145) could be synthesised from the cyanoketone (146) by alkylation with bromoacetone to the cyano-diketone (147), followed by base catalysed cyclisation, hydrolysis and decarboxylation, and methylation as before leading to the same 9-aza-16-oxosteroid (145).



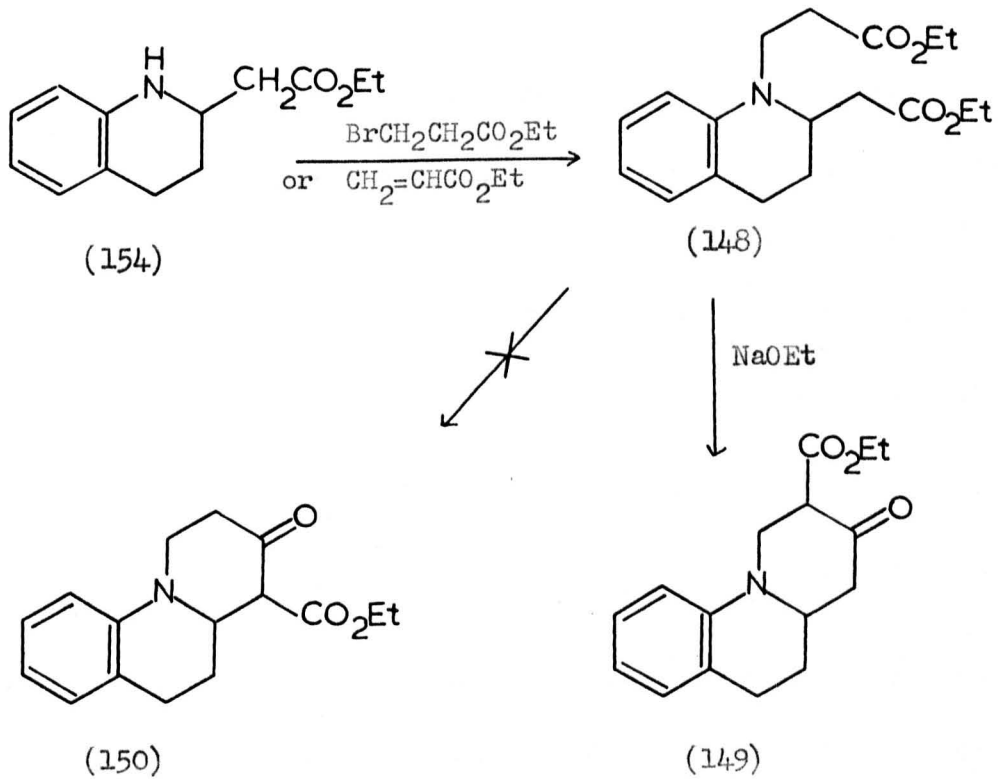
Later experiments involved the synthesis of 2-cyclopentyl quinoline derivatives, which would constitute rings A, B, and D of the 9-azasteroid system. Ring C could be constructed by addition of a two or three carbon chain at the quinoline nitrogen or 2-position of the cyclopentane ring and subsequent cyclisation. A typical intermediate in this type of synthesis would be 2-quinolyl-2-cyclopentanone. The 9-azasteroid system could be synthesised as shown below.



Syntheses based on these methods of approach have been used and will be discussed later.

SYNTHESIS OF 1,2,3,4,5,6-HEXAHYDRO-3-OXO-4aH-BENZO[c]QUINOLIZINES

The synthesis of intermediates of this type involved the preparation of bifunctional derivatives of 1,2,3,4-tetrahydroquinoline which could be cyclised by the Dieckmann procedure. Synthesis and cyclisation of the diester (148) led preferentially to the formation of the β-ketoester (149) and not to the desired isomer (150).[105]

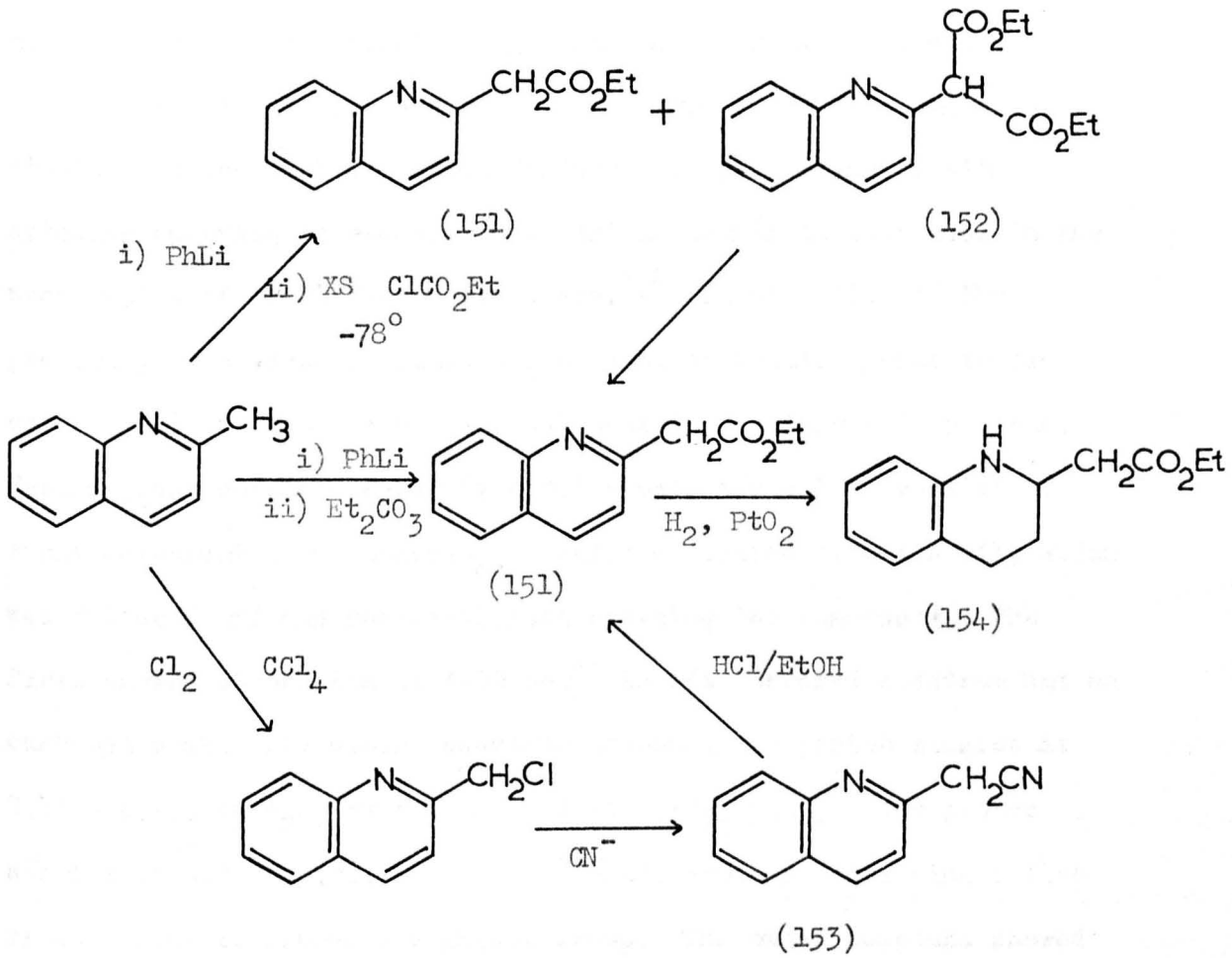


(154) (148) (150) (149)

Preparation and cyclisation of ethyl 1-(2-ethoxycarbonylethyl)-1,2,3,4-tetrahydro-2-quinolylacetate (148).

Ethyl 2-quinolylacetate (151) was prepared both from quinaldine and 2-chloromethylquinoline. The former method was a modification of that used by Hammick, Johnston, and Morgan, involving the treatment of quinaldyl lithium with diethyl carbonate.[106] When the method of these workers was followed, the yield of the ester (151) was never better than 25% and a number of by-products were encountered which were difficult to remove. The procedure leading to the purest product, although still in low yield, involved the reversal of the addition processes of the preparation, i.e. the addition of the ethereal solution of phenyl lithium to quinaldine and the addition of the solution of quinaldyl lithium to diethyl carbonate, and was the modification described by Wood.[107] One of the by-products encountered in the procedure of Hammick et al.,[106] a higher boiling oil showing no ester peak in its infrared spectrum, is thought to arise from the addition of phenyl lithium to the azomethine linkage of quinaldine, and such addition reactions have been reported by Clemo and Nath.[108] The use of ethyl chloroformate[109] in place of diethyl carbonate did not give an improved yield unless an excess of ethyl chloroformate was added to the quinaldyl lithium at -78°C, when a large proportion of diethyl 2-quinolyl malonate (152) was formed compared with ethyl 2-quinolyl acetate (151). Diethyl 2-quinolylmalonate (152) was converted to ethyl 2-quinolylacetate (151) by the procedure of

Breslow et al. for the preparation of acetates from malonates.[110]



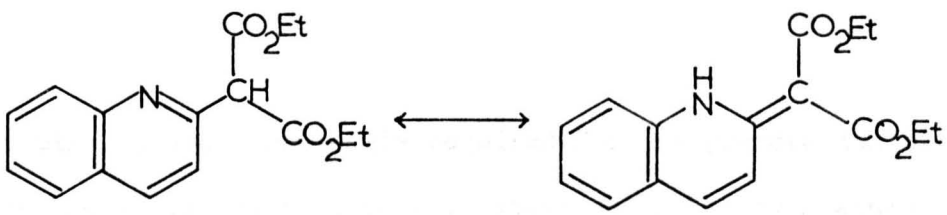
2-Chloromethylquinoline was prepared by treatment of quinaldine in carbon tetrachloride with chlorine.[111] The preparation of ethyl 2-quinolylacetate from 2-chloromethylquinoline involved the conversion of the latter first to 2-quinolylacetonitrile (153) by a procedure similar to that reported by Carelli et al.,[112] and Nagata.[113] The 2-quinolylacetonitrile was purified by vacuum distillation and trituration with ether. Treatment of the nitrile with hydrogen chloride

in ethanol[113] then gave the ester (151) which was pure after a single distillation, although the overall yield was only slightly better than that obtained in the single stage preparation from quinaldine.

An attempt was made to prepare ester (151) from quinaldyl lithium and dry carbon dioxide followed by esterification with hydrogen chloride in ethanol in a similar manner to that used in the preparation of ethyl 2-pyridylacetate.[114] Distillation of the product gave a viscous orange oil of similar boiling point to the ester (151) but showing no carbonyl peak in its infrared spectrum. Vapour phase chromatography (v.p.c.) showed the oil to consist of eight components. On standing, a solid separated from the oil, which was filtered off and recrystallised yielding two compounds. The first showed absorbtion at 3250 $cm.^{-1}$ in its infrared spectrum but no carbonyl peak. Its n.m.r. spectrum showed a one proton singlet at 2.33 p.p.m., an A_2B_2 system centred at 3.12 p.p.m., a one proton singlet at 5.22 p.p.m., and nine aromatic protons containing a five proton singlet, probably a phenyl group. The other compound showed no characteristic peaks in its infrared spectrum and its n.m.r. spectrum only showed aromatic protons.

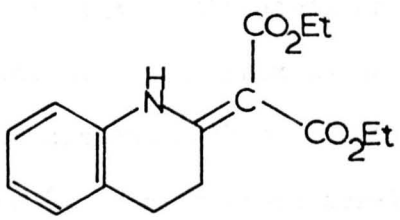
Hydrogenation of the ester (151) in glacial acetic acid over Adams' catalyst was quite rapid at room temperature and pressure, and required to be interrupted after the uptake of two moles of hydrogen. The reduction product consisted almost entirely of the tetrahydro-ester (154) with a more volatile compound, probably the decahydro-ester.

The n.m.r. spectrum of diethyl 2-quinolylmalonate (152) showed two distinct triplets centred at 1.28 p.p.m. and 1.31 p.p.m. corresponding to the ester methyl group, and a singlet at 5.02 p.p.m. corresponding to approximately one quarter of a proton. The infrared spectrum showed peaks at 1630 $cm.^{-1}$ and 1683 $cm.^{-1}$ consistent with an α,β-unsaturated ester. Obviously, the ester (152) is a mixture of the tautomers (152) and (152a) with the relative proportions being



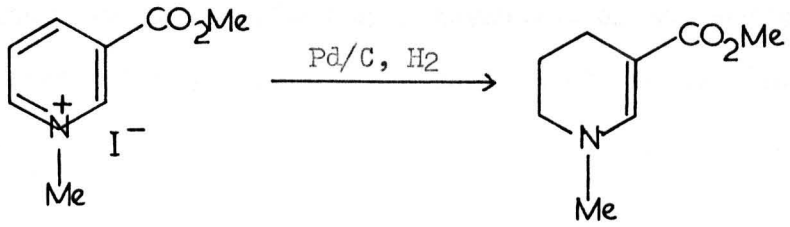
(152) (152a)

approximately 3:1 in favour of the tautomer (152a) which contains the exocyclic double bond. Hydrogenation of the di-ester (152) using Adams' catalyst was extremely slow and only one mole of hydrogen was taken up to produce the amino-ester (155) which still contained an exocyclic double bond.



(155)

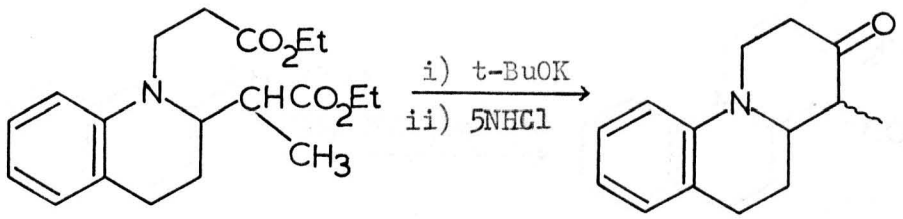
Wenkert et al. have reported the catalytic hydrogenation of, for example, 3-carbomethoxy-pyridine methiodide to give the stable enamine as shown.[136]



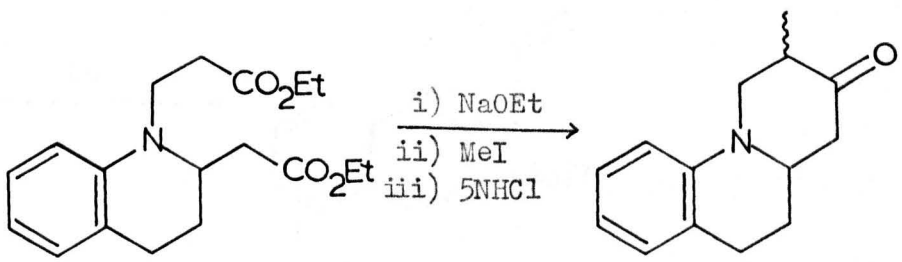
The ethyl 3-bromopropionate required for the preparation of the di-ester (148) was prepared by the method described by Mozingo and Patterson for the methyl ester.[115] The bromoester showed a tendency to revert to ethyl acrylate with elimination of hydrogen bromide, and distillation of the product was conducted at rather lower pressures than used by Mozingo and Patterson in order to obtain a neutral product. Alkylation of ethyl 1,2,3,4-tetrahydro-2-quinolylacetate with excess ethyl 3-bromopropionate was conducted at 140° in the presence of excess anhydrous potassium carbonate and a trace of potassium iodide which has been reported to catalyse the amination of bromo-nitriles.[116] Yields of the di-ester (148) varied considerably since dehydrobromination of the bromoester was always a competing reaction. A more consistent method of obtaining the di-ester (148) was by heating the ester (154) with ethyl acrylate and glacial acetic acid

containing a trace of cuprous chloride as catalyst.[67]

Dieckmann cyclisation of the di-ester (148) was accomplished in high yield using sodium ethoxide in xylene. Proof that the keto-ester formed was (149) and not the isomer (150) was given by Jones and Wood who synthesised the methyl ketone (160) and found it to be different from the methyl ketone obtained by methylation of the sodium salt of the keto-ester (149) from the cyclisation of diester (148),[105] as shown below.



(160)

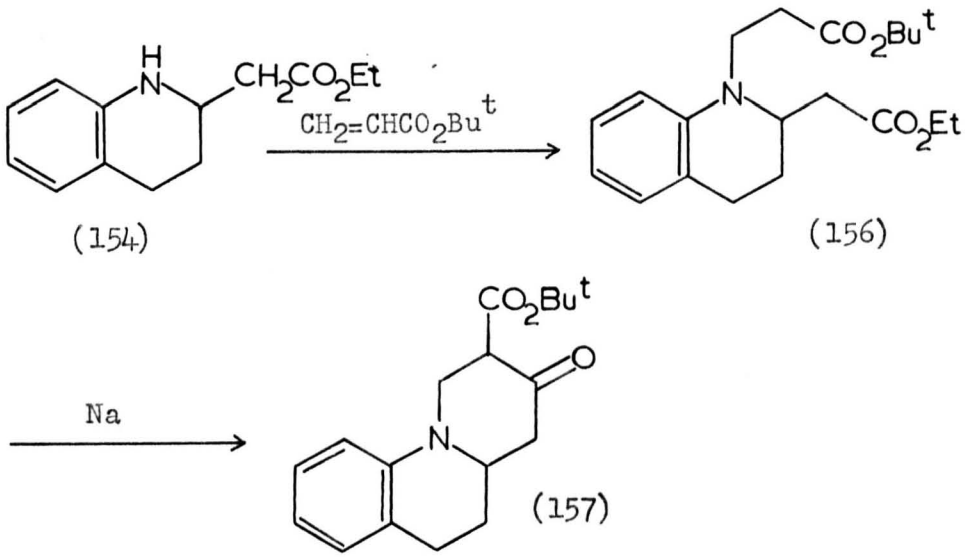


(148) (159)

In an attempt to obtain the keto-ester (150) it was decided to synthesise the diester (156) with the possibility that base catalysed cyclisation would preferentially lead to the keto-ester (150), since the t-butyl group could sterically hinder the α-methylene protons on the 2-propionate group.

Treatment of ester (154) with t-butyl acrylate, glacial acetic acid, and cuprous chloride for twenty hours led to the di-ester (156) in moderate yield.

Dieckmann cyclisation of the di-ester (156) was accomplished with a suspension of sodium in xylene, the sodium salt of the resulting keto-ester (157) forming a thick yellow slurry. The free keto-ester was isolated in the organic phase by addition of water and neutralisation with hydrochloric acid until the mixture was just acid.

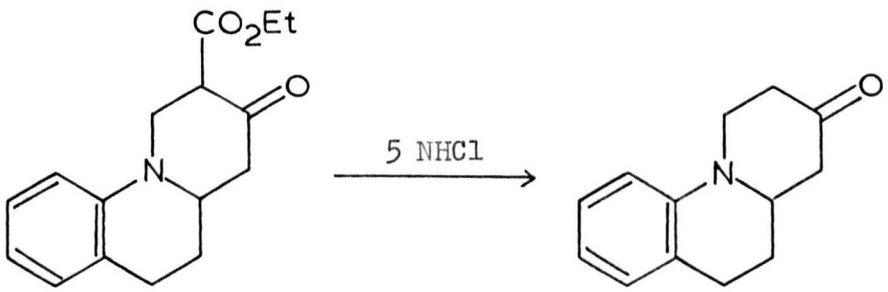


(154) (156) (157)

The n.m.r. spectrum of keto-ester (157) clearly showed a peak in the t-butyl region, which did not constitute nine protons, with no sign of any ethyl protons. The infrared spectrum showed the characteristic peaks for a keto-enol mixture. During the cyclisation of di-ester (156),

a slow distillation of alcohol and xylene was maintained, the n.m.r. spectrum of the mixture showing no t-butyl peak. Clearly, the type of ester group plays no part in the directional effect on Dieckmann cyclisations. Purification of keto-ester (157) could not be accomplished by distillation since this resulted in decomposition and considerable charring.

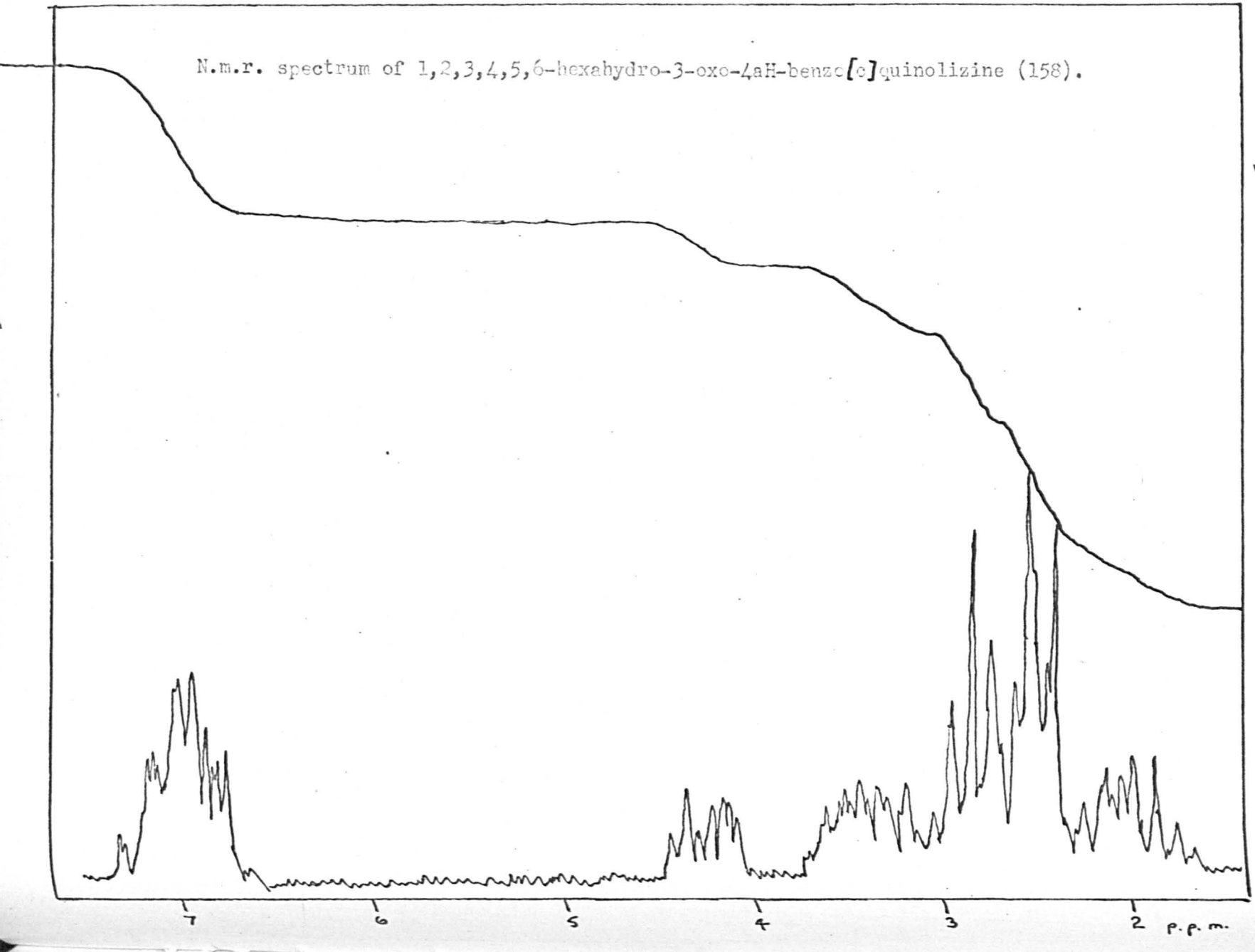
Hydrolysis and decarboxylation of the keto-ester (149) was accomplished by boiling in 5N hydrochloric acid. Distillation of the neutralised ketone and trituration with petrol gave the solid ketone (158) in moderate yield.



(149) (158)

The configuration of the quinolizidine ring fusion in the hexahydro-3-oxo-benzo[c]quinolizine (158) cannot be stated with certainty. Although it was expected that Dieckmann cyclisation would lead to the more stable trans-fused system, spectroscopic evidence for trans-fusion has not been found. The benzo[c]quinolizine (158) did not show strong

N.m.r. spectrum of 1,2,3,4,5,6-hexahydro-3-oxo-4aH-benzo[c]quinolizine (158).

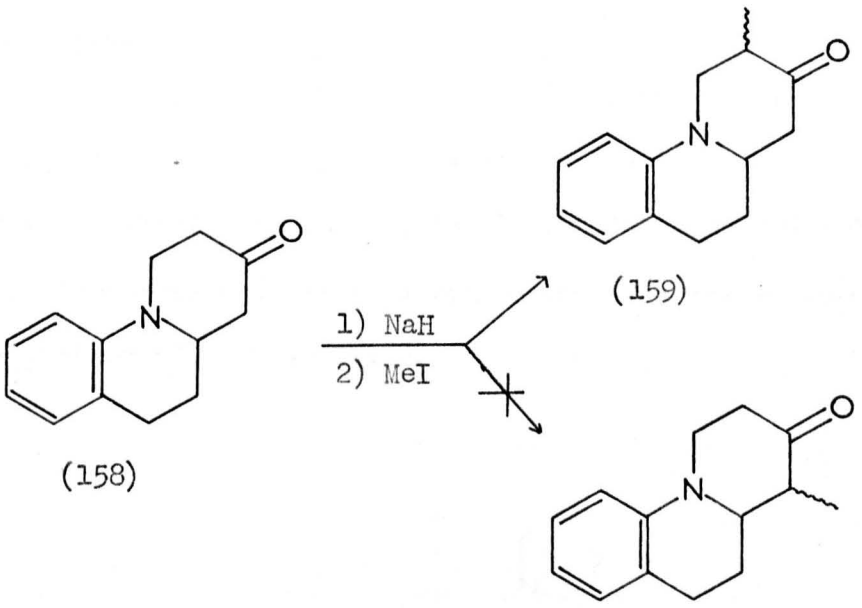


infrared absorption in the region 2700-2800 cm.$^{-1}$, characteristic of two hydrogen atoms trans diaxial to the lone electron pair on nitrogen,[117] although a medium intensity peak occurred at 2825 cm.$^{-1}$ and very weak peak occurred at 2730 cm.$^{-1}$ In the n.m.r. spectrum of ketone (158) a multiplet equivalent to one proton occurred at 4.21 p.p.m. although in the case of the keto-ester (149) there was a tendency for the signal due to the methylene protons of the ester group to obscure other signals in this region. Uskokovic et al. reported that the angular proton in benzo[a]quinolizidines appeared in the n.m.r. spectrum at a field below 3.8 p.p.m. for cis-fusion.[118]

Alkylation reactions of 1,2,3,4,5,6-hexahydro-3-oxo-4aH-benzo[c]quinolizine.

Cyclisation of di-ester (148) had produced the keto-ester (149) which was unsuitable for further use in a 9-azasteroid synthesis.[105] It was therefore necessary to re-alkylate ketone (158) in an attempt to obtain the 4-alkyl ketone. The sodium salt of ketone (158) was obtained by heating with sodium hydride in dimethoxyethane and then treated with a slight excess of methyl iodide in the same solvent. After boiling under reflux for three hours and standing overnight the reaction yielded a dark brown gum, which showed several peaks on v.p.c., one of which corresponded to the original ketone (158). The n.m.r. spectrum of this crude material showed a methyl signal consisting of two doublets centred at 0.99 and 1.13 p.p.m., that at 0.99 p.p.m. being the stronger of the two. Partial purification of the crude material was obtained by

column chromatography and v.p.c. analysis of the main constituent showed it to have the same retention time as the 2-methyl ketone (159) and different from the 4-methyl ketone (160).[105]



(158)

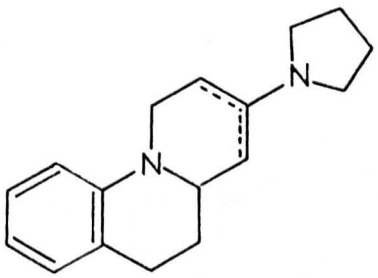
(159)

(160)

It is known that C-alkylation of basic ketones by means of enolate anions is not a satisfactory reaction. McElvain found that N-alkylation occurred rather than C-alkylation.[119] The low yield encountered in this type of preparation prompted a study of other methods of alkylating a basic ketone. The successful use of enamines as intermediates in the alkylation of ketones,[120] suggested that they might be useful in this synthesis. While aware that alkylation on the nitrogen would be a competing reaction, it was thought that the nucleophilic character of the enamine would allow reaction with alkyl halide to proceed at the desired position α to the carbonyl group.

The pyrrolidine enamine of ketone (158) was obtained by the standard procedures[120] as a brown solid which could not be distilled. The n.m.r. spectrum of the crude solid showed a vinyl hydrogen at 4.15 p.p.m. (J = 2 c.p.s.).

The reaction of the enamine (161) with methyl iodide was performed in benzene solution. A slight excess of methyl iodide was added to a solution of the enamine in benzene. A mildly exothermic reaction occurred and the solution became dark red in colour with the precipitation of a brown solid.



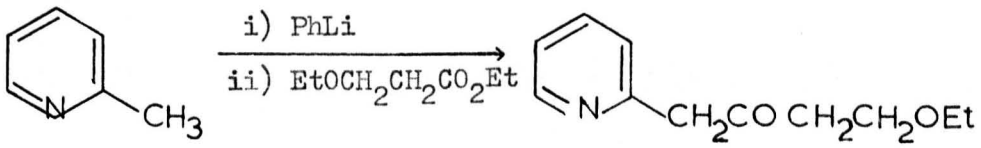
(161)

After refluxing overnight, the enamine was decomposed by warming with water. Extraction of the product gave a dark brown, tarry product, which on v.p.c. analysis showed five peaks, one of which was shown to have the same retention time as the methyl ketone (159), and two other peaks with approximately the same retention time as the other methyl ketone (160). Due to the long syntheses involved in obtaining ketone (158)

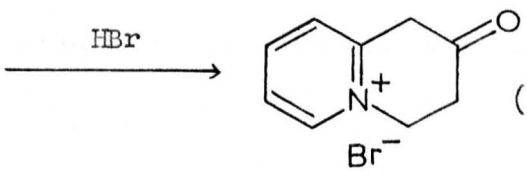
it was decided to attempt other synthetic routes to the tricyclic ketone (158) before abandoning this particular approach to 9-azasteroids.

Attempted preparation of 1,2,3,4-tetrahydro-2-oxo-benzo[c]quinolizinium bromide (165).

Glover prepared and cyclised the keto-ether (162) to give the quarternary compound (163) in 70% yield.[121]

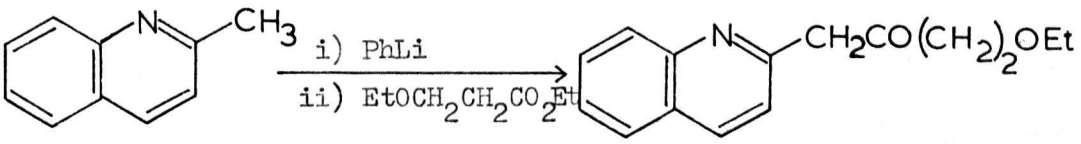


(162)

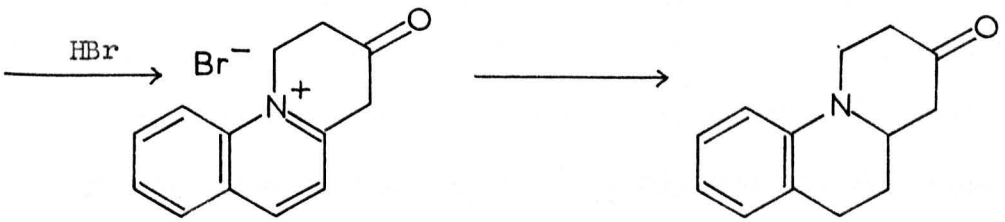


(163)

It was therefore decided to use a similar technique with quinaldine in place of α-picoline to obtain the benzo[c]quinolizinium bromide (165), which should be easily hydrogenated to the tricyclic ketone (158).



(164)

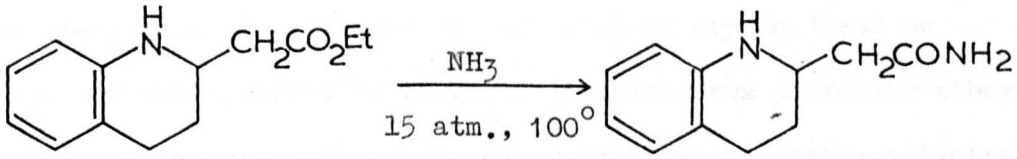


(165) (158)

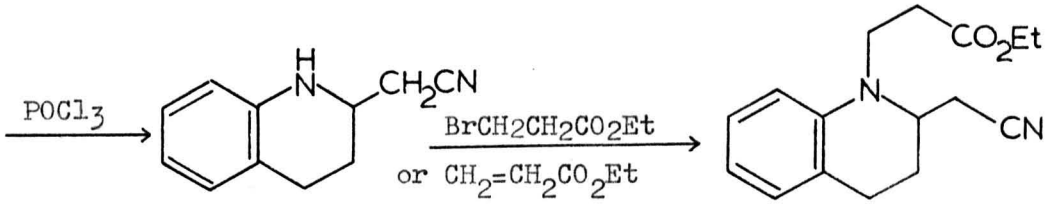
When the method of Glover was followed, i.e. addition of the ethyl 3-ethoxy propionate to the ethereal solution of quinaldyl lithium, none of the required keto-ether (164) was obtained, and when the reverse addition was used a yield of 24% of the keto-ether (164) was obtained. Infrared and n.m.r. spectra pointed to the compound being a mixture of ketone and enol. The ketone (164) was purified by distillation but was still only approximately 90% pure by v.p.c. analysis. The compound was analysed as its picrate. Heating compound (164) with 50% hydrobromic acid led to a hard, purple resin which could not be identified.

Preparation of 4-cyano-1,2,3,4,5,6-hexahydro-3-oxo-4aH-benzo [c]-quinolizine (146).

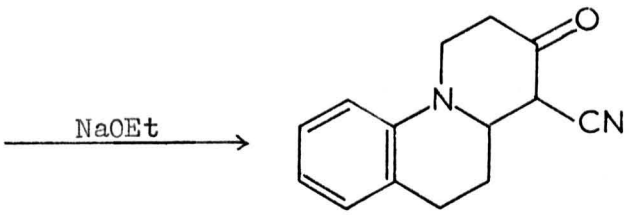
Jones and Wood decided to prepare and cyclise the cyano-ester (168) in the hope that the superior electronegativity of the cyano-group would ensure cyclisation in the desired direction.[105] 1,2,3,4-Tetrahydro-2-quinolylacetonitrile (167) required for the alkylation step was not obtainable from 2-quinolylacetonitrile since catalytic hydrogenation led to a mixture of primary amines and nitriles. The required nitrile (167) was readily prepared from ethyl 1,2,3,4-tetrahydro-2-quinolylacetate (154) by conversion into the amide (166) and dehydration. High pressure and elevated temperature were used for the ammonolysis of the ester (154), which was carried out using methanol as solvent. The dehydration of the amide (166) was achieved with phosphorus oxychloride in ethylene dichloride. The nitrile (167) was obtained on distillation as a pale yellow oil which slowly crystallised on standing, but darkened quite rapidly in air. The alkylation of the nitrile (167) with ethyl 3-bromopropionate



(154) (166)



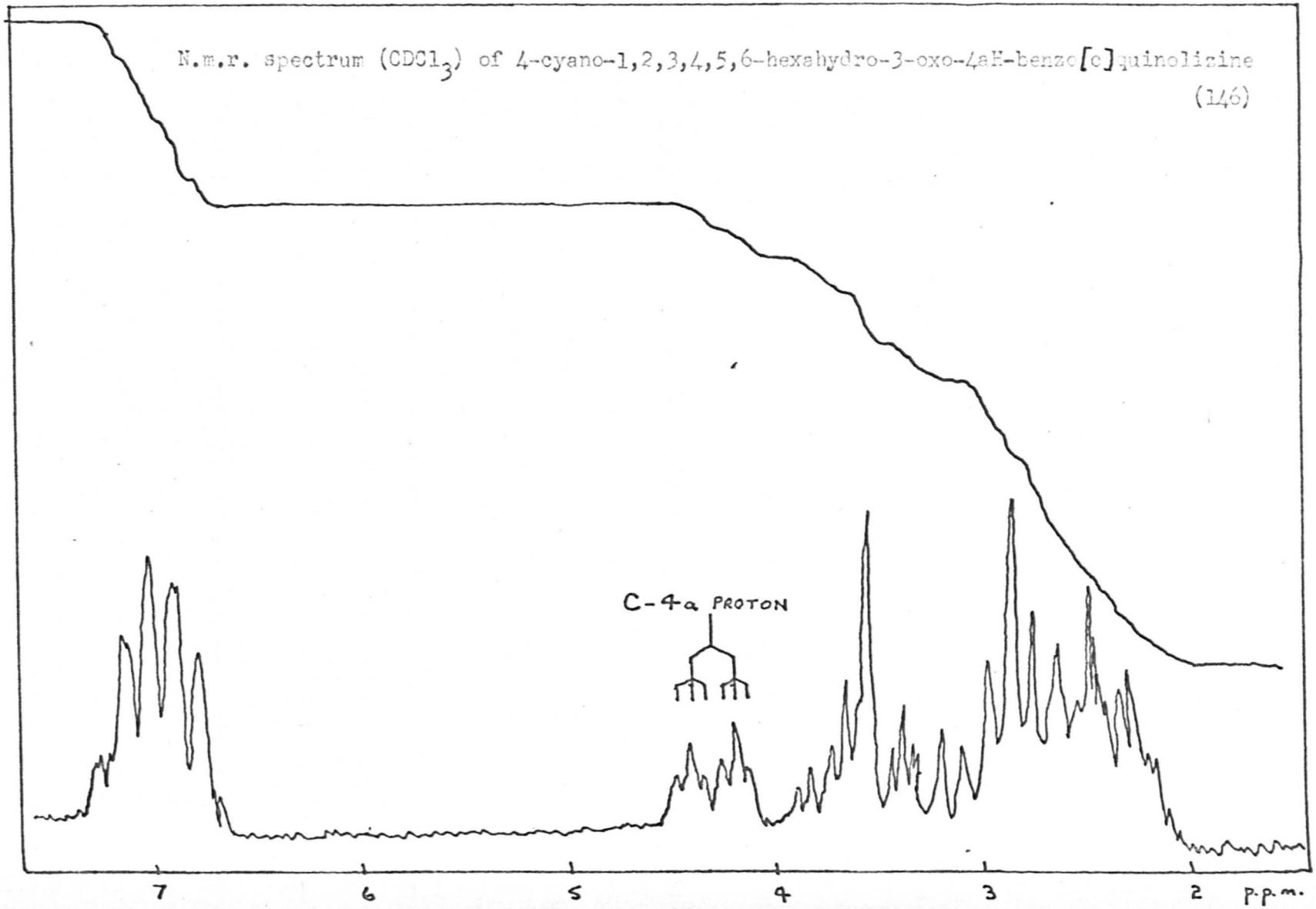
(167) (168)



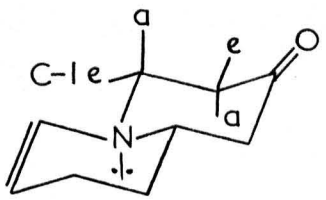
(146)

was found to be extremely slow at 140°, the elimination of hydrogen bromide from ethyl 3-bromopropionate usually taking place before the alkylation reaction. Reaction at 145° was found to take place giving a very small yield of the required cyano-ester (168), whereas the elimination reaction was quite rapid. To obtain enough cyano-ester for further synthetic use, the cyano-ester (168) was separated from the unreacted nitrile (167) by distillation at very low pressure, and then the reaction and distillation repeated several times. The use of ethyl acrylate in glacial acetic acid as alkylating agent did not improve the yield. The viscous oil so obtained crystallised on standing, and was purified by recrystallisation from petroleum ether. Dieckmann cyclisation of the cyano-ester (168) was smoothly affected with sodium ethoxide in boiling xylene. The product separated as a yellow sodium salt which was neutralised with dilute hydrochloric acid

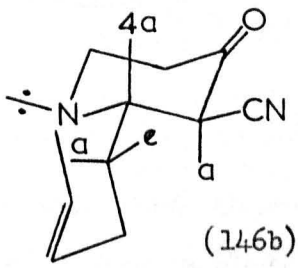
N.m.r. spectrum ($CDCl_3$) of 4-cyano-1,2,3,4,5,6-hexahydro-3-oxo-4aH-benzo[c]quinolizine (146)



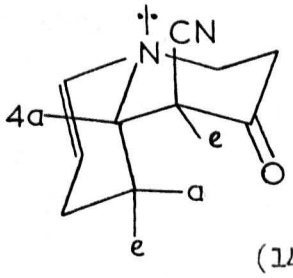
to give the cyano-ketone (146). No evidence of enolisation was detected in the infrared spectrum of the cyano-ketone (146) in carbon tetrachloride solution. The n.m.r. spectrum of the cyano-ketone (146) in deuterochloroform showed a well resolved sextet centred at 4.28 p.p.m. consisting of two triplets (J = 4 c.p.s. and J = 13 c.p.s.), which corresponded to one proton. This unique proton could be assigned to the angular 4a-proton if the ring fusion was cis or to the C-1 equatorial proton if the ring fusion was trans. Uskokovic et al. reported that a low field proton below 3.8 p.p.m. is characteristic of cis conformations in benzo[a] quinolizidines.[118]



(146a)



(146b)



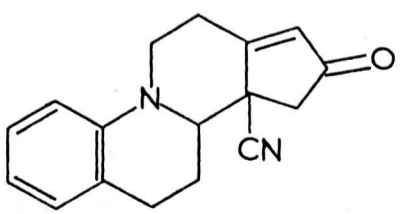
(146c)

The infrared spectrum showed no prominent bands between 2700 cm.$^{-1}$ and 2800 cm.$^{-1}$ and hence the rings are probably cis-fused.[117] A highly

deshielded proton in the trans-fused form of cyano-ketone (146a) is the equatorial proton at C-1, but since the adjacent methylene protons and the C-1 axial proton would give, in general, similar splittings in the n.m.r. spectrum, this would result in a 1:3:3:1 quartet which is not observed. The observed two 1:2:1 triplets, with small ae and ee splittings and large aa splitting, would be assigned to cis-isomer (146b) if the cyano group was equatorial and to cis-isomer (146c) if the cyano group was axial. It is assumed,therefore, that cyano-ketone (146) is cis-fused and the low field proton must be assigned to the angular 4a proton.

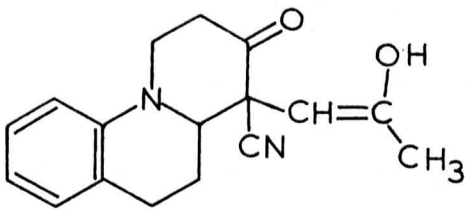
Alkylation of 4-cyano-1,2,3,4,5,6-hexahydro-3-oxo-4aH-benzo[c]-quinolizine (146).

It was decided that alkylation of the sodium salt of cyano-ketone (146) with bromoacetone should lead to the diketone (147) which on base catalysed cyclisation should produce the α,β-unsaturated ketone (169),[122] having the 9-azasteroid nucleus.

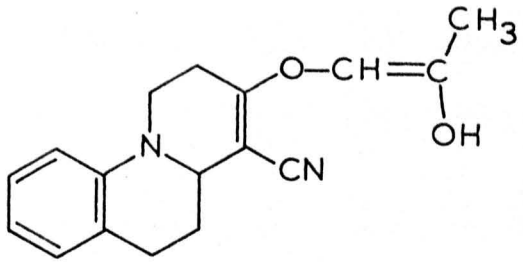


(169)

The sodium enolate of cyano-ketone (146) was obtained as a white insoluble solid when sodium hydride was added to a solution of cyano-ketone (146) in dimethoxyethane. Reaction was immediate but the solution was boiled under reflux for a further two hours before cooling when an equivalent amount of bromoacetate in dimethoxyethane was added. There was no visible reaction or colour change. After boiling under reflux for twelve hours most of the solvent was removed by evaporation before neutralisation of the base, which was extracted with chloroform to give a brown, viscous liquid. This crude material showed the presence of a vinyl type proton at 4.0 p.p.m. in its n.m.r. spectrum, as well as a one proton multiplet at 4.28 p.p.m., a broad, one proton peak at 5.48 p.p.m., and a three proton singlet at 2.32 p.p.m. The infrared spectrum showed prominent peaks at 3495 $cm.^{-1}$, 3350 $cm.^{-1}$, 2208 $cm.^{-1}$, and 1635 $cm.^{-1}$, with weak absorption at 1605 $cm.^{-1}$ and 1735 $cm.^{-1}$ The crude material darkened rapidly in air and could not be purified without decomposition. An analysis was obtained by formation of the hydrochloride from anhydrous ether. The analysis and spectral data suggested the C-alkylation product (147a) or the O-alkylation product (170), either of which appeared to be in the enolic forms.



(147a)



(170)

Finally, in an attempt to elucidate the structure of the alkylation product of the cyano-ketone (146), it was boiled under reflux with 20% hydrochloric acid for several hours, the product obtained on basification of the residue showing no infrared absorption due to nitrile, and the appearance of a peak at 1700 $cm.^{-1}$ The n.m.r. spectrum of the crude material showed a one proton multiplet at 4.25 p.p.m. as well as a three proton singlet at 2.25 p.p.m. No peak at 4.0 p.p.m. or 5.43 p.p.m. was observed. This evidence suggested that the correct structure was that of the C-alkylated product (147a) since acid hydrolysis would have removed the acetone residue of the O-alkylated product (170). Attempts to purify the crude hydrolysis product of (147a) or form a stable derivative failed.

Attempts to cyclise the diketone (147) using potassium t-butoxide in t-butanol at room temperature initially, and heating for one hour gave a very dark residue, which contained mainly starting material.

Further attempts to investigate synthetic routes from cyano-ketone (146) to the 9-azasteroid system (145) were restricted because of the time involved and the low yields encountered in the synthesis of cyano-ketone (146). It was decided at this point to investigate routes for obtaining 4-substituted derivatives of the tricyclic ketone (158) in better yield before proceeding with this line.

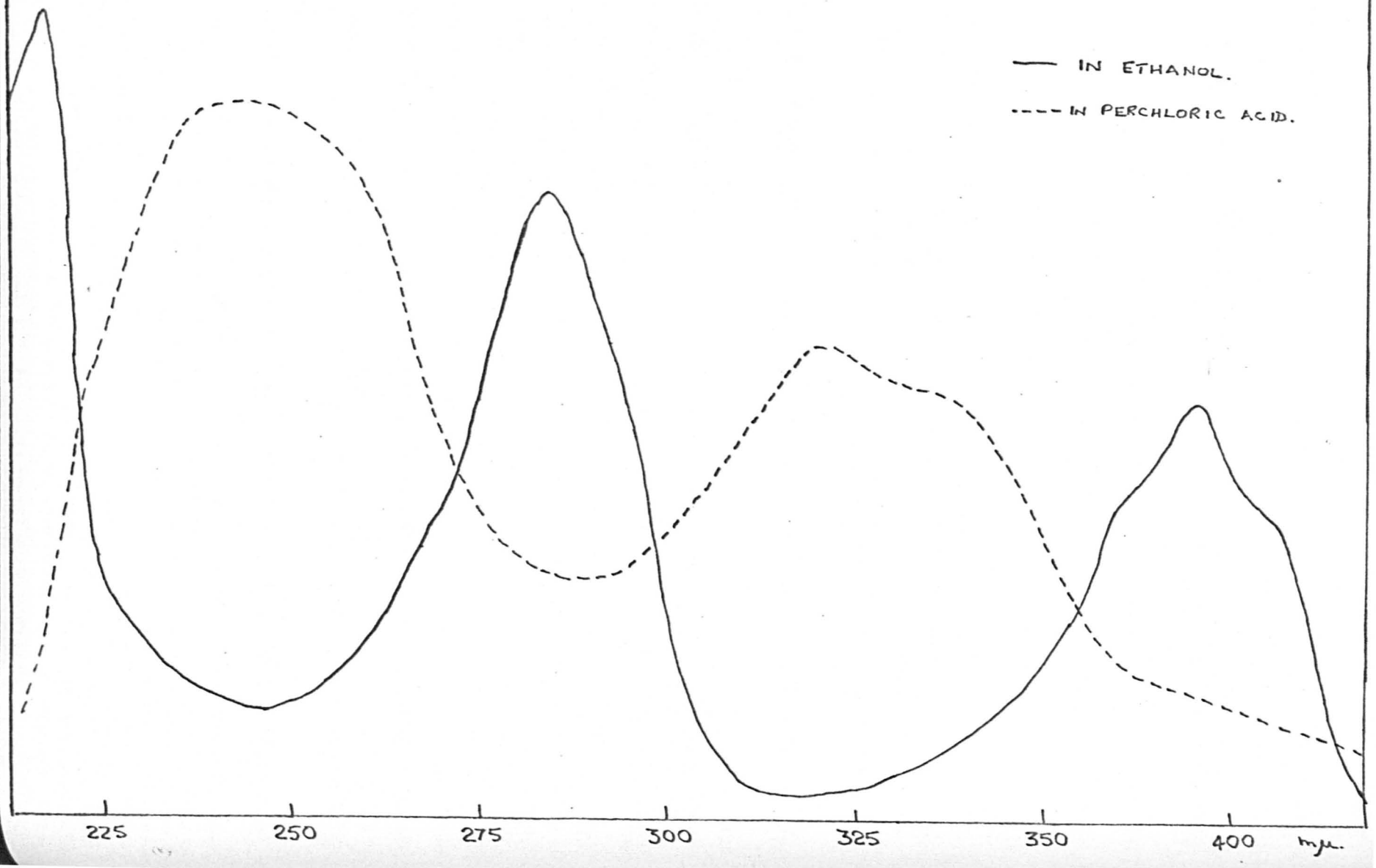
Reactions of quinoline-1-oxide with compounds containing reactive hydrogens in the presence of acetic anhydride.

The difficulties encountered in the synthesis of 4-substituted derivatives of the ketone (158) were, firstly, that cyclisation of the di-ester (148) gave the unsuitable keto-ester (149), and secondly, substitution of the acetate ester group in ester (154) by a nitrile group led to a decrease in the basic strength of the quinoline nitrogen leading to increased difficulty of N-alkylation. Although the substitution of a nitrile group for an ester group to give the cyano-ester (168) ensured cyclisation in the desired direction, the difficulties encountered in the alkylation step became much greater. The present experiments were directed towards finding an alternative to a nitrile group which would have superior electronegativity over an ester group but would still allow N-alkylation to occur.

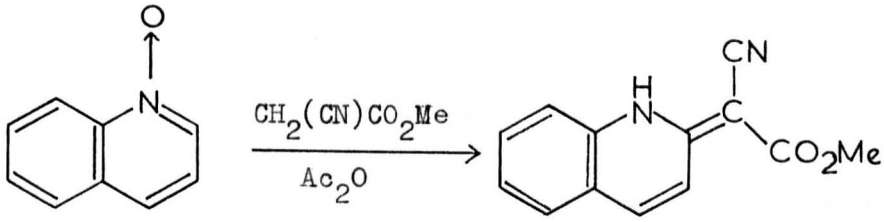
Hamana and Yamazaki reported that many compounds with active hydrogens reacted with quinoline-1-oxide in the presence of acetic anhydride to give mainly 2-substituted quinolines.[123] This reaction suggested a promising method for introducing a carbon substituent into the 2-position of a quinoline ring.

When methyl cyanoacetate was added to a solution of quinoline-1-oxide in acetic anhydride, an exothermic reaction occurred and crystals separated from the reaction mixture in a similar manner to that reported for ethyl cyanoacetate.[123] The reaction was allowed to proceed at 35-40°C overnight and the pale yellow crystals filtered and recrystallised

Ultraviolet spectrum of methyl 1,2-dihydro-2-quinolylidene cyanoacetate (171)



from ethanol to give the addition product (171), in 78% yield.



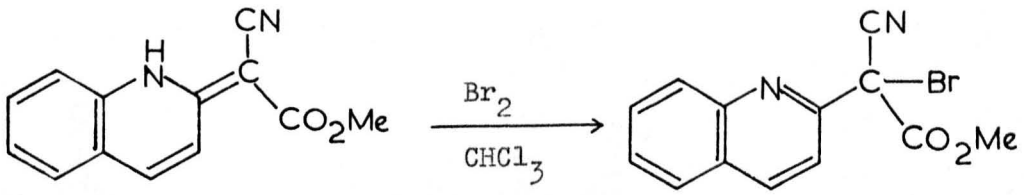
(171)

The infrared spectrum of cyano-ester (171) showed peaks 2207 cm.$^{-1}$ due to α,β-unsaturated nitrile, and 1636 cm.$^{-1}$ due to α,β-unsaturated ester, but no sign of a peak due to the NH stretching. The n.m.r. spectrum showed a 3 proton singlet at 3.88 p.p.m. due to the ester methyl and a broad one proton peak at 13.6 p.p.m. due to the amino-hydrogen. The ultraviolet spectrum showed maxima at 217, 284, and 392 mμ in ethanol solution, whilst maxima appeared at 322 and 337 mμ in perchloric acid solution.

Catalytic hydrogenation of cyano ester (171) using Adams' catalyst in glacial acetic acid was extremely slow and produced a mixture of primary amines and nitriles.

Bromination of cyano-ester (171) in chloroform with an equivalent amount of bromine in chloroform occurred readily to give a red solution which on neutralisation gave an almost quantitative yield of the mono-bromo compound (172) as pale-yellow plates. The infrared spectrum

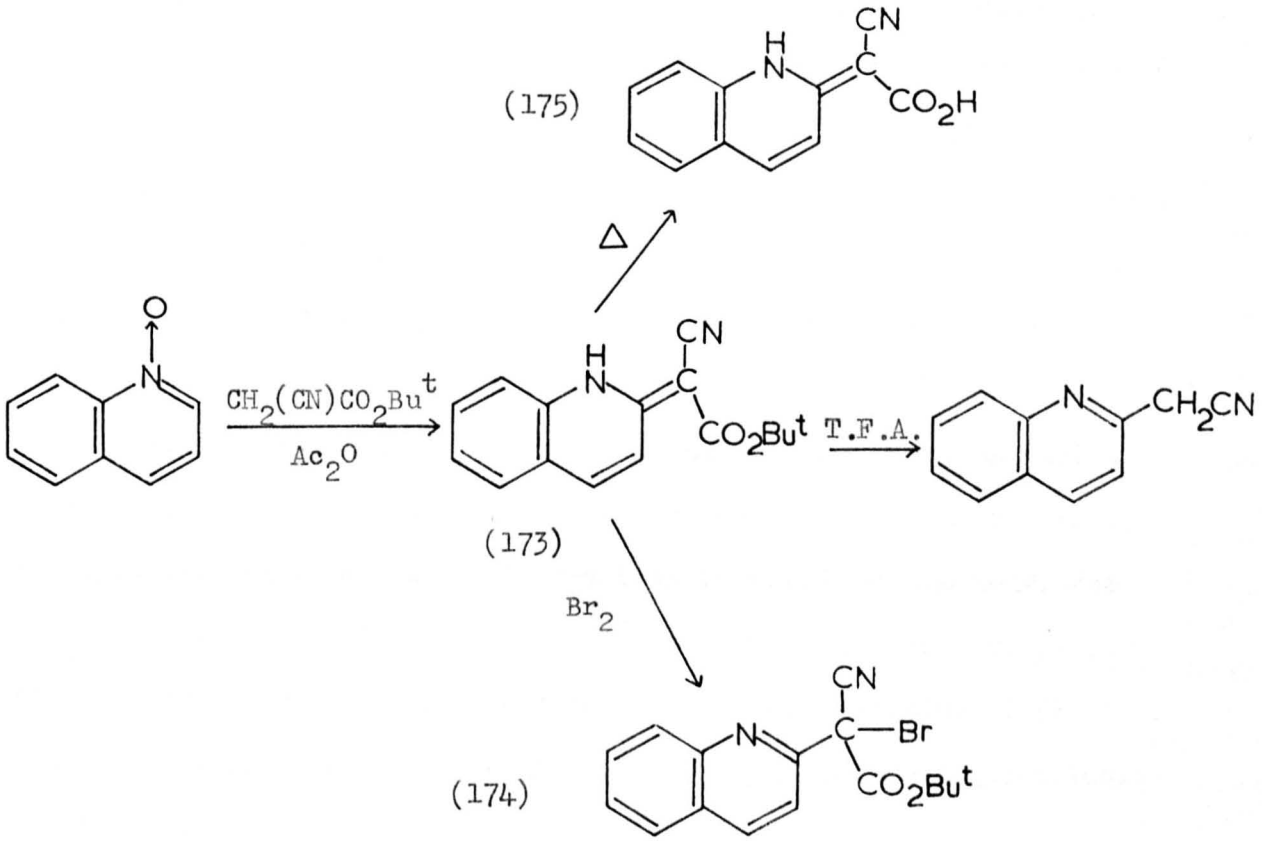
showed peaks at 2207 cm.$^{-1}$ and 1743 cm.$^{-1}$. The n.m.r. spectrum showed only a three proton singlet at 4.02 p.p.m. and six aromatic protons. These spectral data are consistent with the formation of the C-bromo compound as (172).



(171) (172)

Addition of t-butyl cyanoacetate[124] to a solution of quinoline-1-oxide in acetic anhydride, in a similar manner to that used for the methyl ester, led to a 65% yield of the t-butyl ester (173) as yellow needles. The infrared spectrum showed peaks at 2205 cm.$^{-1}$, 1640 cm.$^{-1}$, and 1615 cm.$^{-1}$. The n.m.r. spectrum showed a nine proton peak at 1.62 p.p.m., six aromatic protons, and a broad one proton peak at 13.75 p.p.m. Warming of ester (173) in trifluoroacetic acid produced, as expected, 2-quinolylacetonitrile. Pyrolysis of ester (173) was accomplished by heating to its melting point until the evolution of gases ceased. It was reported that pyrolysis would remove the carbo-tert-butoxy group,[124] but the orange solid obtained in this

pyrolysis appeared to have lost only the t-butyl group probably as isobutylene.

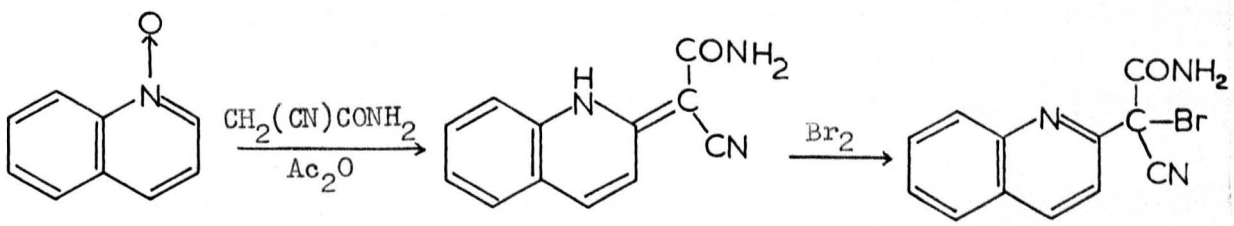


The orange compound obtained on pyrolysis of ester (173) was recrystallised from chloroform to give orange plates which did not give a satisfactory melting point. The infrared spectrum showed peaks at 2190 cm.$^{-1}$, 1625 cm.$^{-1}$, and 1615 cm.$^{-1}$. The n.m.r. spectrum showed only aromatic protons. The spectral evidence suggests that the acid (175) was produced. Although no satisfactory analyses could be obtained for

the acid (175), the analyses did show that the compound contained approximately the same number of oxygen atoms as nitrogen atoms.

Bromination of ester (173) in chloroform with an equivalent amount of bromine in chloroform was accomplished in a similar manner to the bromination of the methyl ester (171) to give a high yield of the mono-bromo-compound (174) as pale yellow plates. The infrared spectrum showed a weak peak at 2210 $cm.^{-1}$, and strong peaks at 1750 $cm.^{-1}$ and 1775 $cm.^{-1}$. The n.m.r. spectrum showed a nine proton singlet at 1.65 p.p.m.

When cyanoacetamide was added to quinoline-1-oxide in acetic anhydride, a vigorous exothermic reaction occurred with the separation of crystals. After allowing the reaction to stand for one hour, the crystals were filtered and recrystallised from ethanol to give yellow micro-prisms in 90% yield. The α-cyano-2-quinolylacetamide (176) obtained was insoluble in chloroform, and ether, and sparingly soluble in ethanol.



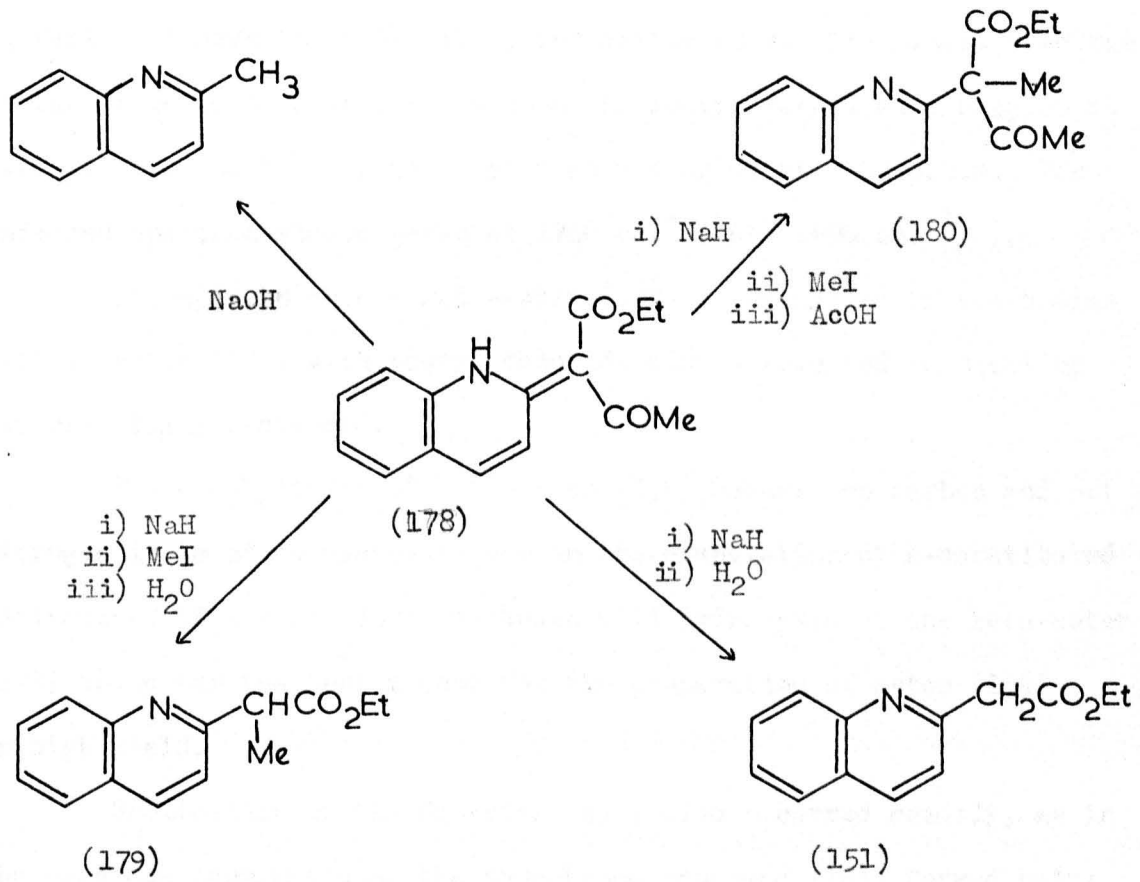
(176) (177)

The infrared spectrum showed peaks at 3390 cm.$^{-1}$, 3330 cm.$^{-1}$, 3265 cm.$^{-1}$, 2190 cm.$^{-1}$, 1633 cm.$^{-1}$, and 1615 cm.$^{-1}$.

When an equivalent amount of bromine was added to a warm solution of amide (176) in chloroform a red precipitate formed which was neutralised with base and extracted with the chloroform. The yellow solid obtained on evaporation was recrystallised from petroleum ether as pale yellow plates. Analysis showed the compound to be the mono-bromo-amide (177). The infrared spectrum showed peaks at 3470 cm.$^{-1}$, 3400 cm.$^{-1}$, 3260 cm.$^{-1}$, 2190 cm.$^{-1}$, and 1717 cm.$^{-1}$. The n.m.r. spectrum showed only protons in the aromatic region.

Ethyl acetoacetate was added dropwise, with cooling, to a solution of quinoline-1-oxide in acetic anhydride, an exothermic reaction occurred and the solution turned orange. No separation of solid took place and the mixture was stood at 40-50° for eight hours. Methanol was added to destroy the excess acetic anhydride and the whole evaporated to an orange oil. On cooling, the oil crystallised and was filtered to produce an 86% yield of ethyl α-acetyl-2-quinolylacetate (178). Recrystallisation of the crude product from petroleum ether gave the keto-ester (178) as yellow micro-prisms. The infrared spectrum showed peaks at 1690 cm.$^{-1}$, 1632 cm.$^{-1}$, and 1615 cm.$^{-1}$, and the n.m.r. spectrum showed a three proton singlet at 2.40 p.p.m. for the acetyl protons, five ethyl protons, six aromatic protons, and a broad, one proton singlet at 13.0 p.p.m. The spectral evidence again indicates the keto-ester (178) to have the exocyclic double bond.

In an attempt to determine whether alkylation would occur on the nitrogen or carbon, the sodium salt of the keto-ester (178) was obtained using sodium hydride and an equivalent amount of methyl iodide added to the cold suspension of the sodium enolate. The base was extracted with dilute hydrochloric acid and neutralised with sodium carbonate solution. The orange oil isolated was found to have identical spectral properties with ethyl α-(2-quinoline) propionate (179) prepared by Jones and Wood.[105]



The experiment was repeated where the sodium salt of the keto-ester (178) was prepared and destroyed by water and extracted. The product was

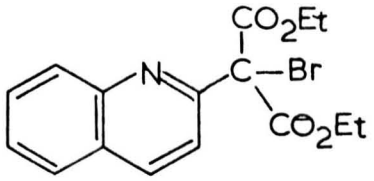
found to be ethyl 2-quinolylacetate (151). When keto-ester (178) was shaken with dilute sodium hydroxide a quantitative yield of ester (151) was obtained, and on standing in air the keto-ester (178) decomposed to acetic acid and ester (151). More vigorous hydrolysis of keto-ester (178) produced quinaldine. Ethyl α-acetyl-α-(2-quinoline)propionate (180) was obtained by formation of the sodium salt of keto-ester (178), methylation with methyl iodide, and acidification with acetic acid. Evaporation gave the crude substituted keto-ester (180) but all attempts to purify it gave the ester (179) and acetic acid. The n.m.r. spectrum of the crude keto-ester (180) showed the acetyl methyl as a singlet at 2.20 p.p.m., and the C-methyl group as a singlet at 1.82 p.p.m. The infrared spectrum showed peaks at 1740 $cm.^{-1}$, and 1690 $cm.^{-1}$

Attempts to obtain keto-ester (180) by acylation of the sodium salt of ester (179) with acetyl chloride always resulted in starting material being recovered.

Since alkylation of keto-ester (178) occurs on carbon and not on nitrogen it is of no synthetic use in the preparation of 4-substituted derivatives of ketone (158), although mild hydrolysis of the keto-ester (178) is by far the best method for the preparation of ester (151) in high yield.

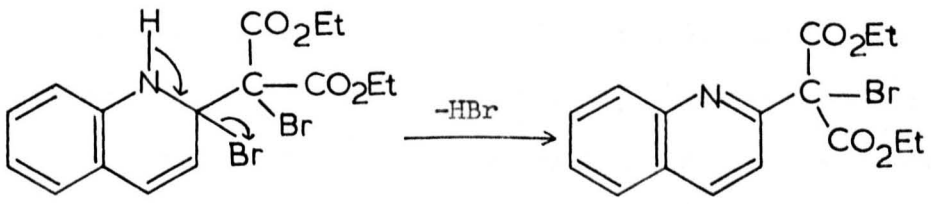
Bromination of the di-ester (152) also occurred readily, as in the previous brominations, the mono-bromo compound (181) formed being a pale yellow, viscous liquid which was shown to be pure by v.p.c. analysis. The n.m.r. spectrum showed six aromatic protons, a four

proton ester methylene quartet, and a six proton triplet centred at 1.35 p.p.m. The infrared spectrum showed absorption at 1750 cm.$^{-1}$



(181)

Golankiewicz reported the bromination of ethyl 2-quinolylmalonate (152) with an equivalent of bromine in chloroform to produce a compound containing five bromine atoms.[125] A possible explanation of this is that bromination of the exocyclic double bond takes place to give the dibromide (182), which on basification, dehydrobrominates to give the mono-bromo compound (181).



(182) (181)

If no basification is involved then the dibromide (182) may crystallise as the hydrotribromide. Golankiewicz also reported that ethyl 4-quinolylmalonate brominated to give the hydrobromide of ethyl 4-quinoline-bromomalonate.

Attempts to N-alkylate ethyl 2-quinolylmalonate (152) under the same alkylation conditions used for the alkylation of ester (154), using ethyl 3-bromopropionate or ethyl acrylate always led to the recovery of unchanged ester (152).

Preparation of ethyl 6-methoxy-1,2,3,4-tetrahydro-2-quinolylacetate (184).

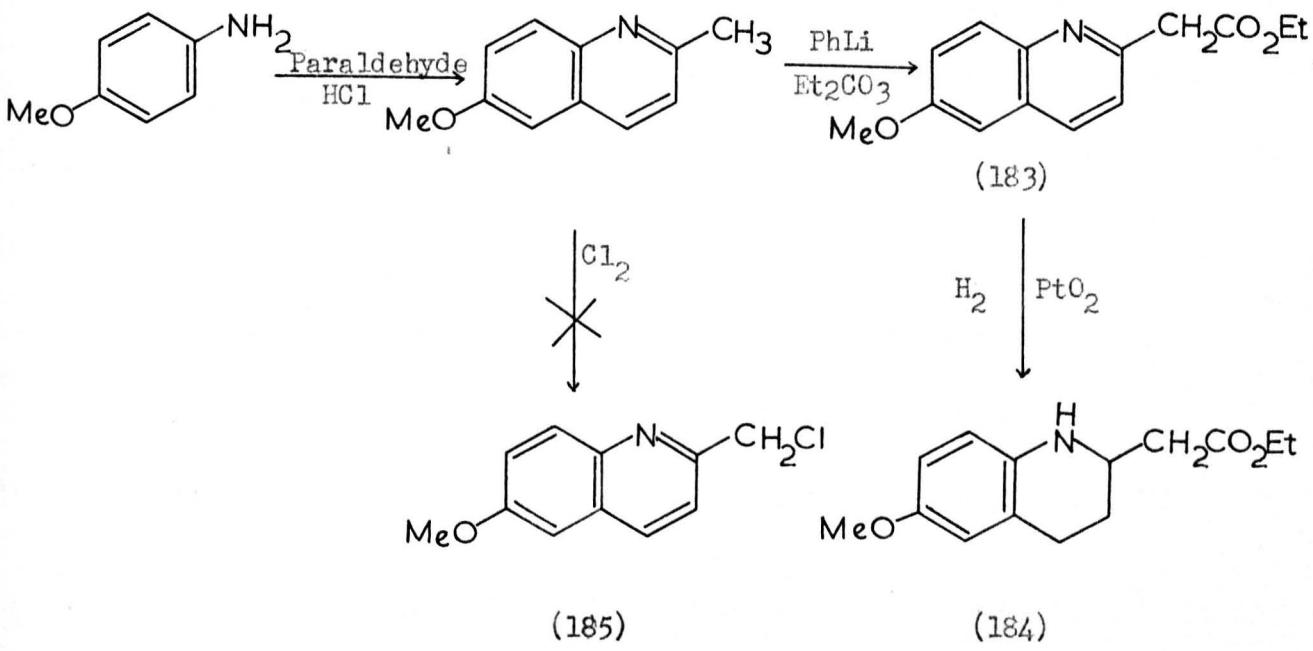
Due to the success encountered in the preparation of the tricyclic ketone (158) it was decided to follow a similar synthetic pathway from a 6-substituted quinoline. The methoxy group in 6-methoxyquinaldine could be easily converted eventually into the 3-hydroxyl group of a 9-azasteroid.

6-Methoxyquinaldine was prepared from p-anisidine and paraldehyde using the procedure of Bergstrom and Furst.[126]

Ethyl 6-methoxy-2-quinolylacetate (183) was prepared by the method of Hammick et al.[106] for ethyl 2-quinolylacetate. The yield of the ester (183) was never better than 15%, even when the modified method of Wood was used.[107] A number of by-products were encountered which were difficult to remove, one by-product being precipitated as the hydrochloride on addition of hydrochloric acid to the crude reaction mixture. The ester (183) was obtained on distillation as a viscous orange liquid, which solidified on standing.

The second method attempted for the preparation of ester (183) was via chlorination of the 2-methyl group in 6-methoxy quinaldine to the chloromethyl compound (185). When chlorine was passed into a solution of 6-methoxyquinaldine in carbon tetrachloride,[111] a white solid precipitated. When one equivalent of chlorine had passed into the solution, the white solid was filtered and recrystallised from ethanol as colourless needles. This solid was shown to be a hydrochloride, but not of the 2-chloromethyl-6-methoxyquinoline (185) expected. Extraction of the neutralised hydrochloride gave a white solid which still showed two three-proton singlets in the n.m.r. spectrum, due to the methyl and methoxy protons, but only four aromatic protons. Obviously, chlorination had occurred in the aromatic nucleus in preference to the side chain. Good analytical data could not be obtained to support the spectral data, possibly due to contamination by dichloro derivatives. Further attempts to chlorinate the side chain were unsuccessful.

Attempts to chlorinate the side chain of 6-nitroquinaldine, prepared by the method of Huisgen,[127] also failed. No reaction occurred at all, even when more drastic conditions were used, e.g. boiling carbon tetrachloride. The 6-nitro group might also have been useful as a precursor for a 3-hydroxy group in 9-azasteroids.



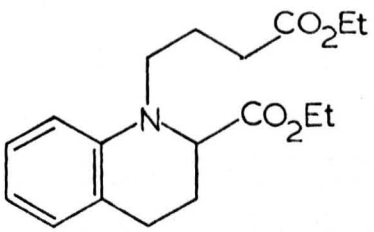
Hydrogenation of the ester (183) was accomplished at room temperature and pressure using Adams' catalyst in glacial acetic acid, to give the tetrahydro-ester (184), which was shown to be 95% pure after distillation.

Further syntheses in the field of 6-substituted quinolines were abandoned due to the lack of success in further attempts to elaborate ring D of the 9-azasteroid system from ketone (158) and cyano-ketone (146).

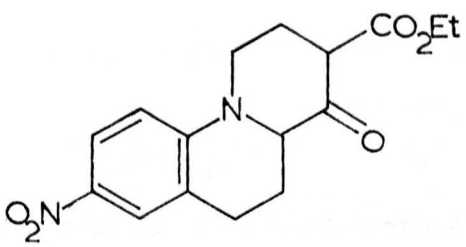
Nitration Studies.

It was decided that introduction of a nitro group in position-6 of the di-ester (148) or position-8 of ketone (158) would serve two purposes. Deactivation of the tertiary nitrogen atom, leading to reduction of its nucleophilic power, would facilitate C-alkylation rather than N-alkylation, and the nitro group would be easily converted to the 3-hydroxy group in a 9-azasteroid.

Schaarschmidt et al. found that nitration of N,N-dimethylaniline with dinitrogen tetroxide in carbon tetrachloride at about -10° proceeded smoothly giving the p-nitro-derivative in high yield.[128] Jones and Wood reported the nitration of the di-ester (186) with dinitrogen tetroxide, to give the corresponding 6-nitro derivative, which was cyclised to the



(186)



(187)

nitro-keto-ester (187).[105]

Quinoline and quinaldine appeared to be suitable tertiary bases to conduct preliminary experiments. Addition of dinitrogen tetroxide

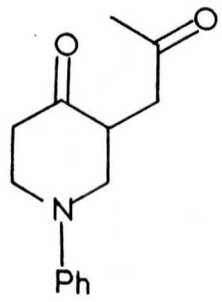
in carbon tetrachloride to a solution of quinoline or quinaldine at -5° gave, in each case, a yellow solid. The yellow solid was allowed to stir at -5° for three hours and then filtered. Recrystallisation from ethanol gave colourless needles for both the quinoline and quinaldine derivative. Analysis and spectral data showed that the compounds were quinolinium nitrate and quinaldinium nitrate. Evaporation of the mother liquors gave only the salts with no sign of any nitro-products. The salts obtained from the reaction were identical with authentic samples of quinolinium and quinaldinium nitrate. Davenport et al. reported that quinoline formed a solid adduct with nitrogen tetroxide in ether at -75° which was unstable at room temperature.[129] Since the yields of the quinolinium nitrate were good in both cases, it seems that the unstable adduct reported by Davenport et al. was formed, and decomposed in the presence of atmospheric moisture to the salts.

Further nitration studies were abandoned when a very low yield was encountered in the nitration of N-phenyl-4-piperidone (see later).

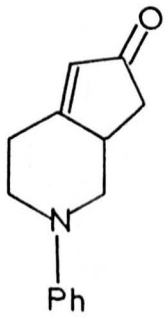
Synthesis and alkylation of N-phenyl-4-piperidone.

The synthetic problem in the synthesis of a 9-azasteroid from derivatives of 4aH-benzo[c]quinolizine (141) was the efficient fusion of a 5-membered ring across the 3 and 4 positions. Because of the similarity of tricyclic ketone (158) and N-phenyl-4-piperidone, the latter compound was chosen as a model compound for further synthetic approaches to a 9-azasteroid.

The construction of the five membered ring system could be achieved by addition of a three or four carbon chain at position 3 of the 4-piperidone and subsequent cyclisation of an activated carbon in the chain onto the 4-carbonyl group in the piperidone ring, which could be converted into a perhydro-pyrindene structure. A typical intermediate would be compound (188) which could be cyclised to the α,β-unsaturated ketone (189).



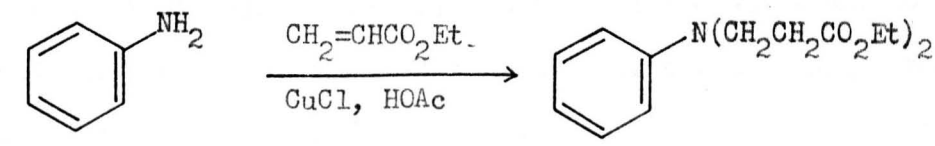
(188)

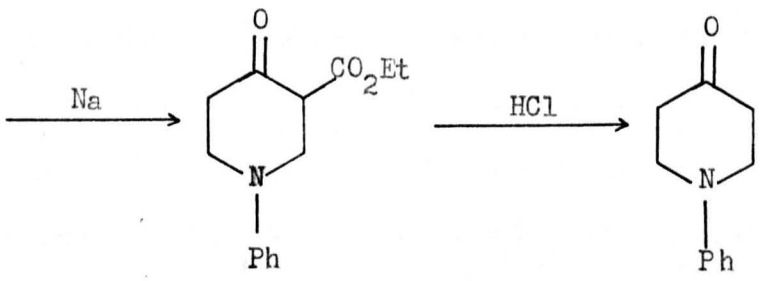


(189)

Attempts to synthesise diketone (188) were made and will be discussed.

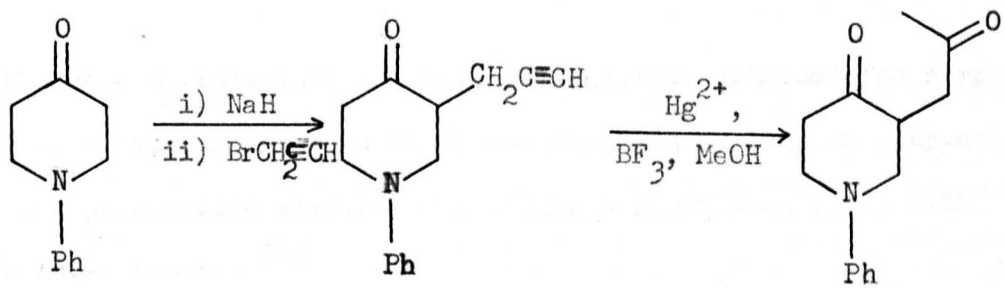
N-Phenyl-4-piperidone (100) was synthesised by the method used by Gallagher and Mann,[67] as shown below. This method gave an overall yield of piperidone (100) of 25%.





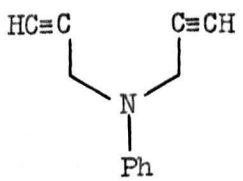
(100)

The synthetic approach used was alkylation of the sodium enolate of piperidone (100) with propargyl bromide in an attempt to obtain 1-phenyl-3-(prop-2-ynyl)-4-piperidone (190). Hydration of the acetylene (190) would give the diketone (188).



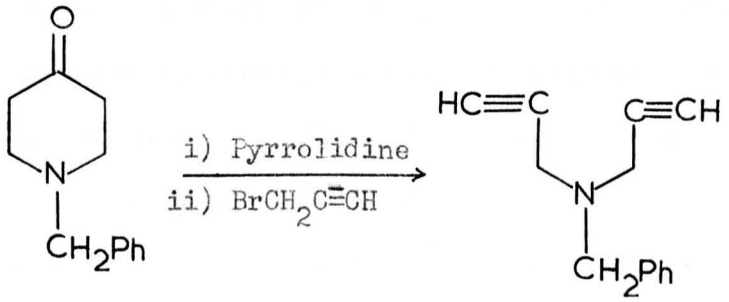
(190) (188)

The sodium enolate of piperidone (100) was obtained using sodium hydride in dimethoxyethane and heating the mixture for three hours. Propargyl bromide in dimethoxyethane was added to the ice-cold suspension of the sodium salt. The colour changed to orange and a suspension formed. Stirring was continued for a further ten hours. Evaporation of the solution gave a dark brown gum, most of which was insoluble in ether and appeared to be a quarternary salt. The ether extract on evaporation gave a small yield of a red oil which on chromatography yielded a colourless oil. Its infrared spectrum showed an acetylene hydrogen at 3290 $cm.^{-1}$. No carbonyl group appeared to be present in the molecule. The n.m.r. spectrum showed only three peaks. A 5-proton aromatic signal occurred at 7.15 p.p.m. A sharp 4-proton doublet centred at 3.90 p.p.m. (J = 2 c.p.s.), and a sharp 2-proton triplet at 2.00 p.p.m. (J = 2 c.p.s.), were the only remaining peaks. This information led to the structure (191) for this compound.



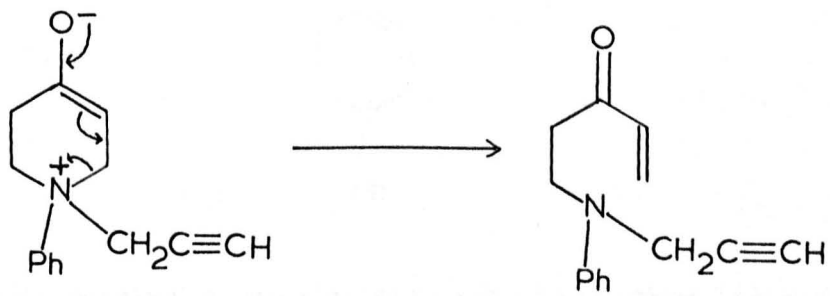
(191)

Although a satisfactory analysis could not be obtained for compound (191), a similar compound (193) was obtained by Baty on alkylation of the pyrrolidine enamine of N-benzyl-4-piperidone (192) with propargyl bromide.[131]



(192) (193)

The production of N,N-di(prop-2-ynyl)aniline (191) from the enolate can be explained if initial reaction of the enolate with propargyl bromide occurs at the nitrogen in the 4-piperidone ring. This will produce the intermediate (194) which could open as indicated to give a structure such as (195).

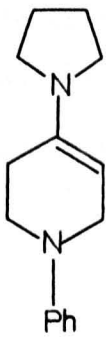


(194) (195)

Further reaction of the intermediate (195) could lead to N,N-di(prop--2-ynyl)aniline.

No other identifiable products were isolated from the crude reaction product although several products showed an acetylene hydrogen in their infrared spectrum and signs of an acetylene proton in their n.m.r. spectrum. The low yields encountered in the alkylation of sodium enolates of basic ketones prompted the study of the use of enamines as intermediates in the alkylation of ketones.[120]

The pyrrolidine enamine of N-phenyl-4-piperidone (196) was prepared in high yield by the standard procedure.[120] The solid enamine was unstable to distillation but the n.m.r. spectrum showed a single vinyl hydrogen as a triplet centred at 4.15 p.p.m. (J = 3 c.p.s.) and the infrared spectrum showed a peak at 1657 $cm.^{-1}$ due to the isolated double bond. There was no sign of the carbonyl peak.



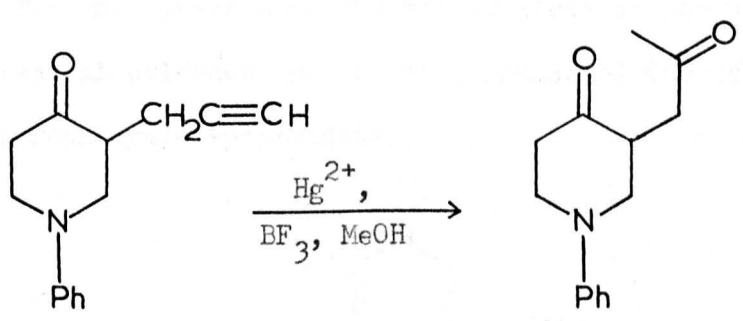
(196)

The crude enamine on washing with petroleum ether had a melting point of 76-81°.

The reaction of the enamine (196) with propargyl bromide was performed in benzene solution. When an equimolar quantity of propargyl bromide was added to the enamine at room temperature a

mildly exothermic reaction occurred, and the solution became dark red in colour, with the separation of a dark brown solid. The solution was stirred for sixteen hours at room temperature and heated to boiling for a half-hour. The enamine was decomposed with warm water, and the product extracted to give a viscous, brown oil. The brown product was very unstable, and quickly formed a tar on exposure to the atmosphere. An n.m.r. spectrum of the crude product showed the acetylenic proton as a triplet centred at 1.95 p.p.m., and the infrared spectrum showed peaks due to the acetylene group and carbonyl peak. No identifiable products were obtained on chromatography on Woelm alumina.

An attempt to hydrate the crude product from the alkylation by the method of Islam et al.[122] always gave crude starting material. It was hoped that the crude acetylene compound (197) would hydrate with boron trifluoride-mercuric oxide catalyst in methanol to give the diketone (188), which could be cyclised to the dicyclic ketone (189).

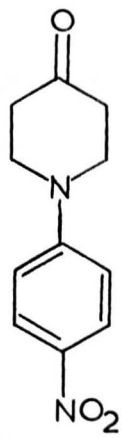


(197) (188)

To reduce the basicity of the tertiary nitrogen in N-phenyl-4-piperidone and hence reduce the amount of N-alkylation, it was necessary to introduce an electron-withdrawing group into the benzene ring. Such a group would be a nitro-group in the para-position of the benzene ring.

As reported earlier, nitration of N,N-dimethylaniline with dinitrogen tetroxide proceeds in high yield to give the para-derivative.[128]

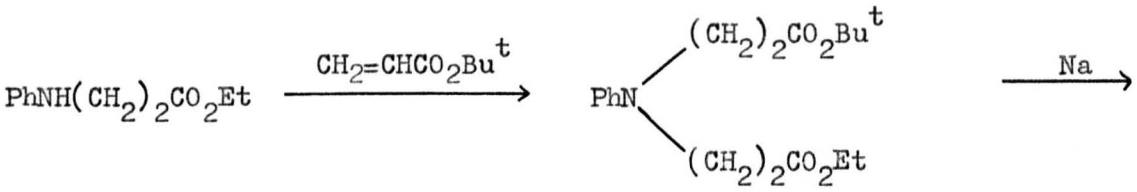
Nitration of N-phenyl-4-piperidone was carried out in carbon tetrachloride using dinitrogen tetroxide at $-5^{\circ}C$. The reaction product was extracted as a carbonaceous solid. Some N-phenyl-4-piperidone was extracted from the crude product using ether and the remainder of the solid was heated with ethanol and decolourising charcoal. Evaporation of the ethanol gave a yellow solid which was recrystallised from ethanol. Its infrared spectrum showed peaks at 1710 $cm.^{-1}$, 1315 $cm.^{-1}$, and 830 $cm.^{-1}$, due to the carbonyl group, nitro-group, and two adjacent aromatic protons. The n.m.r. spectrum showed two doublets (J = 9 c.p.s.) centred at 6.91 p.p.m., and 8.21 p.p.m. each constituting two protons each. The only peaks were the two triplets of the piperidone ring. This spectral evidence and analysis indicated structure (198), N-(p-nitrophenyl)-4-piperidone.



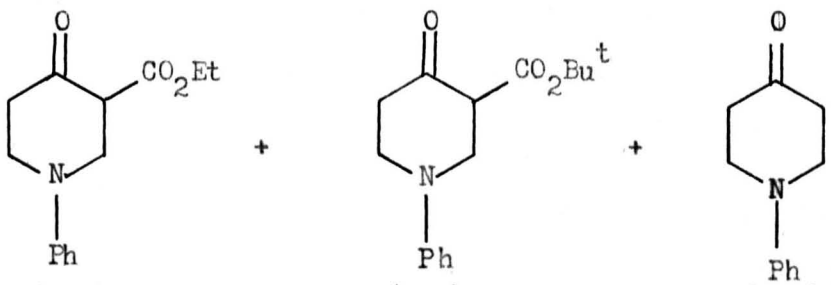
(198)

The yield of piperidone (198) was less than 10% and hence of no further synthetic use.

It was finally decided to synthesise and cyclise the di-ester (199) in an investigation of the directional effect exerted by the t-butyl group in a Dieckmann cyclisation.



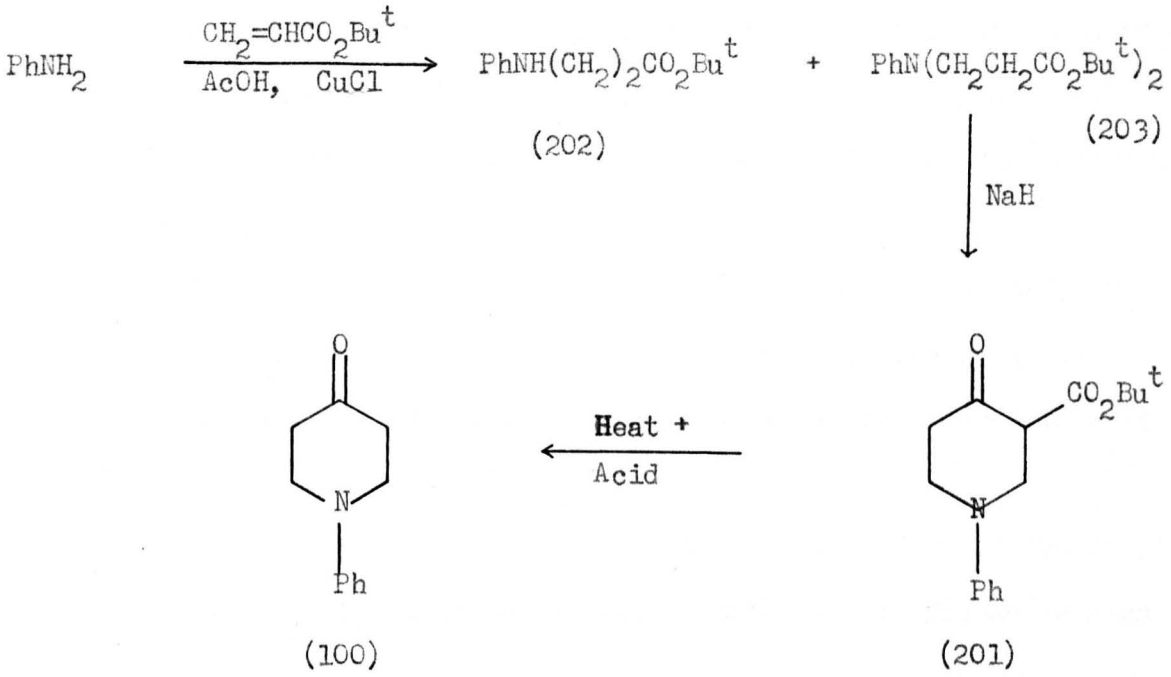
(199)



(200) (201) (100)

Ethyl N-phenyl-β-alaninate[67] was alkylated with t-butyl acrylate in glacial acetic in the presence of cuprous chloride. Distillation of the product gave acetanilide, produced by dehydration of anilinium acetate, recovered ethyl N-phenyl-β-alaninate, and the desired diester (199) as a yellow oil. The infrared spectrum of diester (199) showed a peak at 1725 $cm.^{-1}$ and the n.m.r. spectrum showed a nine proton singlet at 1.45 p.p.m. due to the t-butyl protons.

Dieckmann cyclisation of the diester (199) was performed using sodium in xylene, a mixture of alcohol and xylene being distilled during the cyclisation. An n.m.r. spectrum of this mixture showed that ethanol and t-butanol were both present in approximately equal quantities, indicating that the t-butyl ester group has no, or very little, effect on the direction of cyclisation. The sodium salt of the keto-ester was extracted with water, and the organic layer further extracted with aqueous sodium hydroxide. Neutralisation of the sodium salts of the keto-esters and extraction gave the keto-esters as a viscous orange oil. Evaporation of the organic layer gave a small quantity of N-phenyl-4-piperidone (100). The infrared spectrum showed the expected peaks for a keto-enol mixture. The n.m.r. spectrum showed both ethyl protons and t-butyl protons. Two t-butyl singlets appeared at 1.45 p.p.m. and 1.54 p.p.m. Partial separation of the diesters was accomplished on chromatography using Woelm alumina. Brief heating of di-ester (201) showed that the size of the t-butyl peaks in the n.m.r. spectrum had decreased considerably, the peak at 1.54 p.p.m. decreasing more than the peak at 1.45 p.p.m. It is known that t-butyl esters are unstable to heat in the presence of acid, and Rhoads, et al. have shown[130] that some cyclic β-keto-esters decompose on heating to give, it is believed, the corresponding ketones. It seemed that by using the combined instability of t-butyl esters and cyclic β-keto-esters, a convenient route to 4-piperidones would be obtained.



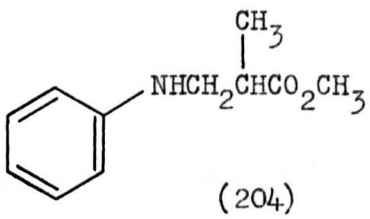
Addition of t-butyl acrylate to aniline was accomplished in boiling acetic acid in the presence of cuprous chloride. Distillation of the product gave aniline, t-butyl—N-phenyl-β-alaninate (202), and the diester (203) as a yellow oil. The infrared spectrum had a peak at 1725 $cm.^{-1}$. The n.m.r. spectrum had an eighteen proton singlet at 1.58 p.p.m. On distillation of the diester (203) it was found that elimination of t-butyl acrylate occurred when pressures of greater than 0.1 mm. were used.

Sodium hydride in boiling benzene was used to cyclise diester (203), the yellow sodium salt of the keto-ester (201) being extracted with water and aqueous sodium hydroxide. Neutralisation of the combined

aqueous extracts and extraction with chloroform gave a red oil showing the expected spectral characteristics of a keto-enol mixture (201). The t-butyl singlets in the n.m.r. spectrum integrated for less than the expected nine protons.

The crude mixture of keto-ester (201) and piperidone (100) was boiled with chloroform in the presence of trifluoroacetic acid; evaporation and further heating gave N-phenyl-4-piperidone (100) in 80% yield from diester (203).

It was hoped that these reactions using t-butyl esters would afford a method of obtaining 1-phenyl-3-methyl-4-piperidone in high yield from amino-ester (204). Ester (204) was synthesised in very



(204)

low yield from aniline and methyl methacrylate, the main product being a polymer.

Attempts to alkylate ester (204) with t-butyl acrylate proved unsuccessful.

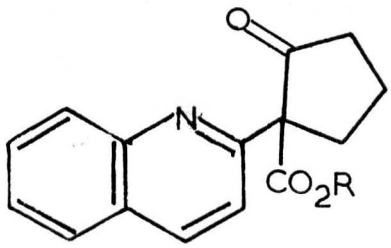
SYNTHESIS OF SOME 2-CYCLOPENTYL QUINOLINES

Due to the lack of success encountered in the synthetic approaches to 9-azasteroids from benzo[c]quinolizines, and the successful preparation of 2-quinolyl-2-cyclopentanone from quinoline-1-oxide and the enamine of cyclopentanone in benzoyl chloride,[131] it was decided to synthesise some cyclopentane derivatives containing active hydrogens and react these with quinoline-1-oxide. The synthetic problem remaining would be the efficient fusion of a two carbon chain from the 2-position of the cyclopentane ring to the nitrogen of the tetrahydroquinoline giving rise to the 9-azasteroid system.

The construction of the 6-membered ring C in the 9-azasteroid system can be performed, theoretically, in two ways and the attempts to achieve this will be discussed.

Reaction between quinoline-1-oxide and a) 2-carbethoxycyclopentanone, b) 2-carbo-t-butoxycyclopentanone in the presence of acetic anhydride.

When 2-carbethoxycyclopentanone was added to quinoline-1-oxide in acetic anhydride, a vigorous reaction took place which required external cooling. The mixture was allowed to stand overnight at room temperature and worked up in a similar manner as in the preparation of the β-keto-ester (178) from quinoline-1-oxide and ethyl acetoacetate.



(205a) R = C_2H_5

b) R = t-C_4H_9

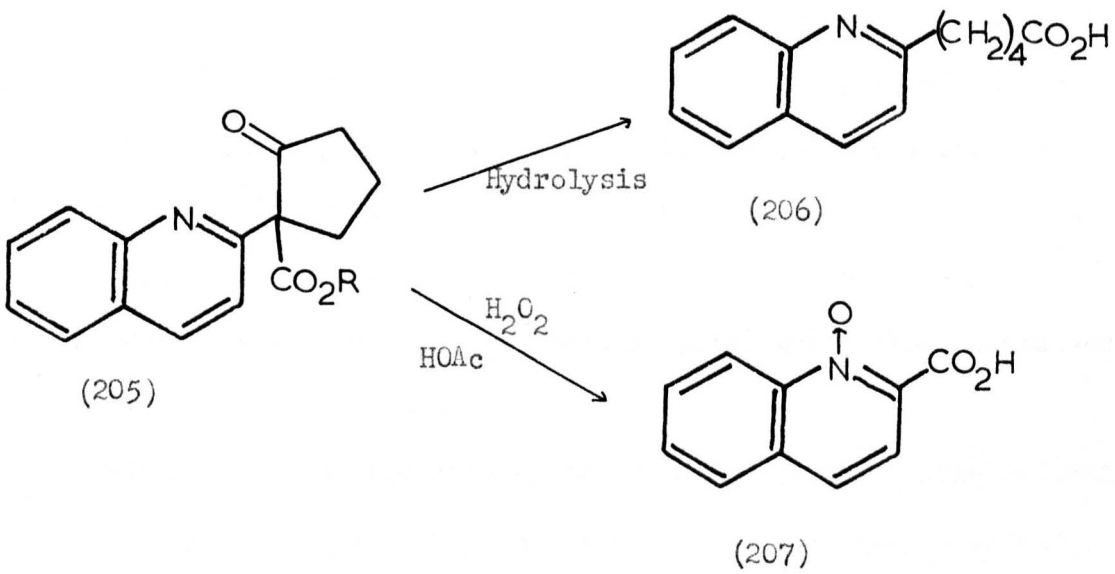
The viscous orange liquid obtained on distillation showed peaks due to ester carbonyl (1725 $cm.^{-1}$) and ketone (1762 $cm.^{-1}$). The n.m.r. spectrum showed a three proton triplet at 1.26 p.p.m. (ester methyl group), a six proton multiplet due to the cyclopentanone methylene protons, and six aromatic protons. The α-proton of quinoline at 8.80 p.p.m. was absent in the n.m.r. spectrum. Analysis and the spectral evidence indicated the structure (205a).

2-Carbo-t-butoxycyclopentanone was obtained from Dieckmann cyclisation of di-t-butyl adipate using sodium hydride in boiling benzene. Di-t-butyl adipate was prepared from adipylchloride[137] and t-butanol in N,N-dimethylaniline.[133]

The keto-ester (205b) was obtained in a similar manner to the preparation of the ethyl ester (205a). The infrared spectrum showed absorption due to ester and ketone carbonyls and the n.m.r. spectrum showed a nine proton t-butyl peak at 1.45 p.p.m. and no sign of the α-proton of quinoline.

Basic hydrolysis of the keto-ester (205a) was performed by

shaking with dilute aqueous ethanolic sodium hydroxide until a homogeneous solution was obtained. Neutralisation with dilute hydrochloric acid and evaporation gave an orange gum. Extraction of this gum with chloroform



(205) (206) (207)

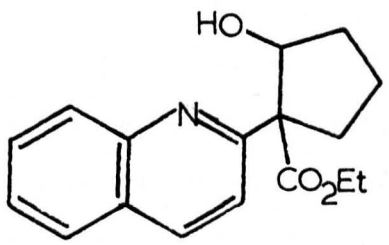
and evaporation of chloroform, followed by trituration with petroleum-ether gave a solid. The infrared spectrum of the recrystallised solid showed a broad band from 2500-2800 $cm.^{-1}$, and a peak at 1690 $cm.^{-1}$. The n.m.r. spectrum showed a four proton multiplet at 1.83 p.p.m., a two proton triplet at 2.83 p.p.m., a two proton triplet at 3.06 p.p.m., six aromatic protons, and a sharp one proton singlet at 11.5 p.p.m. These spectral data and analysis assigned the structure as the acid (206).

Further proof that substitution had occurred in the 2-position and not the 4-position of the quinoline nucleus was afforded by boiling the keto-ester (205a) with hydrogen peroxide in glacial acetic acid.[138] The quinoline carboxylic acid-1-oxide obtained had identical spectral

properties and melting point with an authentic specimen of quinoline-2-carboxylic acid-1-oxide (207) obtained by heating ethyl 2-quinolylacetate with hydrogen peroxide in glacial acetic acid.

It was hoped that because of the combined instability of t-butyl esters and cyclic β-keto-esters the carbo-t-butoxy group could be easily removed from keto-ester (205b). Hydrolysis using 2N hydrochloric acid gave, after working up, the acid (206). Attempts to remove the carbo-t-butoxy group by boiling under reflux with benzene containing p-toluene sulphonic acid, and by boiling under reflux with chloroform containing trifluoroacetic acid always gave a crude material which still contained a t-butyl peak in the n.m.r. spectrum.

Hydrogenation of the keto-ester (205a) in ethanol using palladium-charcoal catalyst at room temperature and pressure was very slow and stopped after the uptake of one mole of hydrogen. Filtration, and evaporation of the product, followed by distillation gave an orange liquid which showed no absorption due to ketone carbonyl in its infrared spectrum. Analysis showed the product to contain one more mole of hydrogen than the keto-ester (205a). The product is presumably the alcohol (208), although no hydroxyl peak was visible in the infrared spectrum.

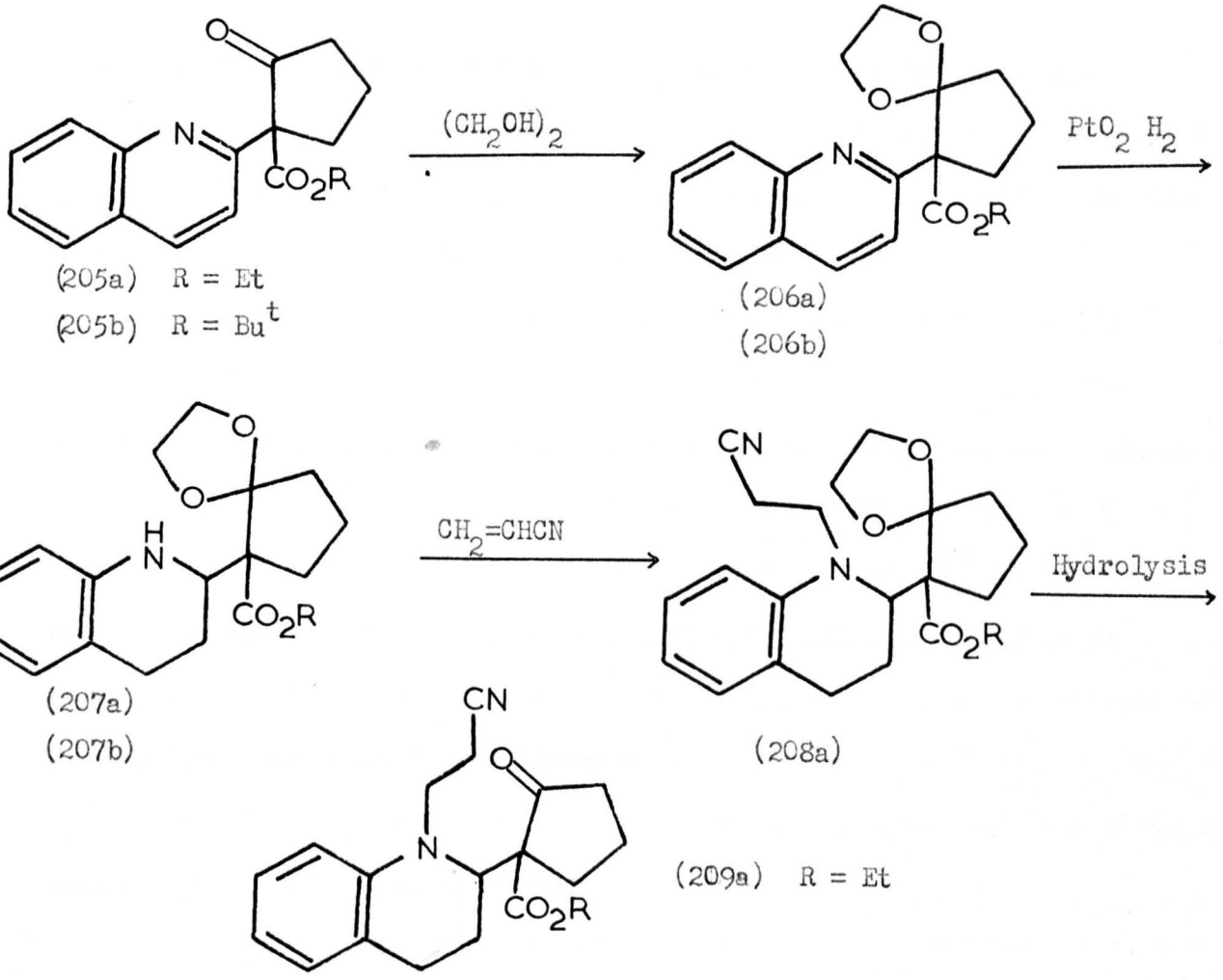


(208)

Branch reported that hydroxyl frequency has been found at 2600 cm.$^{-1}$, in compounds involving a chelated hydroxyl group and a heterocyclic nitrogen atom.[139] In many cases of this type the absence of a hydroxyl absorbtion in the fundamental region has been reported, owing to its being a weak band which has been superimposed upon the strong C-H stretching near 3000 cm.$^{-1}$

Attempted preparation of ethyl 2-(1-2'-cyanoethyl-1,2,3,4-tetrahydro-2-quinolyl)-cyclopentanone-2-carboxylate (209a).

Before attempting to hydrogenate the quinoline ring in keto-ester (205) it was necessary to protect the ketonic group. This was performed by ketal formation with ethylene glycol. The keto-ester (205a) was heated under a water separating device with benzene and a trace of p-toluene sulphonic acid for 12 hr. At the end of this time the amount of water separated did not constitute complete reaction. Heating under reflux for a further 20 hr. did not alter the amount of water in the separator. Evaporation of the benzene gave a residue which still showed absorption due to the ketone carbonyl in its infrared spectrum. This excess ketone was extracted from the mixture using Girard-T reagent. The ketal (206a) was purified by chromatography on Woelm alumina using benzene. The ketal (206a) showed only a peak at 1725 cm.$^{-1}$ in the carbonyl region of its infrared spectrum. The n.m.r. spectrum showed six protons in the region 3.60 p.p.m. to 4.35 p.p.m. belonging to the methylene proton of the ester and of the ethylenedioxy group.



(205a) R = Et
(205b) R = Bu^t

(206a)
(206b)

(207a)
(207b)

(208a)

(209a) R = Et

Further attempts to obtain complete ketal formation by using toluene or xylene in place of benzene led to ethylene glycol being lost on azeotropic distillation. The low yield encountered in this ketal formation is probably due, in part, to hydrolysis of the keto-ester (205).

Hydrogenation of the ketal (206a) using Adams' catalyst in glacial acetic acid was relatively slow at room temperature and pressure and was interrupted after the uptake of two moles of hydrogen. The reduction product was purified by chromatography in benzene on Woelm alumina. The infrared

spectrum of the secondary amine (207a) showed NH absorbtion at 3400 cm.$^{-1}$ and no peak due to ketone carbonyl. Attempts to form a benzoyl derivative or hydrochloride of amine (207a) were unsuccessful. Any solid derivative formed immediately decomposed on exposure to atmosphere.

When amine (207a) was boiled under reflux with acrylonitrile and glacial acetic acid with a trace of cuprous chloride for 20 hr., unreacted starting material only was obtained. Cookson and Mann found that aniline does not combine appreciably with boiling acrylonitrile in the presence of acetic acid but will combine with acrylonitrile at 150° in acetic acid.[70] Heating amine (207a) in a sealed tube with acrylonitrile in acetic acid at 150° for 4 hr. gave a crude mixture which on chromatography did not give any identifiable products.

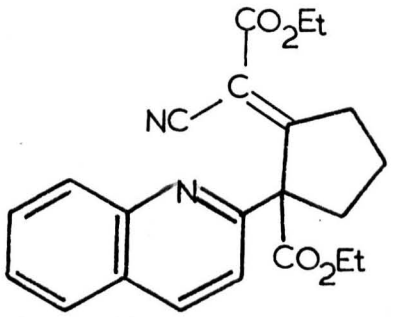
The t-butyl compounds (206b) and (207b) were obtained in a similar manner to that of the ethyl ester.

Attempted Knoevenagel condensation of ethyl 2-2'-quinolylcyclopentanone-2-carboxylate with ethyl cyanoacetate.

Due to the lack of success encountered in the synthetic route involving N-cyanoethylation of the amine (207a) it was decided to attempt the addition of the required two carbon chain on to the cyclopentanone residue.

When equimolar quantities of keto-ester (205a) and ethyl cyanoacetate containing a trace of piperidine were allowed to react by the procedure of Kon and Nanji,[141] the product, after work-up, showed mainly unreacted starting material and only a trace of a product showing

absorption due to α,β-unsaturated nitrile in its infrared spectrum.



(210)

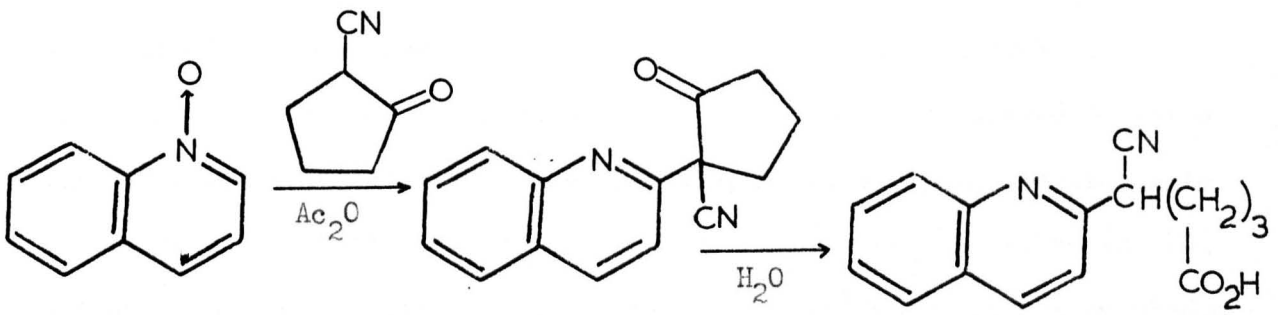
Other methods used in attempts to prepare condensation product (210) involved the use of ammonium acetate in acetic acid as catalyst,[142] and also acetic anhydride as dehydrating agent. Neither method gave any of the desired product. Refluxing a mixture of keto-ester (205a) and ethyl cyanoacetate with benzylamine and piperidine as catalyst gave starting material as well as some N-Benzyl-cyanoacetamide.

Reaction between quinoline-1-oxide and 2-cyanocyclopentanone in the presence of acetic anhydride.

2-Cyano-cyclopentanone was prepared by hydrolysis of the cyano-amine obtained from cyclisation of adiponitrile using potassium t-butoxide in benzene.

Dropwise addition of 2-cyano-cyclopentanone to a solution of quinoline-1-oxide in acetic anhydride gave a very vigorous reaction which required external cooling. The red mixture was allowed to stand at room temperature for a further hour and then cooled to -5° when a solid

separated. Filtration of the mixture and trituration of the filtrate with warm petroleum ether gave 2-cyano-2-(2'-quinolyl)cyclopentanone (211) in 68% yield.



(211) (212)

The infrared spectrum of cyano-ketone (211) showed peaks at 2242 cm.$^{-1}$ and 1768 cm.$^{-1}$. The n.m.r. spectrum showed six aromatic protons and six protons due to the cyclopentanone ring.

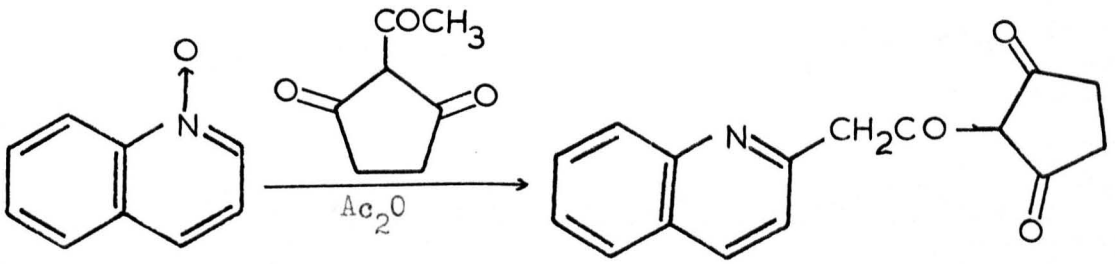
Hydrolysis of the cyanoketone (211) with dilute sodium carbonate solution gave a quantitative yield of the acid (212). On standing in air the cyanoketone (211) slowly decomposed to the acid (212). The infrared spectrum showed peaks at 1722 and 2240 cm.$^{-1}$. The n.m.r. spectrum showed a four proton multiplet at approximately 2.1 p.p.m., a two proton triplet at 2.48 p.p.m. (methylene group α to COOH), a one proton triplet at 4.38 p.p.m. (proton α to CN), six aromatic protons, and a one proton singlet at 10.98 p.p.m.

Any attempts to perform a Knoevenagel condensation on the cyanoketone (211) gave starting material and the acid (212).

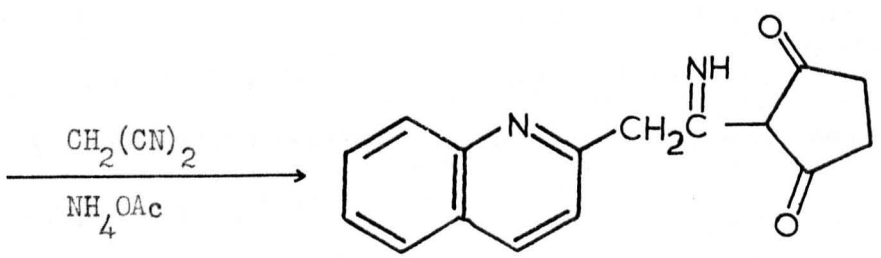
Reaction between quinoline-1-oxide and 2-acetyl-cyclopentane-1,3-dione.

2-Acetyl-cyclopentane-1,3-dione was prepared by the method of Merenyi and Nelson.[143]

When a solution of the dione in acetic anhydride was added to quinoline-1-oxide in acetic anhydride a vigorous reaction took place with the formation of an orange solid. The mixture was allowed to stand for 1 hr. and then filtered. The filtrate, after recrystallisation gave an orange solid which was only slightly soluble in organic solvents, but extremely soluble in organic bases and aqueous sodium hydroxide to give a yellow solution. Its infrared spectrum showed absorption at 1680 $cm.^{-1}$ and a broad band from 1640 to 1605 $cm.^{-1}$. The n.m.r. spectrum showed a four proton singlet at 3.02 p.p.m. a two proton singlet at 5.16 p.p.m., and six aromatic protons.



(213)



(214)

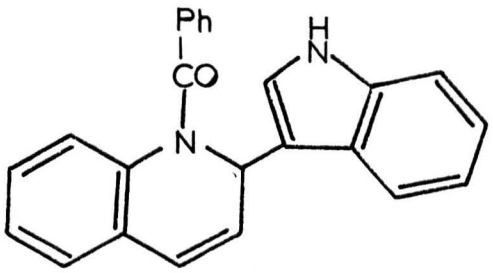
It was originally thought that addition of quinoline-1-oxide had occurred at the very reactive 2-position of the cyclopentane-1,3-dione but analysis showed that reaction had occurred at the less active acetyl methyl to give the triketone (213). Hamana reported that quinoline-1-oxide did not react with acetone or acetophenone.[123]

With the thought that the expected adduct was formed, attempts to perform a Knoevenagel condensation were unsuccessful, although a solid was obtained when the ketone (213) was heated with malononitrile in benzene using ammonium acetate as catalyst. This compound showed peaks at 3250, 1685, and 1625 $cm.^{-1}$ in its infrared spectrum. Its n.m.r. spectrum showed a four proton singlet at 2.57 p.p.m., a two proton singlet at 4.87 p.p.m., and seven protons in the aromatic region. From this spectral data and analysis, the compound was assigned the structure as the imine (214).

Neither of the compounds (213) or (214) were of any further synthetic value.

Reactions of quinoline with 2-carbethoxy-cyclopentanone and 2-cyano-cyclopentanone in the presence of acid chlorides.

Von Dobeneck reported that quinoline reacted with compounds containing active hydrogens in the presence of acid chlorides to give mainly 2-substituted-N-acetyl-1,2-dihydroquinolines.[144] For example, quinoline and indole react in the presence of benzoyl chloride to give the 2-substituted quinoline (215).

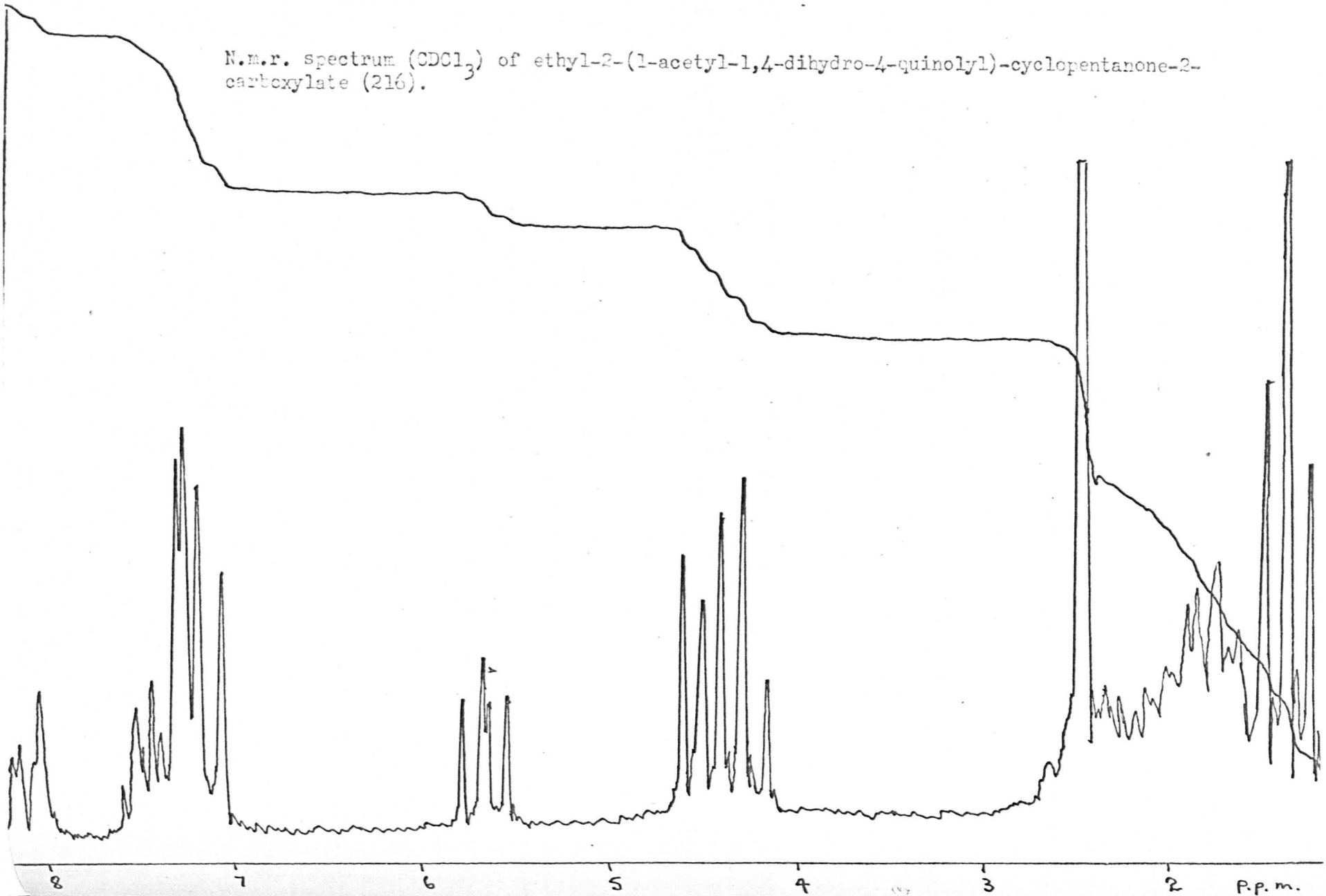


(215)

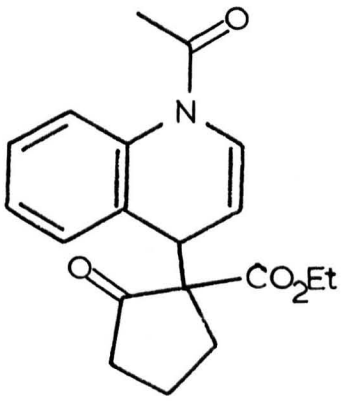
This reaction seemed a good method for introducing a cyclopentane ring in the 2-position of the quinoline ring while adding the two carbon chain on the quinoline nitrogen necessary to form ring C of the azasteroid nucleus.

When acetyl chloride was added to a solution of excess quinoline and 2-carbethoxycyclopentanone in benzene no immediate reaction took place. On standing the mixture a precipitate of quinoline hydrochloride slowly formed. After standing for about 3 days the smell of acetyl chloride disappeared. The quinoline hydrochloride was filtered and washed with ether. The excess quinoline was extracted with dilute hydrochloric acid and the ether was evaporated to give a residue from which a solid separated. Trituration and recrystallisation of the solid gave colourless cubes. The infrared spectrum showed absorption at 1750, 1720, 1690 and 1655 $cm.^{-1}$. The n.m.r. spectrum (see figure) showed a triplet at 1.32 p.p.m., (ester methyl group), six cyclopentanone protons, a singlet at 2.43 p.p.m., (acetyl methyl), a quartet at 4.31 p.p.m. (ester methylene group), a doublet at 4.52 p.p.m. (J = 7 c.p.s., C-4 proton), a slightly split triplet at 5.62 p.p.m. (J = 7 c.p.s. and 6 c.p.s., C-3 proton), four protons in the region 7.0-7.6 p.p.m., and a split doublet at

N.m.r. spectrum ($CDCl_3$) of ethyl-2-(1-acetyl-1,4-dihydro-4-quinolyl)-cyclopentanone-2-carboxylate (216).



8.05 p.p.m., constituting one proton. This one proton is assigned either to the C-2 proton or C-8 proton in compound (216). Nagarajan et al.

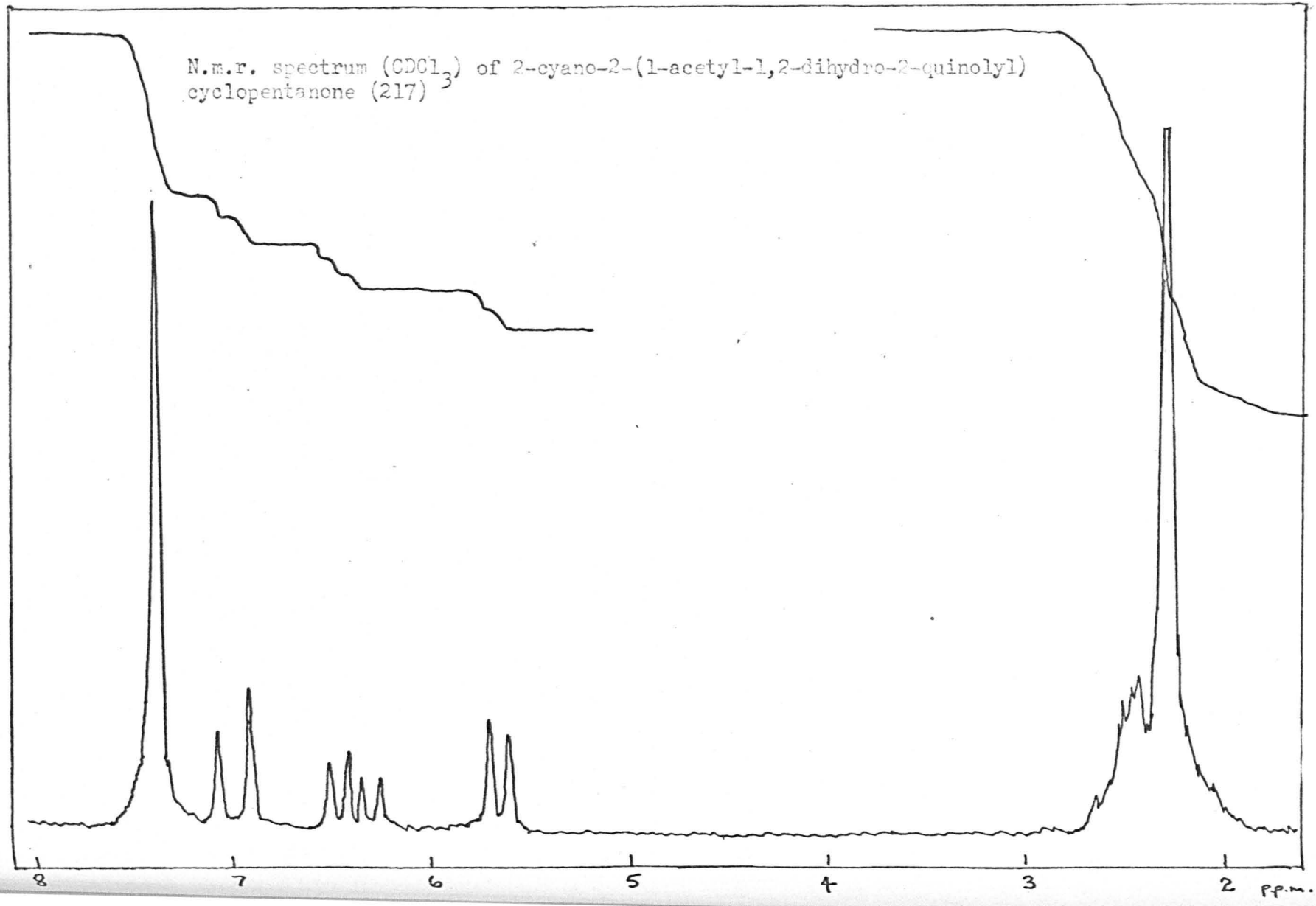


(216)

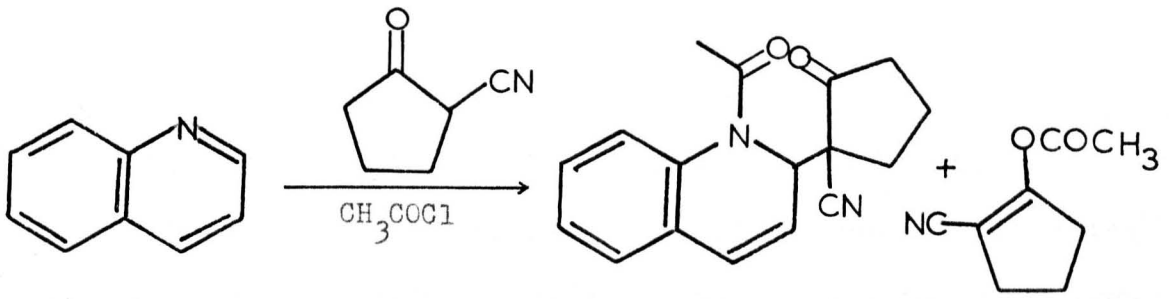
reported that the C-8 proton in N-acyltetrahydroquinolines is not separated from other aromatic protons in its n.m.r. spectrum and has the configuration where the CO group is oriented away from the benzene ring.[145] In contrast, in all the N-acyl indolines studied by Nagarajan, the n.m.r. spectra indicated that the CO group was preferentially oriented towards the phenyl ring since the C-7 proton was separated from the other aromatic protons. If it is assumed that the downfield proton in compound (216) is the C-8 proton then in this case the CO group is oriented towards the phenyl ring and the C-1 proton is masked by the other aromatic protons.

The dihydroquinoline is obviously of no further synthetic use in the preparation of aza-steroids.

When acetyl chloride was added to a solution of 2-cyanocyclopentanone and excess quinoline in dry benzene an exothermic reaction took place with the precipitation of quinoline hydrochloride. The reaction was allowed to proceed for another hour and the quinoline hydrochloride filtered. Excess


N.m.r. spectrum ($CDCl_3$) of 2-cyano-2-(1-acetyl-1,2-dihydro-2-quinolyl) cyclopentanone (217)
8
7
6
5
4
3
2
p.p.m.

quinoline was removed from the filtrate which was then evaporated. On cooling the residue a solid separated which was filtered and recrystallised to give colourless cubes.

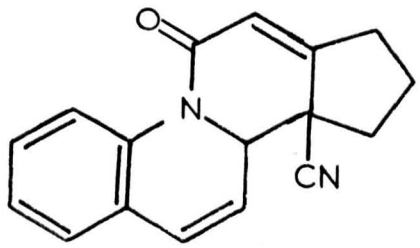


(217) (218)

The infrared spectrum of the solid showed absorption at 2245, 1752, 1662, and 1656 cm.$^{-1}$. The n.m.r. spectrum (see figure) showed a singlet at 2.25 p.p.m., (acetyl methyl), six cyclopentanone protons, a doublet at 5.65 p.p.m. (J = 6 c.p.s., C-2 proton), a quartet at 6.37 p.p.m. (J = 6 c.p.s. and 10 c.p.s., C-3 proton), a doublet at 6.98 p.p.m. (J = 10 c.p.s., C-4 proton), and a four proton singlet at 7.83 p.p.m. (aromatic protons). This pattern in the aromatic region is similar to that observed in styrene derivatives.

The residue remaining after filtration of the amide (217) was distilled to give a colourless liquid. Its infrared spectrum showed absorption at 2230, 1783, and 1660 cm.$^{-1}$. The n.m.r. spectrum showed a singlet at 2.21 p.p.m. and six cyclopentane protons only. This spectral data and analysis was consistent with the O-acylated product (218).

In an attempt to cyclise amide (217) to obtain the tetracyclic amide (219), the amide (217) was heated in dry dimethoxyethane with sodium hydride. After acidification with glacial acetic acid and working up the residue was found to contain some quinoline with no other identifiable products.

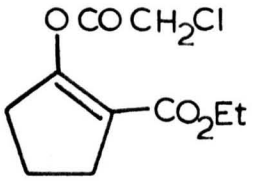


(219)

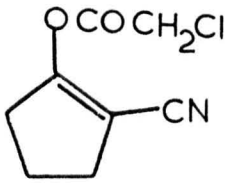
The failure to cyclise the amide (217) was due probably to the low reactivity of the acetyl methyl. It was decided to prepare some acid chlorides with more active methylene groups which then may take part in a Knoevenagel type condensation on the ketonic group of the tricyclic amides.

Chloroacetyl chloride was prepared by the action of phosphoryl chloride on chloroacetic acid.

When chloroacetyl chloride was added to quinoline and 2-carbethoxy-cyclopentanone in dry benzene an exothermic reaction took place. After working up as for the previous experiments, the main product was shown from analysis and spectral data to be the O-acylated compound (220), with no amide.



(220)



(221)

When chloroacetyl chloride was added to quinoline and 2-cyanocyclopentanone in dry benzene an exothermic reaction took place. Working up as in the previous experiments gave, from analysis and spectral data, mainly the O-acylated product (221), and no amide.

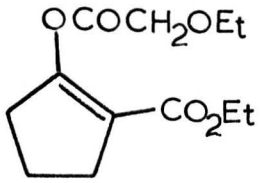
Cyanoacetyl chloride was prepared from cyanoacetic acid and phosphorus pentachloride.[124]

The reaction of cyanoacetyl chloride with quinoline and 2-cyanocyclopentanone gave, after work up, a very crude product with no identifiable products. Cyanoacetyl chloride contains a very reactive methylene group itself and can take part as the nucleophilic reagent and the acylating agent to produce a variety of products.

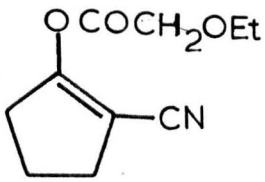
Since cyanoacetyl and chloroacetyl chloride had produced none of the desired amide it was decided to prepare an acid chloride containing a less reactive methylene group. Ethoxy-acetyl chloride was prepared from ethoxy-acetic acid and benzoyl chloride by the method reported by Brown.[146]

Ethoxy-acetyl chloride was reacted with quinoline and 2-carbethoxycyclopentanone in dry benzene. An exothermic reaction took place and the reaction mixture was allowed to stir for a further hour. On working up,

the only product, from analysis and spectral data, was the O-acylated product (222).



(222)



(223)

The reaction between ethoxyacetyl chloride, quinoline and 2-cyanocyclopentanone was conducted in a similar manner to the reaction using 2-carbethoxycyclopentanone giving the O-acylated compound (223) in high yield.

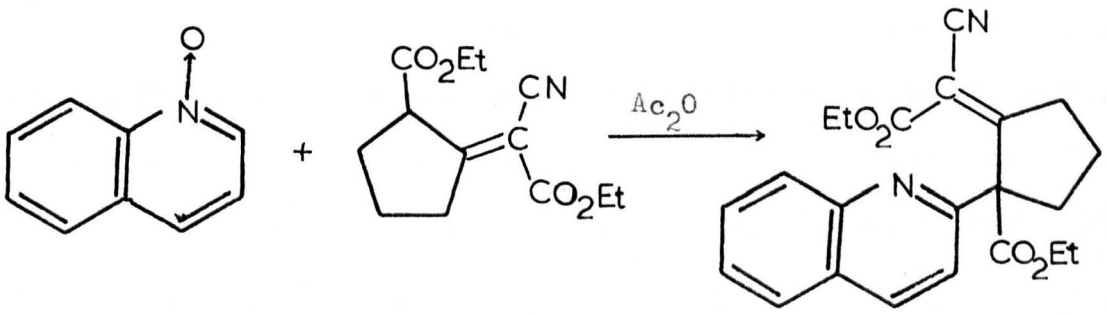
Preparation of some cyclopentylidene derivatives and their reaction with quinoline-N-oxide in acetic anhydride.

In view of the failure of the keto-ester (205a) to undergo a Knoevenagel condensation with ethyl cyanoacetate to give the compound (210) it was decided to carry out Knoevanagel condensations on cyclopentanone and its derivatives before they are reacted with quinoline-1-oxide in an attempt to synthesise the tricyclic compound (210).

2-Cyanocyclopentanone would not undergo a Knoevanagel condensation by any of the standard methods, although infrared and n.m.r. spectra indicated that it was completely ketonic.

Ethyl 2-carbethoxy-cyclopentylidene cyanoacetate (224) was prepared by the method of Kon and Nanji.[141]

When the cyano-ester (224) was added to a cooled solution of quinoline-1-oxide in acetic anhydride an exothermic reaction took place with the formation of a blood red colour [illegible]. The reaction was allowed to proceed for a further hour and then methanol added to destroy the excess acetic anhydride. After work-up the viscous red oil was chromatographed on Woelm alumina to give some recovered cyano-ester (224) and an orange oil which darkened rapidly in the atmosphere.



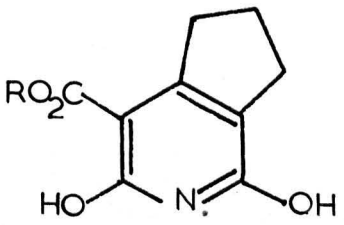
(224) (210)

The infrared spectrum of this oil showed three sets of triplets at approximately 1.2 p.p.m. due to ester methyls (cyclic ester methyl, and cis and trans exocyclic ester methyls), six cyclopentane protons (two of which were distinctly further downfield than the bulk), a multiplet consisting of three quartets (ester methylene groups), and six aromatic protons with no downfield α proton of the quinoline. The infrared spectrum showed absorption at 2230, 1730, and 1625 $cm.^{-1}$. Although a satisfactory analysis could not be obtained the structure as (210) was assigned to the product from spectral data. Attempts at purification failed, chromatography on too active alumina leading to decomposition on the column.

Hydrogenation of compound (210) in ethanol over palladium-charcoal was extremely slow and gave a crude mixture which showed NH stretching and no C≡N stretching in its infrared spectrum. Attempts to hydrogenate the exocyclic double bond in compound (210) using Adams' catalyst in ethanol or acetic acid gave crude mixtures showing weak C≡N stretching in the infrared spectrum. Reduction of the exocyclic double bond using sodium borohydride in ethanol or iso-propanol were also unsuccessful.

In view of the unsuccessful attempts to hydrogenate the compound (210) without reducing the nitrile group, attempts were made to hydrolyse the nitrile group to an ester group using, firstly, ethanolic hydrochloric acid, and secondly, ethanol containing a trace of concentrated sulphuric acid. In both cases, a crude material was obtained which still contained a nitrile group, shown by its infrared spectrum.

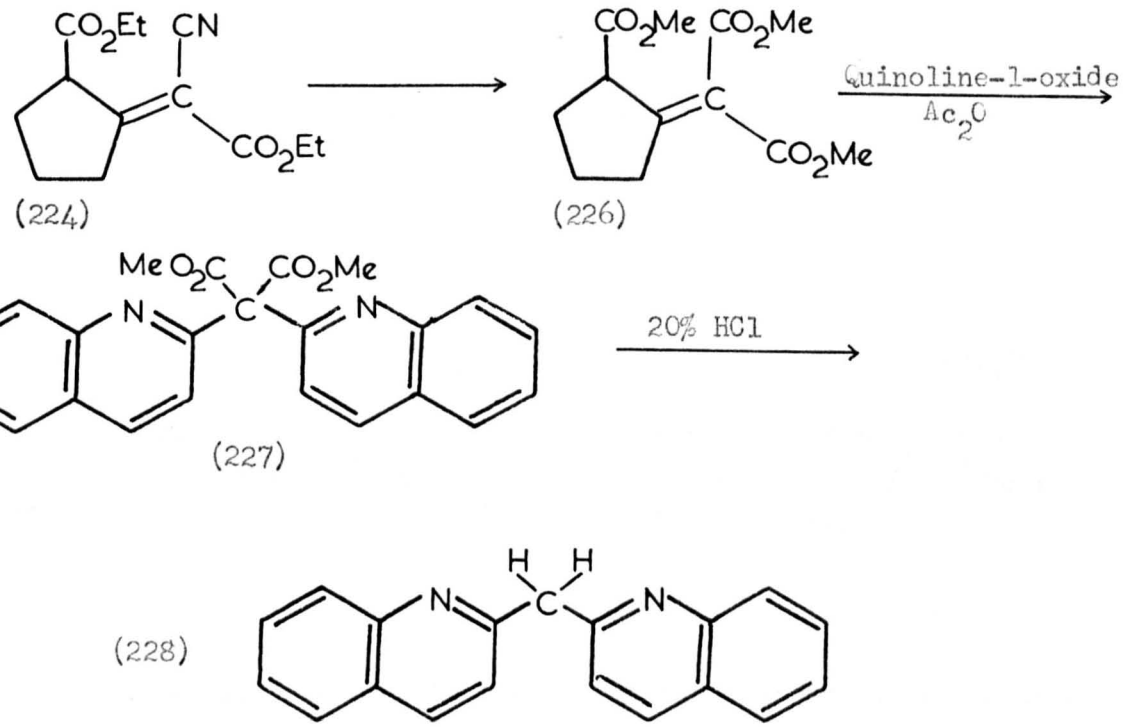
The next step in this approach to the 9-aza-steroid system was the attempted hydrolysis of the nitrile group in the cyano-ester (224) before reacting it with quinoline-1-oxide. When the cyano-ester (224) was boiled under reflux with ethanol containing concentrated sulphuric acid a solid product was obtained after work up, as well as some of the original cyano-ester (224). The infrared spectrum of the solid showed absorption at 3370, 3120, 2800, 2700, 1655, and 1620 $cm.^{-1}$. The n.m.r. spectrum showed a triplet at 1.56 p.p.m. (three protons), a quartet at 2.42 p.p.m. (two protons), a triplet at 3.06 p.p.m. (two protons), a triplet at 3.55 p.p.m. (two protons), and a quartet at 4.70 p.p.m. (two protons). From the analysis and this spectral data the solid was assigned the structure as (225a).



(225a) R = Et
(225b) R = Me

The pyrindene (225a) was reported by Kon and Nanji when attempting to hydrolyse cyano-ester (224) with concentrated hydrochloric acid. Obviously the nitrile group in the cyano-ester (224) is hydrolysed to the imino-ether which then condenses with the cyclopentyl ester group to form the pyrindene system (225a). When cyano-ester (224) was boiled under reflux with methanolic hydrochloric acid a solid was isolated from the reaction product which was shown to be (225 b) from analysis and spectral data. The remaining residue showed methyl and ethyl groups in its n.m.r. spectrum and cyano stretching in its infrared spectrum. These results indicate that trans-esterification of cyano-ester (224) took place.

Hydrolysis of cyano-ester (224) was performed using ethanolic potassium hydroxide to a crude mixture of acids.[147] This crude mixture was boiled under reflux with dry methanol containing concentrated sulphuric acid and the resulting ester distilled. The n.m.r. spectrum showed the distillate to be mainly the required tri-ester (226) but containing other material, probably di-esters resulting from decarboxylation during the hydrolysis stage.

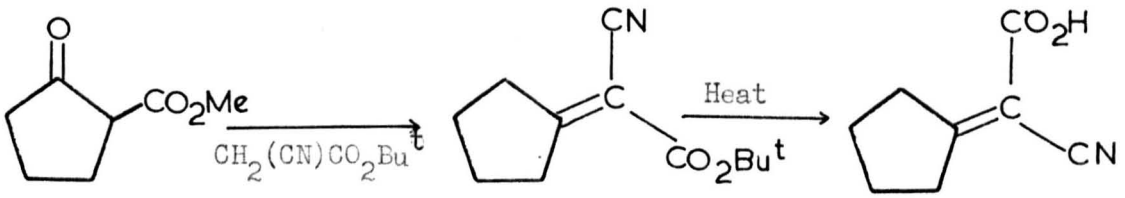


Reaction of the crude tri-ester (226) with quinoline-1-oxide gave only a small amount of the quinolyl ester (227) as the only identifiable product. Hydrolysis of the ester (227) with 20% hydrochloric acid solution gave a base (228) which was identical with the base obtained by hydrolysis of diethyl di-(2-quinolyl)malonate.[123]

Corey reported the use of isopropylidene malonic acid[148] in the preparation of α,β-unsaturated malonic acid derivatives.[149] Attempts to condense isopropylidene malonic acid with 2-carbethoxycyclopentanone using the technique of Corey,[148] or using piperidine as catalyst were unsuccessful.

An attempt to condense t-butyl cyanoacetate with 2-carbomethoxy-cyclopentanone using piperidine as catalyst[141] gave only recovered starting materials. More vigorous conditions, e.g. refluxing in xylene, gave some

of the cyano-ester (229), which may be formed by condensation of the t-butyl cyanoacetate with 2-carbomethoxy-cyclopentanone followed by hydrolysis and decarboxylation. Pyrolysis of cyano-ester at 220° did

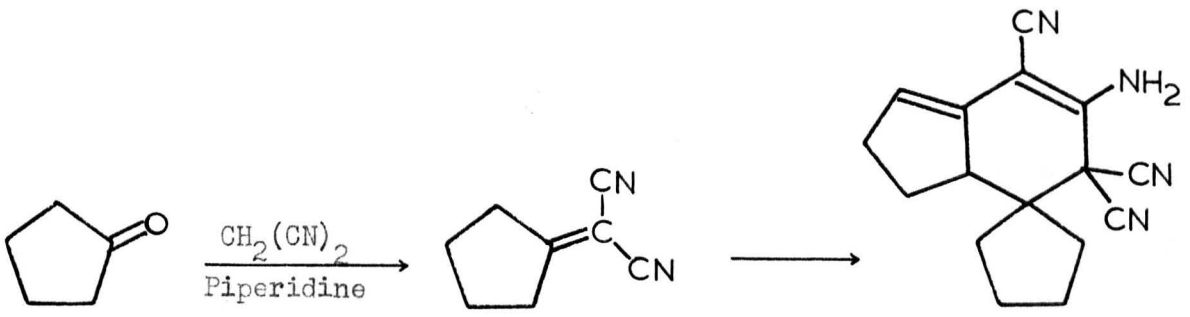


(229) (230)

not give the product expected by removal of the carbo-t-butoxy group but the acid (230).

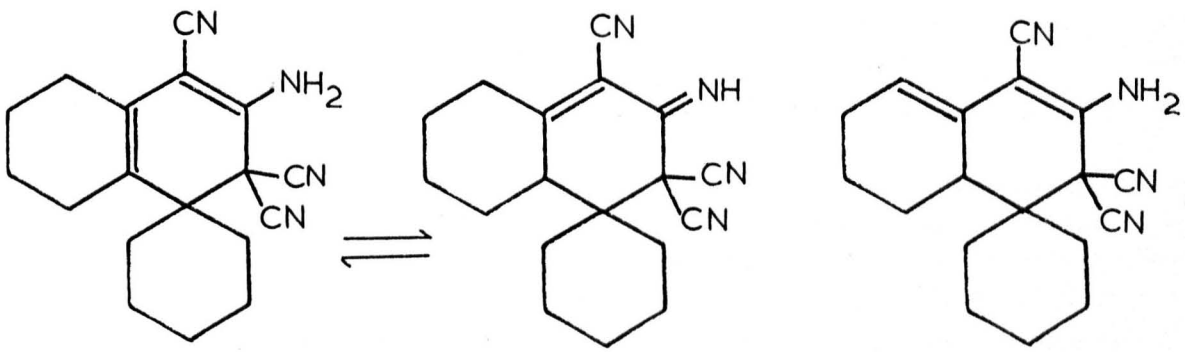
It was decided to synthesise some cyclopentylidene derivatives which did not contain 2-substituents in an attempt to obtain a reaction with quinoline-1-oxide in the desired position of the cyclopentane ring.

On addition of a few drops of piperidine to a solution of malononitrile in cyclopentanone an exothermic reaction took place with the precipitation of a solid. The reaction was allowed to proceed for 30 mins. and the solid filtered at the pump. Recrystallisation of the solid gave a compound which showed absorption at 3465, 3385, 3200, 2220, and 1632 $cm.^{-1}$ in its infrared spectrum. Its n.m.r. spectrum showed a multiplet at approximately 1.8 p.p.m. (10 protons), a two proton multiplet at approximately 2.5 p.p.m., a broad two proton multiplet at 7.25 p.p.m., a broad two proton singlet at 5.38 p.p.m., and a vinyl type proton at 5.87 p.p.m. Analysis and this spectral evidence indicated the structure as (232).



(231) (232)

Weir and Hyne reported a similar dimer when they condensed malononitrile with cyclohexanone.[150] They reported the product as being tautomeric between the structures (233a) and (233b). In a



(233a) (233b) (234)

later paper, Weir and Hyne reported that the structure (234) was more likely for the dimer and misinterpretation of the n.m.r. spectrum had led them to assign structures (233a) and (233b).[151]

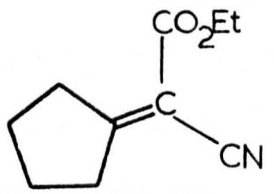
Since the cyclopentylidene malononitrile (231) initially formed quickly dimerises in the presence of base it was necessary to carry out the reaction in chloroform with a few drops of piperidine for about

10 mins. Acidification of the reaction mixture with dilute hydrochloric acid gave the dinitrile (231) in good yield.

When the dinitrile (231) was added to a solution of quinoline-1-oxide in acetic anhydride a vigorous reaction took place with a blood red colouration. The mixture darkened rapidly to give a tarry material which could not be identified.

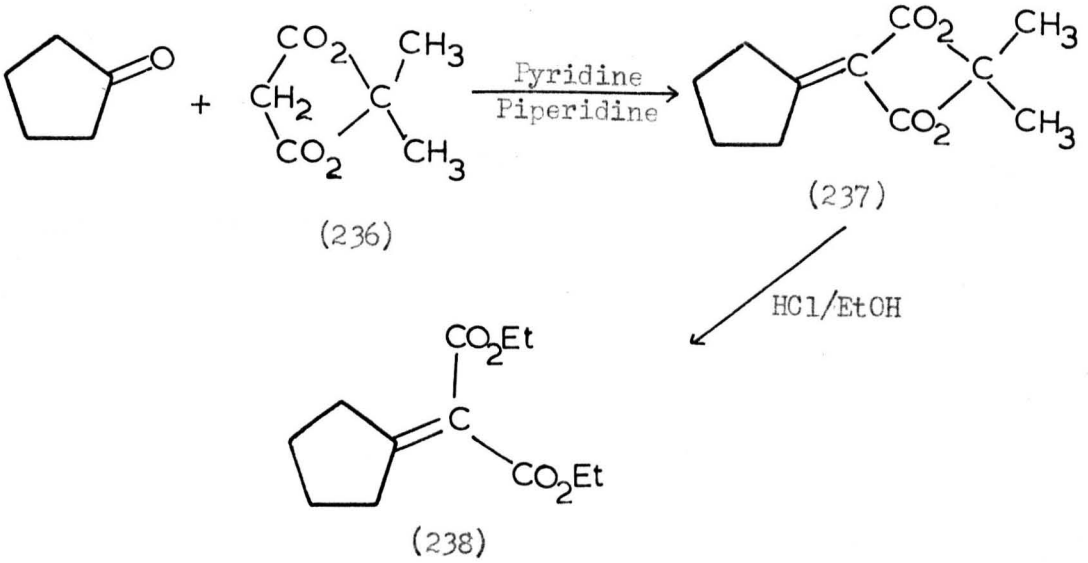
Ethyl cyclopentylidene cyanoacetate (235) was prepared by the method of Vogel.[147]

The cyano-ester (235) reacted with quinoline-1-oxide in acetic anhydride to give a crude mixture from which no identifiable products could be obtained.



(235)

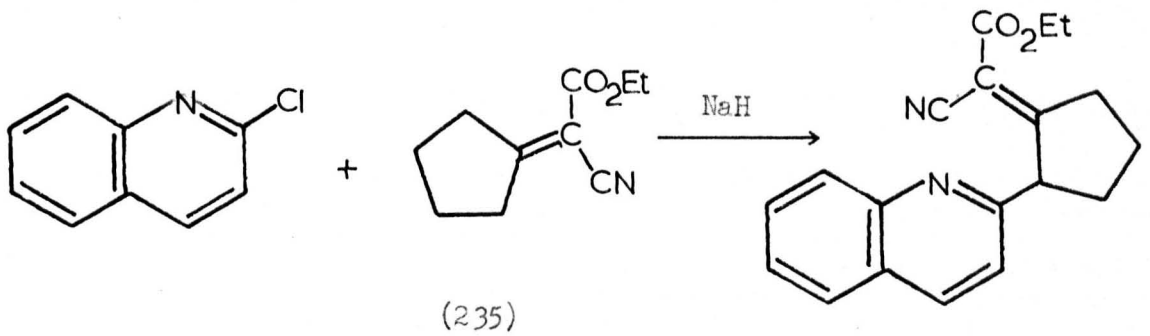
The ester (237) was prepared by condensation of isopropylidene malonate (236) with cyclopentanone in the presence of pyridine and piperidine.



(236) (237) (238)

Refluxing the ester (237) with ethanol containing a trace of dry hydrochloric acid did not give the expected half-ester[148] but the di-ester (238). Both esters (237) and (238) reacted with quinoline-1-oxide in acetic anhydride to give crude mixtures from which no identifiable products could be obtained.

In a final attempt to obtain a tricyclic system such as compound (239), 2-chloroquinoline was boiled with the sodium salt of ethyl cyclopentylidene cyanoacetate in benzene.



(235) (239)

Starting material was recovered even when toluene or xylene was used as solvent. Nizuno et al. reported a quantitative yield of α-phenyl-2-quinolylacetonitrile from 2-chloroquinoline and benzyl cyanide,[140] but Hamana reported the failure of the reaction between ethyl cyanoacetate and 2-chloroquinoline.[123]

EXPERIMENTAL

Preliminary Notes

Melting points were determined on a Kofler block and are uncorrected.

Infrared absorption spectra were measured with Perkin Elmer Infracord, 221 and 257 spectrometers. The spectra of solids were determined as Nujol mulls, indicated by (Nujol) or in solution (e.g. CCl_4). The spectra of liquids were determined as liquid films (film) or in solution (e.g. CCl_4).

Ultraviolet absorption spectra were measured on a Unicam SP 700 instrument.

Nuclear magnetic resonance (n.m.r.) spectra were recorded on a Perkin Elmer 60 megacycle instrument and are quoted in parts per million (p.p.m.) from an internal tetramethyl silane standard (0.p.p.m.).

Analytical gas-liquid partition chromatography (v.p.c.) was performed on a 10 ft. spiral glass column packed with Gaschrom P coated with 1% SE-30 silicone grease.

All reactions involving dry solvents were carried out in an atmosphere of nitrogen.

Sodium hydride was used as a 50% by weight dispersion in liquid paraffin.

Microanalyses were carried out by Drs. Weiler and Strauss of Oxford and by Mr. J. Boulton of Keele University.

PREPARATION OF 1,2,3,4,5,6-HEXAHYDRO—3-OXO-4aH-BENZO[c]QUINOLIZINE (158).

Ethyl 2-quinolylacetate (151) (a) From quinaldine. The preparation followed the procedure of Hammick et al.[106] with the following modifications. The ethereal solution of phenyl lithium was rapidly filtered through glass wool into a separating funnel, previously flushed out with nitrogen, and added over 1 hr. to quinaldine with stirring. The ethereal quinaldyl lithium solution was boiled under reflux for 1 hr., cooled, filtered through glass wool as before, and added over 1 hr. to an ethereal solution of redistilled diethyl carbonate. The deep orange mixture was then boiled under reflux for 3 hr., then worked up as described by Hammick et al.[106] giving a net yield of the ester of ca. 25% with some recovered quinaldine. Several byproducts were encountered but were not further investigated.

Substitution of ethyl chloroformate[109] in place of diethyl carbonate did not give an improved yield of ethyl 2-quinolylacetate unless an excess of ethyl chloroformate was used at -78°C. Quinaldyl lithium (0.5 mole) was prepared as by previous methods and cooled in a "Drikold"-acetone bath to -78°C. Ethyl chloroformate (0.8 mole) was added to the stirred solution over 1 hr. and the yellow mixture was allowed to warm up to room temperature over 2 hr. The mixture was cooled in ice and 3N hydrochloric acid (200 ml.) added with stirring. The two layers were separated and the ether layer extracted with further portions of 3N hydrochloric acid (2 x 50 ml). The aqueous layers were neutralised with sodium carbonate and the free bases extracted with ether. The ether extracts were dried and the ether evaporated off. The residual oil

was distilled, giving recovered quinaldine (23.4 g.) ethyl 2-quinolylacetate (18.6 g., 17%) b.p. 130-135°/0.2 mm. (lit.[106] 128-135°/0.8 mm.) and diethyl 2-quinolylmalonate (25.6 g., 18%), b.p. 170-175°/0.2 mm. The diethyl 2-quinolylmalonate solidified and was recrystallised from 60/80° petroleum ether to give yellow needles, m.p. 72-73° (lit. 73-74° [123]) ν_{max}(Nujol) 1630, 1682 cm.$^{-1}$. The n.m.r. spectrum (CCl_4) showed two sets of triplets centred at 1.28 and 1.31 p.p.m. (ester methyl group), a quartet at 4.23 p.p.m. (ester methylene group), and a singlet at 5.02 p.p.m. corresponding to one quarter of a proton. The n.m.r. spectrum (T.F.A.) showed only one ester methyl triplet and a one proton singlet at 5.74 p.p.m.

Diethyl 2-quinolylmalonate was converted to ethyl 2-quinolylacetate by a similar procedure to the one used by Breslow et al.[110] Diethyl 2-quinolylmalonate (27.0 g., 0.095 moles) was dissolved in absolute ethanol (100 ml.) and potassium hydroxide (5.2 g., 0.095 mole) in absolute ethanol (60 ml.) added with stirring over 0.5 hr. The solution was stirred for 3 hr. and left overnight. The mixture was cooled in ice and filtered, the filtrate being washed with ether. The filtrate was neutralised to pH 7 with 3N hydrochloric acid and extracted with ether, dried, and ether distilled off. The residue was heated to 120° under vacuum until the evolution of carbon dioxide ceased, and distilled giving quinaldine (2.3 g.) and ethyl 2-quinolylacetate (18.0 g., 88%).

Reaction of dry carbon dioxide with quinaldyl lithium and esterification with hydrogen chloride in ethanol, as for the method of preparation of ethyl 2-pyridylacetate,[114] gave a mixture containing seven components, none of which was ethyl 2-quinolylacetate. Two components,

both solid, were isolated from the mixture. One gave colourless needles from carbon tetrachloride, m.p. 96-98°.

Found: C, 86.6; H, 6.97; N, 6.7%

λ_{max} 215 mμ in ethanol.

ν_{max}(nujol) 3380, 1642, 800, 774, 758, 698 cm.$^{-1}$

The n.m.r. spectrum (CCl_4) showed a sharp singlet at 2.33 p.p.m. corresponding to one proton, a four proton multiplet centred at 3.12 p.p.m., a one proton singlet at 5.22 p.p.m., and nine aromatic protons containing a five proton singlet at 7.45 p.p.m., presumably corresponding to a phenyl group. The structure of this compound has not yet been elucidated. The other solid isolated gave colourless rods from 60/80 petroleum ether, m.p. 252-253°C.

Found: C, 81.3; H, 4.75; N, 6.4%

ν_{max}(nujol) 798, 772, 760, 732, 698, 670 cm.$^{-1}$

The n.m.r. spectrum showed a sharp singlet at 7.86 p.p.m. (presumably corresponding to five protons) and a six proton aromatic pattern between 8 and 9 p.p.m. No structure has been assigned to this compound.

(b) From 2-chloromethylquinoline. 2-Chloromethylquinoline was prepared by chlorination of quinaldine by the method of Mathes and Schuely.[111] 2-Chloromethylquinoline was converted to 2-cyanomethylquinoline by the methods of Carelli et al., [112] and Nagata.[113] The n.m.r. spectrum of 2-cyanomethylquinoline showed a 2-proton singlet at 3.95 p.p.m., corresponding to the methylene group of the acetonitrile residue.

A solution of 2-quinolylacetonitrile (44.1 g.) in absolute

ethanol (400 ml.), to which water (6 ml.) had been added, was saturated with dry hydrogen chloride at approximately 60° and boiled under reflux for 3 hr. The mixture was worked up in a similar manner to that used by Jones and Wood.[105] The residual oil was distilled, giving ethyl 2-quinolylacetate as an orange oil. (43.0 g., 75%), b.p. 136-140°/0.4 mm.

Ethyl 1,2,3,4-tetrahydro-2-quinolylacetate (154).

Ethyl 2-quinolylacetate (151) was hydrogenated over Adams' catalyst in glacial acetic acid by the method of Jones and Wood.[105]

Diethyl 1,2,3,4-tetrahydro-2-quinolylidenemalonate (155).

Diethyl 2-quinolylmalonate (152) (2.20 g.) in pure glacial acetic acid (30 ml.) was hydrogenated over Adams' catalyst (60 mg.) at room temperature and pressure. The hydrogenation was very slow and stopped when 1 molar equivalent of hydrogen had been absorbed (ca. 3 hr.). The acetic acid with suspended platinum was evaporated and the residue made alkaline with cold aqueous sodium bicarbonate solution and ether added to dissolve the liberated base. The mixture of aqueous and ethereal layers was rapidly filtered, and the ether layer separated and dried. Evaporation of the ether gave a yellow solid which was recrystallised from 60/80 petroleum ether to give yellow plates (2.01 g., 91%), m.p. 40-41°.

Found: C, 66.7; H, 6.49; N, 4.9%

$C_{16}H_{19}NO_4$ requires: C, 66.4; H, 6.62; N, 4.84%

ν_{max}(Nujol) 1688, 1648, 1250, 747 cm.$^{-1}$

The n.m.r. spectrum (CCl_4) showed a triplet (J = 7 c.p.s.) at 1.32 p.p.m.

(ester methyl groups), a sharp four proton singlet at 2.82 p.p.m., and a quartet (J = 7 c.p.s.) at 4.21 p.p.m. (ester methylene group). The n.m.r. spectrum (T.F.A.) showed a four proton sextet (J = 6 c.p.s.) at 2.98 p.p.m. (two adjacent ring methylenes).

Ethyl 3-bromopropionate was prepared as described by Mozingo and Patterson[115] for the methyl ester but distilled at a lower pressure to avoid decomposition.

Ethyl 1-(2'-carbethoxyethyl)-1,2,3,4-tetrahydro-2-quinolylacetate (148).

a) The ester (154) was alkylated using ethyl 3-bromopropionate by the method of Jones and Wood.[105] The yields of the di-ester (148) varied considerably using this method due to dehydrobromination of ethyl 3-bromopropionate.

b) A mixture of ethyl 1,2,3,4-tetrahydro-2-quinolylacetate (20.0 g., 0.091 mole), ethyl acrylate (15.0 g., 0.15 mole), glacial acetic acid (15 g.), and cuprous chloride (1.8 g.) was stirred and heated under reflux in an atmosphere of nitrogen for 20 hr. Ether (100 ml.) was added to the cold solution which was washed with water (2 x 50 ml.), and 1:1 aqueous ammonium hydroxide (2 x 50 ml.). The ether extracts were dried and evaporated to remove ethyl acrylate. The residue was distilled giving recovered tetrahydro-ester (3.9 g.), b.p. 110-120°/0.001 mm., and the required di-ester (19.0 g., 66%) as a viscous yellow oil, b.p. 140-155°/ 0.001 mm.

Ethyl 1-(2'-carbo-t-butoxyethyl)-1,2,3,4-tetrahydro-2-quinolylacetate (156).

A mixture of ethyl 1,2,3,4-tetrahydro-2-quinolylacetate (21.9 g., 0.10 mole), t-butyl acrylate (29.0 g., 0.15 mole) (prepared from acrylyl chloride[132] and t-butyl alcohol[133]), glacial acetic acid (12 g.) and cuprous chloride (1.8 g.) was stirred and heated under reflux in an atmosphere of nitrogen for 20 hr., and then worked up as for the ethyl ester (148). Distillation gave ethyl 1,2,3,4-tetrahydro-2-quinolylacetate (8.8 g.) b.p. 110-122°/0.001 mm., and the required diester (17.4 g., 50%) as a viscous yellow oil, b.p. 150-165°/0.001 mm. A sample was fractionated for analysis, b.p. 163-165°/0.001 mm.

Found: C, 69.3; H, 8.16; N, 4.1%

$C_{20}H_{29}NO_4$ requires: C, 69.13; H, 8.41; N, 4.03%

ν_{max}(film) 1730, 1155, 745 cm.$^{-1}$.

The n.m.r. spectrum (CCl_4) showed a nine proton singlet at 1.45 p.p.m.

2-Carbethoxy-1,2,3,4,5,6-hexahydro-3-oxo-4aH-benzo[c]quinolizine (149).

The diester (148) was cyclised using sodium ethoxide in boiling xylene by the method used by Jones and Wood.[105]

2-Carbo-t-butoxy-1,2,3,4,5,6-hexahydro-3-oxo-4aH-benzo[c]quinolizine (157).

A solution of the diester (156) (7.5 g., 0.022 mole) in dry xylene (50 ml.) was added over 0.5 hr. to powdered sodium (0.52 g., 0.022 mole) in xylene (50 ml.); a slow distillation of xylene and ethanol being maintained during the addition and for 1 hr. afterwards. The thick yellow slurry of the sodium salt of the ketoester (157) was cooled to 0°, cold

water (100 ml.) added, and the pH adjusted 6. Ether was added and the layers separated. The aqueous layer was extracted with ether and the ether extracts dried and evaporated giving a viscous orange oil (5.8 g.).

Consistent analyses on this compound could not be obtained and attempts to prepare the hydrochloride and picrate gave hygroscopic solids, which could not be analysed.

$\nu_{max}(CCl_4)$ 1730 (C=O, ester), 1708 (C=O, ketone), 1653 (C=O, α-β unsaturated ester), 1612 (C=C, α-β unsaturated ester), (film), 748 $cm.^{-1}$

The n.m.r. spectrum ($CDCl_3$) was confused by the presence of enol and keto tautomers but showed singlets at 1.45 p.p.m. and 1.54 p.p.m. for ester t-butyl groups which did not consistute nine protons.

1,2,3,4,5,6-Hexahydro-3-oxo-4aH-benzo[c]quinolizine (158).

A solution of the crude keto-ester (149, 13.0 g.) in 5N hydrochloric acid (200 ml.) was boiled under reflux in an atmosphere of nitrogen for 5 hr. The resulting solution was evaporated in vacuo to a reddish brown hygroscopic hydrochloride. A solution of the latter in the minimum volume of ethanol was treated with saturated aqueous sodium bicarbonate solution and the liberated oil extracted with ether. The ether extracts were dried and evaporated, giving a brown oil, which gave a viscous yellow oil, b.p. 119-124°/0.003 mm., on distillation. The oil, on trituration with 60/80 petroleum ether, gave a solid (4.8 g., 44%), which was recrystallised from 60/80 petroleum ether to give colourless needles m.p. 77-78.5°.

Found: C, 77.8; H, 7.55; N, 7.1%

$C_{13}H_{15}NO$ requires: C, 77.58; H, 7.51; N, 6.96%

$\nu_{max}(CCl_4)$ 1712, (nujol) 748 cm.$^{-1}$.

The n.m.r. spectrum (CCl_4) showed a one proton multiplet centred at 4.21 p.p.m. and ten other aliphatic protons.

Methylation of 1,2,3,4-hexahydro-3-oxo-4aH-benzo[c]quinolizine via sodium enolate.

A solution of ketone (158) (1.60 g., 0.0062 mole) in dry dimethoxyethane (10 ml.) was added over 0.5 hr. to a suspension of sodium hydride (0.15 g., 0.0065 mole) in dry dimethoxyethane (50 ml.). The mixture was slowly heated to boiling over 0.5 hr., boiled under reflux for 1.5 hr., and then cooled. To the cold solution, methyl iodide (1.0 g., 0.0071 mole) in dimethoxyethane (10 ml.) was added over 0.5 hr. The temperature was raised to boiling over 2 hr. and then refluxed for a further 1 hr. and stood at room temperature overnight. Most of the dimethoxyethane was removed by evaporation and the residue dissolved in ether (50 ml.), cold water (50 ml.) added, and the pH adjusted to 6. The ether was separated and the aqueous layer re-extracted with ether. The organic extracts were dried and evaporated giving a viscous brown oil (1.8 g.). V.p.c. analysis of this oil showed five peaks, one of which corresponded to the original ketone (158) by comparison of retention times. The oil was chromatographed in 20% benzene-90% petroleum ether on Woelm alumina grade IV, and yielded 1.0 g. of a yellow oil which was 90% pure

by v.p.c. The main constituent had the same retention time as the 2-methyl ketone (159).

ν_{max} (film) 1715 cm.$^{-1}$

The n.m.r. spectrum showed a methyl signal as a pair of doublets at 0.99 and 1.14 p.p.m.

Enamine of 1,2,3,4,5,6-hexahydro-3-oxo-4aH-benzo[c]quinolizine (161).

A solution of ketone (158) (3.30 g., 0.016 mole) and pyrrolidine (1.6 g., 0.022 mole) in dry benzene (50 ml.) was boiled under a water separating device, until the calculated amount of water had been formed. The benzene and excess pyrrolidine were then removed under reduced pressure to a brown solid which decomposed on attempted distillation. The n.m.r. spectrum ($CDCl_3$) indicated a vinyl hydrogen at 4.15 p.p.m. (J = 2 c.p.s.).

Methylation of enamine (161).

The enamine of ketone (158) was dissolved in dry benzene (50 ml.) and methyl iodide (2.5 g., 0.0178 mole) in dry benzene (10 ml.) added over 0.5 hr. to the cold solution. The reaction was slightly exothermic and the solution became deep red in colour with the precipitation of a brown solid. The solution was then boiled under reflux for 12 hr. and then water (50 ml.) added to the solution. This solution was then warmed on a steam bath for 30 min. to decompose the enamine, and then extracted with chloroform. After drying and evaporation of the chloroform extracts, 3.1 g. of material were obtained as a dark brown tar. V.p.c. analysis showed five peaks, one of which had the same retention time as the 2-methyl ketone (159), and another minor peak having the same

retention time as the 4-methyl ketone (160).

ATTEMPTED PREPARATION OF 1,2,3,4-TETRAHYDRO-2-OXO-BENZO[c]QUINOLIZINIUM BROMIDE (165).

Ethyl β-ethoxypropionate

This was prepared by the method of Rehberg et al.[134]

4-Ethoxy-1-(2'-quinolyl)-butan-2-one (164).

Quinaldine (64 g., 0.45 mole) was added over 1 hr. to a stirred ethereal solution of phenyl lithium (0.5 mole, prepared as in previous methods), and the resulting red mixture stirred and boiled under reflux for 1 hr. After cooling to room temperature the solution of quinaldyl lithium was filtered through glass wool into a separating funnel and added to a stirred solution of ethyl 3-ethoxypropionate (40 g., 0.28 mole) in dry ether (200 ml.) over a period of 30 min. The mixture was boiled under reflux for a further 30 min. and then stood overnight. Cold 5N hydrochloric acid (300 ml.) was added to the orange solution, the acid layer separated, and the ether layer re-extracted with aqueous acid. The acid extracts were neutralised with aqueous sodium carbonate and the free base extracted with ether. The extracts were dried and evaporated. The residue was distilled giving recovered quinaldine (7.8 g.), 60-65°/0.05 mm., and the required ketone (24.6 g., 24% based on unrecovered quinaldine), b.p. 165-175°/0.05 mm. The n.m.r. spectrum (CCl_4) was confused by the presence of keto and enol tautomers.

$\nu_{max}(CCl_4)$ 1732, 1635 cm.$^{-1}$

The compound was analysed as its picrate, prepared in an ethanol solution and recrystallised from ethanol as yellow needles, m.p. 146-148°.

Found: C, 53.0; H, 4.32; N, 11.6%

$C_{21}H_{20}N_4O_9$ requires : C, 53.42; H, 4.26; N, 11.85%

Attempted preparation of 1,2,3,4-tetrahydro-2-oxo-benzo[c]quinolizinium bromide (165).

A solution of keto-ether (164) (3.0 g.) in 48% hydrobromic acid (25 ml.) was boiled under reflux for 20 hr., and then evaporated to dryness under reduced pressure. The dark tarry residue was dissolved in water, treated with aqueous sodium bicarbonate solution and extracted with chloroform. The extracts were dried and boiled under reflux for 5 hr. The chloroform was removed to give a purple residue, from which no identifiable product could be isolated.

PREPARATION OF 4-ACETONYL-4-CYANO-1,2,3,4,5,6-HEXAHYDRO-3-OXO-4aH-BENZO[c] QUINOLINE (147).

1,2,3,4-Tetrahydro-2-quinolylacetamide (166) and 1,2,3,4-Tetrahydro-2-quinolylacetonitrile (167) were prepared by the method of Jones and Wood.[105]

1-(2'-carbethoxyethyl)-1,2,3,4-tetrahydro-2-quinolylacetonitrile (168).

(a) The alkylation of nitrile (167) with ethyl β-bromo-propionate by the method of Jones and Wood[105] gave extremely low yields of the alkylated nitrile (168).

(b) A mixture of 1,2,3,4-tetrahydro-2-quinolylacetonitrile (20.0 g., 0.116 mole), ethyl acrylate (25.0 g., 0.25 mole), acetic acid (12 g.), and cuprous chloride (1.8 g.) were heated under reflux with stirring for 40 hr. and worked up as for the di-ester (148). Distillation gave unreacted tetrahydro-nitrile (17.2 g.), b.p. 100-120°/0.0004 mm. and the cyano-ester (168) as a yellow viscous oil (1.5 g., 5%), b.p. 135-145°/0.0004 mm.

When the alkylation reaction with ethyl acrylate was carried out in a sealed tube at 150°, the product gave a 10% yield of the cyano-ester (168) on distillation.

4-Cyano-1,2,3,4,5,6-hexahydro-3-oxo-4aH-benzo[c]quinolizine (146).

A solution of the cyano-ester (168) (8.70 g., 0.030 mole) in dry xylene (50 ml.) was cyclised using sodium ethoxide in dry xylene by the method of Jones and Wood,[105] to give the cyanoketone (146) (5.67 g., 77%) as a pale yellow solid. Recrystallisation from ethanol gave colourless rhombs, m.p. 138-140° (lit.[105] 135-137.5°).

4-Acetonyl-4-cyano-1,2,3,4,5,6-hexahydro-3-oxo-4aH-benzo[c]quinolizine (147).

A solution of cyano-ketone (146) (3.32 g., 0.015 mole) in dry dimethoxyethane (50 ml.) was added over 15 min. to a suspension of sodium hydride (0.38 g., 0.016 mole) in dimethoxyethane (150 ml.) with stirring. An immediate reaction occurred with formation of a pale yellow sodium salt. The mixture was heated under reflux and stirred for a further 2 hr. A solution of bromoacetone (2.18 g., 0.016 mole) in dimethoxyethane

(20 ml.) was added to the cold mixture over 15 min. The mixture was stirred at room temperature for 1 hr. and then boiled under reflux for a further 12 hr. Most of the dimethoxyethane was removed in vacuo and 3N hydrochloric acid (50 ml.), and ether (50 m .) were added to the cold residue. The aqueous layer was separated and the organic layer further extracted 3N hydrochloric acid (25 ml.). The combined aqueous extracts were neutralised to pH 6 with aqueous sodium carbonate solution and the free base extracted with chloroform. The extracts were dried and evaporated in vacuo giving a brown gum (3.8 g.) which darkened rapidly in air and was stored under nitrogen. The diketone (147) was purified by chromatography on Woelm alumina using 25% benzene-75% petroleum ether as eluent giving a viscous gum (2.21 g., 53%) which darkened on exposure to air.

$\nu_{max}(CCl_4)$ 3495, 3350, 2208, 1735 (weak), 1635, 1605 cm.$^{-1}$ (weak).

The n.m.r. spectrum (CCl_4) showed a three proton singlet at 2.32 p.p.m., a vinyl proton at 4.00 p.p.m., a one proton multiplet at 4.28 p.p.m., and a broad one proton peak at 5.48 p.p.m.

The hydrochloride was prepared by passing dry hydrogen chloride into an ethereal solution of the diketone (147), and was recrystallised from acetone containing a few drops of concentrated hydrochloric acid as colourless needles, m.p. 170-174°.

Found: C, 64.1 ; H, 5.96; N, 8.5

$C_{17}H_{19}N_2O_2Cl$ requires: C, 64.04; H, 5.97; N, 8.79%

Attempted preparation of 4-acetonyl-1,2,3,4,5,6-hexahydro-3-oxo-4aH-benzo[c] quinolizine.

A solution of the diketone (147) (0.61 g.) in 20% hydrochloric acid (100 ml.) was boiled under reflux for 6 hr. and evaporated to dryness in vacuo. The residue was neutralised with aqueous sodium bicarbonate and the free base extracted with chloroform. The chloroform extract was dried and evaporated to give a dark brown oil (0.48 g.).

The n.m.r. spectrum of the crude material showed a three proton singlet at 2.25 p.p.m. (acetonyl methyl) and a one proton multiplet at 4.25 p.p.m.

ν_{max} (film) 1700 cm.$^{-1}$

Attempts to purify the crude product or form a stable derivative were unsuccessful.

Attempted cyclisation of 4-acetonyl-4-cyano-1,2,3,4,5,6-hexahydro-3-oxo-4aH-benzo[c] quinolizine (147).

A solution of the ketone (147) (0.61 g., 0.0022 mole) in dry t-butanol (5 ml.) was added to a solution of potassium (0.086 g., 0.0022 mole) in dry t-butanol (10 ml.) over 15 min. The solution turned dark green and was stirred at room temperature for 30 min., and warmed to 60° for a further 15 min. Ice cold N hydrochloric acid (50 ml.) was added to the cold mixture which was neutralised with aqueous sodium carbonate solution and extracted with chloroform. The chloroform extracts were dried and evaporated to give a dark brown gum (0.52 g.) which was shown to be the original ketone (147) by n.m.r. and infrared spectra.

The crude product was therefore re-treated with potassium t-butoxide in butanol, heated under reflux for 1 hr., and the product worked up as before. The n.m.r. and infrared spectra showed only unreacted ketone (147).

REACTIONS OF QUINOLINE-1-OXIDE WITH COMPOUNDS CONTAINING REACTIVE HYDROGENS IN THE PRESENCE OF ACETIC ANHYDRIDE.

Methyl 1,2-dihydro-2-quinolylidene cyanoacetate (171).

Methyl cyanoacetate (1.80 g., 0.018 mole) was added to a solution of quinoline-1-oxide (2.50 g., 0.017 mole) in acetic anhydride (5.2 g.) over 10 min. with stirring. The reaction was exothermic and crystals separated. After standing overnight at 35-40°, the mixture was cooled in ice and the crystals filtered at the water pump. Recrystallisation from ethanol gave yellow needles (3.01 g., 78%), m.p. 193-193.5°.

Found: C, 69.0 ; H, 4.29; N, 12.2.

$C_{13}H_{10}N_2O_2$ requires: C, 69.01; H, 4.46; N, 12.38%

$\nu_{max}(CCl_4)$ 2207, 1636, 1612 cm.$^{-1}$

λ_{max} 217, 284, 392 mμ in ethanol.

λ_{max} 243, 322, 337 mμ in perchloric acid.

The n.m.r. spectrum showed a 3 proton singlet at 3.88 p.p.m. and a broad one proton singlet at 13.6 p.p.m.

Hydrogenation of cyanoester (171) using Adams' catalyst in glacial acetic acid was very slow and produced a crude mixture of primary amines and nitriles.

Methyl α-bromo-α-cyano-2-quinolylacetate (172).

Bromine (0.80 g., 0.005 mole) in chloroform (5 ml.) was added dropwise to a solution of cyanoester (171) (1.13 g., 0.005 mole) in chloroform (25 ml.). The solution turned red, was stood for 15 min. and then shaken with aqueous sodium bicarbonate. The organic layer was dried and evaporated to give a pale yellow solid which was recrystallised from 60/80 petroleum ether as pale yellow plates (1.41 g., 92%) m.p. 101-102°.

Found: C, 51.4; H, 2.85; N, 9.2%

$C_{13}H_9N_2O_2$ requires: C, 51.1; H, 2.95; N, 9.18%

$\nu_{max}(CCl_4)$ 2207, 1743 cm.$^{-1}$

The n.m.r. spectrum ($CDCl_3$) showed a three proton singlet at 4.02 p.p.m. and six aromatic protons.

t-Butyl-1,2-dihydro-2-quinolylidene cyanoacetate (173).

t-Butyl cyanoacetate was prepared by the method of Ireland and Chaykovsky.[124]

t-Butyl cyanoacetate (3.50 g., 0.025 mole) was added to a stirred solution of quinoline-1-oxide (3.50 g., 0.024 mole) in acetic anhydride (6.0 g.), and allowed to stand for 7 hr. at 35°. The product was worked up as for the methyl ester (171) to give a solid which was recrystallised from ethanol to give yellow needles, (4.22 g., 65%), m.p. 209.5-210° (decomposition).

Found: C, 71.6 ; H, 5.94; N, 10.6%

$C_{16}H_{16}N_2O_2$ requires: C, 71.62; H, 6.01; N, 10.44%

ν_{max} (CCl_4) 2205, 1640, 1615 cm.$^{-1}$

λ_{max} 216, 286, 394 mμ.

The n.m.r. spectrum ($CDCl_3$) showed a nine proton peak at 1.62 p.p.m. and a broad one proton peak at 13.75 p.p.m. The n.m.r. spectrum in trifluoroacetic acid (T.F.A.) showed the appearance of a singlet at 3.95 p.p.m. whilst the peak at 1.62 p.p.m. gradually disappeared.

Pyrolysis of t-butyl 1,2-dihydro-2-quinolylidene cyanoacetate.

The cyano-ester (173) (1.0 g.) was heated to 220° in vacuo when a gas was evolved. Heating was continued until evolution of gases ceased and the orange solid (0.8 g.) was recrystallised from chloroform to give orange needles which darkened rapidly at 280° but did not appear to melt.

Found: C, 70.6; H, 3.75; N, 12.2%

ν_{max} 2190, 1625, 1615 cm.$^{-1}$

The n.m.r. spectrum (T.F.A.) showed only aromatic protons.

t-Butyl α-bromo-α-cyano-2-quinolylacetate (174).

A solution of bromine (0.98 g., 0.061 mole) in chloroform (10 ml.) was added dropwise to a solution of cyanoester (173) in chloroform (50 ml.). The red solution was allowed to stand for 1 hr. and was then shaken with aqueous sodium carbonate solution. The chloroform layer was dried and evaporated to give a yellow solid which was recrystallised from ethanol to pale yellow plates, (1.84 g., 88%) m.p. 84-87°.

Found: C, 55.5 ; H, 4.23; N, 8.0%

$C_{16}H_{15}N_2O_2Br$ requires: C, 55.33; H, 4.32; N, 8.07%

$\nu_{max}(CCl_4)$ 2210, 1775, 1750 cm.$^{-1}$

The n.m.r. spectrum showed a nine proton singlet at 1.65 p.p.m.

1,2-Dihydro-2-quinolylidene cyanoacetamide (176).

A solution of cyanoacetamide (1.68 g., 0.02 mole) in acetic anhydride (3 ml.) was added dropwise to a solution of quinoline-1-oxide (2.90 g., 0.02 mole) in acetic anhydride (4 ml.) with stirring. A vigorous exothermic reaction took place with the precipitation of a solid. The mixture was allowed to stand for 1 hr. and the crystals filtered at the water pump. Recrystallisation from ethanol gave yellow micro-crystals, (3.77 g., 90%), m.p. 256-7°.

Found: C, 67.9; H, 4.17; N, 20.0%

$C_{12}H_9N_3O$ requires: C, 68.23; H, 4.30; N, 19.9%

ν_{max}(Nujol) 3390, 3330, 3265, 2190, 1633, 1615 cm.$^{-1}$

α-Bromo-α-cyano-2-quinolylacetamide (177).

A solution of bromine (0.16 g., 0.001 mole) in chloroform (5 ml.) wasadded dropwise to a solution of amide (176) (0.211 g., 0.001 mole) in chloroform (50 ml.) with shaking. A red precipitate formed and the mixture was allowed to stand for 30 min. The mixture was shaken with aqueous sodium carbonate solution and chloroform layer dried and evaporated. The pale yellow residue was recrystallised from 60/80 petroleum ether to give pale yellow plates, (0.26 g., 90%), m.p. 125-126°.

Found: C, 50.0 ; H, 2.76; N, 14.7%

$C_{12}H_8N_3OBr$ requires: C, 49.65; H, 2.76; N, 14.48%

ν_{max}(Nujol) 3470, 3400, 3260, 2190, 1717 cm.$^{-1}$

Ethyl 1,2-dihydro-2-quinolylidene acetoacetate (178).

Ethyl acetoacetate (9.0 g., 0.069 mole) was added dropwise to a solution of quinoline-1-oxide (10.0 g., 0.069 mole) in acetic anhydride (10 ml.) with stirring. The reaction was exothermic and the solution turned orange. The mixture was allowed to stand at 40-50° for 8 hr. and methanol (10 ml.) was added to destroy the excess acetic anhydride. After evaporation the residue was dissolved in ether (50 ml.) and washed with aqueous sodium bicarbonate until free from acetic acid. The ether extracts were dried and evaporated. The residue was distilled giving a yellow liquid (15.2 g., 86%), b.p. 155-164°/0.1 mm., which solidified on standing. Recrystallisation from 60/80 petroleum ether gave yellow micro-prisms, m.p. 58.5-59°.

Found: C, 70.2 ; H, 5.91; N, 5.6%

$C_{15}H_{15}NO_3$ requires: C, 70.02; H, 5.88; N, 5.44%

ν_{max}(CCl_4) 1690, 1632, 1615 cm.$^{-1}$

Methylation of ethyl 1,2-dihydro-2-quinolylidene acetoacetate.

A solution of keto-ester (178) (0.56 g., 0.0022 mole) in dry dimethoxyethane (20 ml.) was added to a stirred suspension of sodium hydride (0.06 g., 0.0025 mole) in dry dimethoxyethane (40 ml.). A vigorous reaction took place and the mixture was heated under reflux for

a further 30 min. To the cold solution was added methyl iodide (0.32 g., 0.0022 mole) in dry dimethoxyethane (10 ml.) over 15 min. The mixture was allowed to stir at ~ 50° for 30 min., cooled, and most of the dimethoxyethane evaporated in vacuo. Ether (50 ml.) and 3N hydrochloric acid (50 ml.) was added to the residue. The aqueous layer was separated and basified with aqueous sodium carbonate solution. The free base was extracted with ether, which was dried and evaporated to give an orange oil (0.45 g., 90%) which had identical spectral properties with ethyl α-(2-quinolyl)propionate (179).

ν_{max} 1735 cm.$^{-1}$.

The n.m.r. spectrum (CCl_4) showed a triplet centred at 1.16 p.p.m. (ester methyl group), a quartet at 4.07 p.p.m. (ester methylene group), and a doublet at 1.59 p.p.m. and a quartet at 4.03 p.p.m. due to the CH_3CH-group.

The above experiment was repeated without added methyl iodide to give ethyl 2-quinolylacetate in quantitative yield.

Attempted acylation of ethyl α-(2-quinolyl)propionate.

A solution of ester (179) (5.60 g., 0.0246 mole) in dry dimethoxyethane (10 ml.) was added to a stirred suspension of sodium hydride (0.6 g., 0.025 mole) in dry dimethoxyethane (50 ml.). A vigorous reaction took place in the cold and the mixture was heated for 30 min. and then acetyl chloride (1.8 g., 0.023 mole) added to the cold mixture. The mixture was warmed gently for 30 min., stood overnight, and then worked up as for the methylation reaction to give unreacted ester (179).

Ethyl α-acetyl-α-(2-quinolyl)propionate (180).

A solution of keto-ester (178), (2.20 g., 0.0085 mole) in dry dimethoxyethane (10 ml.) was added to a suspension of sodium hydride (0.21 g., 0.0087 mole) and allowed to stand for 2 hr. Methyl iodide (1.20 g., 0.0085 mole) was added to the cold solution and the mixture stirred for 3 hr. Acetic acid (1 ml.) was added to the stirred mixture and the whole evaporated to an orange oil (2.14 g.). The n.m.r. spectrum (CCl_4) of the crude oil showed a triplet centred at 1.30 p.p.m. (ester methyl group), a three proton singlet at 1.81 p.p.m. (methyl group), a three proton singlet at 2.20 p.p.m. (acetyl methyl group), and a quartet at 4.31 p.p.m. (ester methylene group).

$\nu_{max}(CCl_4)$ 1740, 1690 $cm.^{-1}$

The crude oil quickly decomposed to acetic acid and ethyl α-(2-quinolyl)propionate on exposure to moist air.

Hydrolysis of ethyl 1,2-dihydro-2-quinolylidene acetoacetate (178).

The ester (178) (1.0 g., 0.0039 mole) was shaken with N sodium hydroxide (20 ml.) for 3 hr. until a clear solution was obtained. The solution was neutralised with 2N hydrochloric acid and warmed gently on a steam bath for 10 min. Extraction of the solution with ether and evaporation gave quinaldine (0.52 g., 93%).

Diethyl α-bromo-2-quinolylmalonate (181).

A solution of bromine (0.80 g., 0.005 mole) in carbon tetrachloride (5 ml.) was added dropwise to a solution of diethyl 2-quinolylmalonate

(1.44 g., 0.005 mole) in carbon tetrachloride with shaking. A yellow precipitate formed and the mixture was shaken with aqueous sodium bicarbonate solution. The carbon tetrachloride extracts were dried and evaporated to give a yellow oil (1.78 g., 97%) which was pure by v.p.c. analysis.

Found: C, 52.3 ; H, 4.10; N, 3.8%

$C_{16}H_{16}NO_4Br$ requires: C, 52.47; H, 4.37; N, 3.83%

$\nu_{max}(CCl_4)$ 1750 cm.$^{-1}$.

The n.m.r. spectrum showed a four proton quartet at 4.44 p.p.m. and a six proton triplet at 1.36 p.p.m.

Attempted alkylation of diethyl 2-quinolylmalonate with a) ethyl β-bromopropionate b) ethyl acrylate.

The methods used were the same as for the alkylation of ethyl 1,2,3,4-tetrahydro-2-quinolylacetate. Starting material was obtained in both cases.

Preparation of 6-methoxy-1,2,3,4-tetrahydro-quinolylacetate (184).

Ethyl 6-methoxy-2-quinolylacetate (183).

6-Methoxyquinaldine was prepared by the method of Bergstrom and Furst.[126]

The preparation of ester (183) followed the procedure of Hammick et al.[106] for the preparation of ethyl 2-quinolylacetate. Phenyl lithium was prepared from lithium (5.3 g., 0.76 g. atoms) and bromo-benzene (42 ml., 0.40 mole) in ether (500 ml.). A solution of 6-methoxy-quinaldine

(67 g., 0.39 mole) in ether (200 ml.) was added to the stirred solution of phenyl lithium over 30 min. Diethyl carbonate (46 g., 0.39 mole) was added to the blood red solution of the 6-methoxy-quinaldyl lithium over 10 mins. and the mixture refluxed for 3 hr. The mixture was then worked up as described by Hammick et al.[106] Distillation of the residue gave recovered 6-methoxyquinaldine (20.7 g.) b.p. 97-110°/0.1 mm., and the required ester as a viscous orange oil (15.7 g., 16%), b.p. 165-167°/ 0.1 mm. The ester solidified on standing to bright yellow needles, m.p. 38-41° (lit.[135] 45-46°).

Chlorination of 6-methoxy-quinaldine.

The method used was the one used by Mathes and Schuely for the preparation of 2-chloromethylquinoline from quinaldine.[111]

A solution of chlorine (4.0 g., 0.057 mole) in carbon tetrachloride (25 ml.) was added to a stirred solution of 6-methoxy-quinaldine (8.6 g., 0.050 mole) in carbon tetrachloride (50 ml.) over 30 min. An immediate yellow precipitate formed and the mixture was stirred for a further 30 min. The solid was filtered and recrystallised from ethanol to give yellow needles, m.p. 202-205°C. The solid was filtered and recrystallised from ethanol to give yellow needles m.p. 202-205°C. The solid was dissolved in water, ether (50 ml.) added, and aqueous sodium carbonate solution added until the mixture was basic. The ether layer was separated and an aqueous layer further extracted with ether. The combined ether extracts were dried and evaporated to give a colourless solid which was recrystallised from carbon tetrachloride giving colourless needles, (9.0 g., 87%), m.p. 53-55°. Consistent analyses

could not be obtained from either the hydrochloride or the free base, but the n.m.r. spectrum of the free base showed only four aromatic protons, a three proton singlet at 2.68 p.p.m. (methyl group), and a three proton singlet at 4.01 p.p.m. (methoxy group).

Attempts at further chlorination were unsuccessful.

Ethyl 6-methoxy-1,2,3,4-tetrahydro-2-quinolylacetate (184).

A solution of ethyl 6-methoxy-2-quinolylacetate (183) (35.0 g., 0.143 mole) in purified glacial acetic acid (250 ml.) was hydrogenated over Adams' catalyst (0.9 g.) at room temperature and pressure until 2 molar equivalents of hydrogen had been absorbed (ca. 8 hr.). The reduction was stopped at this stage and the acetic acid with suspended platinum evaporated at the water pump. The residue was made alkaline with cold aqueous sodium bicarbonate solution and ether added to dissolve the liberated oil. The mixture of aqueous and ethereal layers was rapidly filtered, and the ether layer separated and dried. The oil remaining after evaporation of the ether was distilled, giving a small forerun, 95-140°/0.1 mm. and a main fraction of the desired tetrahydro-ester (30.7 g., 86%), b.p. 152-156°/0.1 mm., as a pale yellow oil.

ν_{max}(film) 3400 (NH), 1735 (C=O, ester), 747 $cm.^{-1}$

The n.m.r. spectrum (CCl_4) showed a triplet (J = 7 c.p.s.) at 1.26 p.p.m. (ester methyl group), a quartet (J = 7 c.p.s.) at 4.14 p.p.m. (ester methylene group), a doublet (J = 7 c.p.s.) at 2.38 p.p.m. (methylene group of acetate residue), and a singlet at 3.65 p.p.m. (ether methyl).

The N-benzoyl derivative was prepared in pyridine by the action of benzoyl chloride on the ester. Recrystallisation from ethanol gave colourless prisms, m.p. 106-107°.

Found: C, 71.08; H, 6.63; N, 4.09%

$C_{21}H_{23}NO_4$ requires: C, 71.37; H, 6.65; N, 3.96%

ν_{max}(Nujol) 1735 (C=O ester), 1640 (C=O amide) cm.$^{-1}$.

6-Nitroquinaldine was prepared from p-nitroaniline and paraldehyde by the method of Huisgen.[127]

Attempted chlorination of 6-Nitroquinaldine.

This was attempted in a similar manner to the method used for chlorination of 6-methoxyquinaldine. Even when chlorine was passed into a boiling solution of the base in carbon tetrachloride no reaction took place.

Nitration Studies

Quinolinium nitrate. Liquid dinitrogen tetroxide was prepared by strongly heating a dry mixture of two parts lead nitrate and one part sand and trapping the gas evolved in a receiver cooled in an ice-salt bath. An ice cold solution of dinitrogen tetroxide (6.5 g., 0.071 mole) in carbon tetrachloride (80 ml.) was added over 0.5 hr. to a stirred solution of quinoline (9.0 g., 0.070 mole) in carbon tetrachloride (100 ml.) at -5°. A brown solid separated and the mixture was stirred for 3 hr. at -5°. The solid was filtered and recrystallised from 95% ethanol to give colourless needles (10.2 g., 76%), m.p. 120-122°. Evaporation of the

filtrate gave some recovered quinoline and quinolinium nitrate.

An authentic specimen of quinolinium nitrate was prepared by the addition of concentrated nitric acid to a cold solution of quinoline in ethanol, and adding ether to precipitate the salt. Recrystallisation from ethanol gave colourless needles, m.p. 121°. A mixture of the two specimens had a m.p. 121°.

Quinaldinium nitrate was prepared as described for the method of preparation for quinolinium nitrate using dinitrogen tetroxide (4.8 g., 0.037 mole) and quinaldine (5.3 g., 0.037 mole). Recrystallisation of the solid from 95% ethanol gave colourless needles, (5.6 g., 75%), m.p. 125-126°. Evaporation of the above filtrate gave only recovered quinaldine and some quinaldinium nitrate.

An authentic specimen of quinaldinium nitrate was prepared in a similar manner to quinolinium nitrate and gave colourless needles, m.p. 126°.

A mixture of the two specimens had m.p. 125-126°.

PREPARATION AND REACTIONS OF 1-PHENYL-4-PIPERIDONE.

1-Phenyl-4-piperidone was prepared by the method of Gallagher and Mann.[67]

Attempted preparation of 1-phenyl-3-(prop-2-ynyl)-4-piperidone (190).

a) 1-Phenyl-4-piperidone, (6.10 g., 0.035 mole) was dissolved in dry dimethoxyethane (15 ml.) and added to a stirred suspension of sodium hydride (0.89 g., 0.037 mole) in dry dimethoxyethane (100 ml.). The solution was then boiled under reflux for three hours and cooled in ice. The sodium enolate appeared as a yellow precipitate. Propargyl bromide

(4.4 g., 0.037 mole) in dry dimethoxyethane (10 ml.) was added dropwise. The mixture was stirred for a further 10 hr. and then refluxed for 30 min., when the mixture was dark orange in colour. Most of the dimethoxyethane was removed in vacuo, the residue cooled and ether (100 ml.) added. 3N Hydrochloric acid (50 ml.) was added and the layers separated. The ether layer was further extracted with 3N hydrochloric acid and the combined aqueous layers neutralised with aqueous sodium carbonate solution. The free base was extracted with ether which was dried and evaporated to 3.5 g. of a red oil. Chromatography on Woelm alumina, grade III in 50% benzene - 50% petroleum ether gave a yellow oil (2.2 g.).

ν_{max}(film) 3290, 1598, 1496, 752 cm.$^{-1}$

The n.m.r. spectrum (CCl_4) showed five aromatic protons, a sharp four proton doublet centred at 3.90 p.p.m. (J = 2 c.p.s.), and a sharp two proton triplet centred at 2.00 p.p.m. (J = 2 c.p.s.). Although a satisfactory analysis could not be obtained it was thought that the compound was N,N-di(prop-2-ynyl)aniline (191). No other identifiable products were isolated from the crude reaction product.

b) The enamine of 1-phenyl-4-piperidone was prepared in benzene from 1-phenyl-4-piperidone (5.00 g., 0.029 mole) and pyrrolidine (2.8 g., 0.039 mole). The solution was boiled for 20 hr. under a water separating device. On removal of benzene and excess pyrrolidine the enamine formed an orange solid, m.p. 76-81°. ν_{max}(Nujol) 1657 cm.$^{-1}$. The n.m.r. spectrum showed a vinyl hydrogen as a triplet at 4.15 p.p.m. The enamine was reacted in benzene (100 ml.) with propargyl bromide (4.10 g., 0.026 mole)

at room temperature and stirred for 16 hr. The reaction was mildly exothermic on adding the propargyl bromide and became dark red in colour. The mixture was warmed for 30 min. and water (40 ml.) added to the warm mixture to decompose the enamine. The benzene layer was separated, washed with water, dried, and evaporated to give 5.3 g. of a dark oil. This dark oil was unstable in air and quickly formed a resin. ν_{max}(film) 3280, 1708 cm.$^{-1}$. The n.m.r. spectrum showed an acetylenic proton as a triplet at 1.95 p.p.m. Attempts to purify the crude product by chromatography were unsuccessful.

Attempted preparation of 3-acetonyl-1-phenyl-4-piperidone (188).

The crude material from the above experiment in dry methanol (10 ml.) was added dropwise to a catalyst solution prepared from 1.0 g. of red mercuric oxide, 1 ml. of boron trifluoride etherate, 10 mg. of trichloroacetic acid and 5 ml. of methanol. The solution was heated for 3 hr., filtered, and concentrated on the steam bath. It was then added to 50 ml. of dilute sulphuric acid and stirred at $\sim 60^{\circ}$ for 30 min. The solution was cooled and made alkaline with sodium carbonate. Ether (100 ml.) was used to extract the base and the ether extract dried and evaporated to give a residue which still showed an acetylenic peak in its infrared spectrum and no methyl peak in its n.m.r. spectrum.

1-(p-Nitrophenyl)-4-piperidone (198).

An ice cold solution of dinitrogen tetroxide (10.1 g., 0.11 mole) in carbon tetrachloride (80 ml.) was added over 0.5 hr. to a stirred solution of 1-phenyl-4-piperidone (17.8 g., 0.102 mole) in dry carbon tetrachloride (80 ml.) at -5°. The solution became dark and viscous and was stirred at -5° for 2 hr. After allowing the solution to slowly warm up to room temperature the solution was filtered at the water pump. Evaporation of the filtrate gave 1-phenyl-4-piperidone (7.1 g.). The solid from the reaction was dissolved in chloroform (100 ml.) and basified with aqueous sodium carbonate solution. The chloroform extracts were dried and evaporated to give a dark tarry residue. Extraction of this residue with ether gave some 1-phenyl-4-piperidone (3.2 g.). The residue was then dissolved in ethanol (100 ml.) and heated under reflux with decolourising charcoal (5 g.) for 5 hr. Filtration of the hot ethanol solution and evaporation gave a yellow solid which was recrystallised from ethanol as yellow micro-prisms (1.8 g., 8%), m.p. 163-165°.

Found: C, 59.6 ; H, 5.2; N, 12.1%

$C_{11}H_{12}N_2O_3$ requires: C, 59.99; H, 5.49; N, 12.72%

$\nu_{max}(CCl_4)$ 1710, 1315, (Nujol) 830 $cm.^{-1}$.

The n.m.r. spectrum ($CDCl_3$) showed a doublet (J = 9 c.p.s.) centred at 8.21 p.p.m., a doublet (J = 9 c.p.s.) at 6.91 p.p.m., each constituting two protons, and two triplets of the piperidone methylenes.

Acrylyl chloride was prepared by the method of Stempel et al.[132]

t-Butyl acrylate was prepared from acrylyl chloride, t-butanol, and N,N-dimethylaniline using a general method for the preparation of t-butyl esters.[133]

Ethyl t-butyl phenylimino-ββ'-dipropionate (199).

Ethyl N-phenyl-β-alaninate[67] (30.7 g., 0.16 mole), t-butyl acrylate (33 g., 0.26 mole), glacial acetic acid (15 g.) and cuprous chloride (1.8 g.) were boiled under nitrogen with stirring for 20 hr. The cooled solution was diluted with ether (100 ml.) and the mixture washed with water (2 x 50 ml.), aqueous ammonia (1:1, 2 x 50 ml.) and again with water (50 ml.). The ether layer was dried and evaporated and the residue distilled giving acetanilide (3.2 g.) b.p. 95-105/0.03 mm., recovered ethyl N-phenyl-β-alaninate (5.7 g.), b.p. 115-125°/0.03 mm., and the diester (199) (22.8 g., 55% on unrecovered β-alaninate), b.p. 132-145°/0.03 mm. as a yellow oil. A sample, redistilled for analysis, had b.p. 140-145°/0.05 mm.

Found: C, 67.0 ; H, 8.15; N, 4.4%

$C_{18}H_{27}NO_4$ requires: C, 67.25; H, 8.45; N, 4.35%

ν_{max}(film) 1725 cm.$^{-1}$. The n.m.r. spectrum showed a nine proton singlet at 1.45 p.p.m.

Cyclisation of ethyl t-butyl phenylimino-ββ'-dipropionate.

The diester (199) (15.8 g., 0.049 mole) in xylene (50 ml.) was added to a stirred suspension of sodium (1.15 g., 0.05 g. atoms) in boiling xylene (100 ml.). Slow distillation was maintained during the

addition and for 1 hr. afterwards. To the cooled mixture was added ice-water (100 ml.), the aqueous layer separated, and the xylene layer extracted with aqueous sodium hydroxide. The combined aqueous layers were acidified with 3N hydrochloric acid to pH 6 and the keto-ester extracted with ether. Evaporation of the ether gave an orange oil (10.2 g.). Evaporation of the xylene layer gave N-phenyl-4-piperidone (1.1 g.).

The n.m.r. spectrum showed peaks due to ethyl groups and t-butyl peaks. Two t-butyl peaks appeared at 1.45 p.p.m. and 1.54 p.p.m.

$\nu_{max}(CCl_4)$ 1735, 1710, 1655, 1615 cm.$^{-1}$.

Brief heating of the oil showed that the size of the t-butyl peak in the n.m.r. spectrum decreased. Partial separation of the keto-esters was accomplished on chromatography in 30% benzene - 70% petroleum ether on Woelm alumina, grade IV.

Di-t-butyl phenylimino-ββ'-dipropionate (203).

A mixture of aniline (17 g., 0.189 mole), t-butyl acrylate (70 g., 0.55 mole), glacial acetic acid (27 g.), and cuprous chloride (3.0 g.) were boiled under nitrogen for 24 hr. The cooled mixture was filtered to remove cuprous chloride, which was washed with water, aqueous sodium bicarbonate, and again with water. The filtrate was dried and the ether and excess t-butyl acrylate removed by distillation. Distillation of the residue gave a small forerun of acetanilide, t-butyl N-phenyl-β-alaninate (202) (4.2 g.), b.p. 100-102°/0.05 mm.

Found: C, 70.4 ; H, 8.3; N, 6.4%

$C_{13}H_{19}NO_2$ requires: C, 70.55; H, 8.65; N, 6.35%

and the desired diester (203) (32.2 g., 50%), b.p. 140-152°/0.05 mm. Redistilled for analysis, the diester had b.p. 148-150°/0.05 mm.

Found: C, 69.0; H, 8.6; N, 4.1%

$C_{20}H_{34}NO_4$ requires: C, 68.75; H, 8.95; N, 4.0%

ν_{max} 1725 cm.$^{-1}$. The n.m.r. spectrum showed an 18 proton singlet at 1.58 p.p.m.

1-Phenyl-4-piperidone

To a boiling, vigorously stirred, suspension of sodium hydride (2.15 g., 0.088 mole) in benzene (150 ml.) was added during 1 hr. the diester (203) (28.5 g., 0.082 mole). Slow distillation was maintained during the addition and for 1 hr. afterwards. To the cooled mixture was added 150 ml. of ice-water, the aqueous layer separated, and the benzene layer extracted with aqueous sodium hydroxide; the combined aqueous layers were acidified with 3N hydrochloric acid to pH 6, the separated ketoester (201) extracted with ether. Evaporation of the ether gave a red oil (15 g.) showing the expected spectral characteristics of the keto-enol mixture. The n.m.r. peak at 1.45 p.p.m. for the t-butyl group intergrated for less than the expected 9 protons.

The crude keto-ester (201) was dissolved in chloroform (50 ml.), trifluoracetic acid (5 ml.) and the solution boiled for 1 hr. Evaporation to dryness was followed by heating of the residue on the water bath for 0.5 hr. The residue was distilled to give 1-phenyl-4-piperidone (11.2 g.,

80%), b.p. 120°/0.2 mm., m.p. 36-37° (lit.[67] m.p. 37-38°).

Attempted preparation of methyl α-methyl-β-anilinopropionate (204).

A mixture of aniline, methyl methacrylate, acetic acid, and cuprous chloride was heated together and worked up as in the preparation of diester (203). A small amount of the desired ester (204) was obtained but could not be obtained pure due to decomposition on distillation. The main reaction product was a polymer. The n.m.r. spectrum (CCl_4) of the ester (204) showed a three proton multiplet at 2.80 p.p.m., a two proton doublet (J = 7 c.p.s.) at 3.21 p.p.m., a one proton singlet at 3.38 p.p.m. (NH), and a three proton singlet at 3.63 p.p.m.

ATTEMPTED PREPARATION OF ETHYL 2-(1-2'-CYANOETHYL-1,2,3,4-TETRAHYDRO-2-QUINOLYL)-CYCLOPENTANONE-2-CARBOXYLATE (209a).

Ethyl 2-(2-quinolyl)-cyclopentanone carboxylate (205a).

2-Carbethoxycyclopentanone (82.0 g., 0.53 mole) was added over 30 min. to a stirred solution of quinoline-1-oxide (76.0 g., 0.53 mole) in acetic anhydride (70 g.). The reaction was exothermic and required cooling with an ice bath. When the addition was complete the reaction was allowed to stand overnight at room temperature and then methanol (25 ml.) was added to destroy the excess acetic anhydride. The reaction was evaporated at reduced pressure on the steam bath and the orange oil remaining was dissolved in ether. The ether was washed with aqueous sodium bicarbonate solution until free from acetic acid and the ether layer dried and evaporated. Distillation of the residue gave the desired keto-ester (205a, 130.6 g., 87%), b.p. 150-155°/0.2 mm.

Found: C, 72.1; H, 6.25; N, 4.9%

$C_{17}H_{17}NO_3$ requires: C, 72.06; H, 6.05; N, 4.94%

ν_{max}(film) 1725, 1762, 758 cm.$^{-1}$

The n.m.r. spectrum showed a triplet at 1.26 p.p.m. (ester methyl group), a quartet at 4.24 p.p.m. (ester methylene group), a six proton multiplet due to the cyclopentanone protons, and six aromatic protons.

2-Carbo-t-butoxycyclopentanone was prepared by the Dieckmann cyclisation of di-t-butyl adipate using sodium hydride in boiling benzene. Di-t-butyl adipate was prepared from adipyl chloride[137] and t-butanol in N,N-dimethylaniline.[133]

t-Butyl 2-(2-quinolyl)-cyclopentanone-2-carboxylate (205b).

2-Carbo-t-butoxycyclopentanone (18.4 g., 0.10 mole) was added over 15 min. to a stirred solution of quinoline-1-oxide (14.5 g., 0.10 mole) in acetic anhydride (15 g.). The reaction was allowed to stand overnight and worked up as for the ethyl ester (205a). Distillation gave the keto-ester (205b) (21.6 g., 69%) as a viscous orange oil, b.p. 143-146°, 0.0006 mm.

Found: C, 73.4 ; H, 6.49; N, 4.9%

$C_{19}H_{21}NO_3$ requires: C, 73.29; H, 6.80; N, 4.50%

ν_{max}(film) 1728, 1758, 760 cm.$^{-1}$.

The n.m.r. spectrum showed a nine proton peak at 1.45 p.p.m. due to the t-butyl group.

5-(2-Quinolyl)-valeric acid (206).

a) The keto-ester (205a) (3.0 g., 0.0011 mole) was shaken with dilute aqueous ethanolic sodium hydroxide solution until a homogeneous solution was obtained (approximately 15 min.). The reaction was neutralised with 3N hydrochloric acid and evaporated to dryness. The residue was dissolved in ether and water; the ether was separated and dried. Evaporation of the ether gave a gum which on trituration with 60-80 petroleum ether gave a colourless solid. Recrystallisation of the solid from methanol-60-80° petroleum ether mixture gave the acid (206, 2.2 g., 90%), as colourless prisms, m.p. 93-94°.

Found: C, 73.3; H, 6.34; N, 6.1%

$C_{14}H_{15}NO_2$ requires: C, 73.34; H, 6.59; N, 6.11%

ν_{max}(Nujol) 2800-2500 (broad band), 1691, 752 cm.$^{-1}$.

The n.m.r. spectrum showed a four proton multiplet at 1.83 p.p.m., a two proton triplet at 2.83 p.p.m., a two proton triplet at 3.06 p.p.m., six aromatic protons, and a sharp one proton singlet at 11.5 p.p.m.

b) The keto-ester (205b) (3.2 g.) was warmed on a steam bath with 2N hydrochloric acid (25 ml.) for 30 min. The mixture was evaporated to dryness and the residue neutralised with aqueous sodium bicarbonate solution. The aqueous mixture was extracted with ether which was dried and evaporated to give a gum which solidified on trituration with 60-80° petroleum ether. The solid was recrystallised from methanol-60-80° petroleum ether mixture to give the acid (206, 2.3 g.), m.p. 93-94°.

Attempted preparation of 2-(2-quinolyl)-cyclopentanone.

a) A solution of the keto-ester (205b) (5 g.) in benzene (50 ml.) containing a trace of p-toluene sulphonic acid was boiled under reflux for 6 hr. Extraction with sodium carbonate solution and evaporation of the benzene gave the unreacted keto-ester (205b).

The above reaction was repeated using xylene as solvent giving unreacted keto-ester (205b).

b) A solution of the keto-ester (205b) (5 g.) in chloroform (50 ml.) containing trifluoracetic acid (3 ml.) was boiled under reflux for 40 hr. Extraction of the chloroform with aqueous sodium carbonate solution and evaporation gave unreacted keto-ester (205b).

Quinoline-2-carboxylic acid-1-oxide (207).

A solution of the keto-ester (205a) (3.0 g.) was heated on a steam bath with glacial acetic acid (50 ml.) and 30% hydrogen peroxide (30 ml.) for 3 hr. At this time 30% hydrogen peroxide (15 ml.) was added and the mixture heated on the steam bath for a further 4 hr. The mixture was evaporated to dryness under reduced pressure and the residue shaken with chloroform and dilute potassium hydroxide solution. The aqueous layer was separated and made slightly acid with 3N hydrochloric acid. The free acid was extracted with chloroform which was dried (Na_2SO_4) and evaporated to give a yellow solid (1.6 g.). Recrystallisation of the solid from methanol gave the acid (207) as yellow needles, m.p. 166-168° (decomp.).

An authentic specimen prepared by the above method from ethyl 2-quinolylacetate had a m.p. 165-167° (decomp.). A mixture of the authentic specimen and the specimen prepared from keto-ester (205a) had m.p. 165-167° (d.).

Ethyl 2-(2-quinolyl)-cyclopentanol-2-carboxylate (208).

A solution of keto-ester (205a, 10.0 g., 0.035 mole) in ethanol (100 ml.) containing a suspension of 10% palladium-charcoal (0.5 g.) was hydrogenated at room temperature and pressure. When the absorbtion of hydrogen had ceased the solution was filtered and evaporated to a viscous orange oil. Distillation gave the alcohol, (8.8 g., 87%), b.p. 155-160°/ 0.1 mm.

Found: C, 71.7 ; H, 6.62; N, 5.2%

$C_{17}H_{19}NO_3$ requires: C, 71.56; H, 6.67; N, 4.91%

ν_{max}(film) 1725, 752 cm.$^{-1}$.

Ketal of ethyl 2-(2-quinolyl)-cyclopentanone-2-carboxylate (206a).

A solution of keto-ester (205a) (10.0 g., 0.035 mole), ethylene glycol (2.2 g., 0.035 mole), and a trace of p-toluene sulphonic acid, in benzene (300 ml.) was boiled under reflux under a water separating device for 12 hr. The benzene was removed by distillation and dry toluene (300 ml.), and ethylene glycol (1.0 g.) added. The mixture was boiled under reflux under a water separator for a further 20 hr. The toluene was removed by distillation and unreacted keto-ester (205a) was removed by boiling with Girard-T reagent in ethanol-acetic acid mixture for 6 hr. The ethanol-acetic acid was distilled and the residue dissolved in ether. The ether layer was washed with water, aqueous sodium bicarbonate solution, and the ether evaporated to give an orange liquid. The ketal was obtained by chromatography on Woelm alumina, grade IV, using benzene as eluent, as a pale yellow liquid (4.8 g., 42%).

Found: C, 69.1 ; H, 6.60; N, 4.3%

$C_{19}H_{21}NO_4$ requires: C, 69.70; H, 6.47; N, 4.28%

ν_{max}(film) 1725, 750 cm.$^{-1}$

The n.m.r. spectrum showed six protons in the region 3.60 p.p.m. to 4.35 p.p.m. belonging to the protons of the ester and of the ethylenedioxy group.

Ketal of t-butyl 2-(2-quinolyl)-cyclopentanone-2-carboxylate (206b).

This was prepared and purified in a similar manner to that described for the e thyl ester, yield 36%.

Found: C, 70.5 ; H, 7.17; N, 4.2%

$C_{21}H_{25}NO_4$ requires: C, 70.94; H, 7.09; N, 3.94%

ν_{max}(film) 1725, 752 cm.$^{-1}$

The n.m.r. spectrum showed a two proton multiplet at 4.10 p.p.m. and a two proton multiplet at 3.80 p.p.m. due to the ethylenedioxy group, and a nine proton singlet at 1.43 p.p.m. for the t-butyl group.

Ethyl 2-(1,2,3,4-tetrahydro-2-quinolyl)-1',3'-dioxolan-2'-spiro-cyclopentane-2-carboxylate (207a).

A solution of the ketal (206a) (4.5 g., 0.0014 mole) in glacial acetic acid was hydrogenated over Adams' catalyst (200 mg.) at room temperature and pressure until 2 molar equivalents of hydrogen had been absorbed. The acetic acid with suspended platinum was evaporated at the water pump and the residue made alkaline with cold aqueous sodium bicarbonate solution. Ether was added to dissolve the liberated oil and the mixture quickly filtered from the platinum. The ether layer was separated and dried and the ether evaporated. The oil remaining was chromatographed on Woelm alumina, grade III, using benzene to give some of the ketal (206a) (0.7 g.), and the tetrahydro-ketal (207a) (3.6 g., 94% on unrecovered ketal) as a pale yellow oil.

Found: C, 68.3 ; H, 7.39; N, 4.1%

$C_{19}H_{25}NO_4$ requires : C, 68.86; H, 7.55; N, 4.22%

ν_{max}(film) 3410, 1725, 750 cm.$^{-1}$

The n.m.r. spectrum (CCl_4) showed four aromatic protons and twenty one other protons.

t-Butyl 2-(1,2,3,4-tetrahydro-2-quinolyl)-1',3'-dioxolan-2'-spiro-cyclopentane-2-carboxylate (207b).

This was prepared and purified in a similar manner to that described for the ethyl ester, yield 88%.

Found: C, 69.6 ; H, 8.05; N, 3.8%

$C_{21}H_{29}NO_4$ requires: C, 70.17; H, 8.13; N, 3.90%

ν_{max}(film) 3405, 1725, 753 cm.$^{-1}$.

The n.m.r. spectrum (CCl_4) showed four aromatic protons, and twenty-five other protons, containing a nine proton singlet at 1.44 p.p.m. (t-butyl group).

Attempted alkylation of ketal (207a).

A solution of ketal (207a) (3.0 g., 0.009 mole), and acrylonitrile (4.0 g., 0.09 mole) in acetic acid (50 ml.) containing cuprous chloride (0.1 g.) was boiled under reflux for 20 hr. Filtration and evaporation of the mixture gave unreacted starting material.

The above residue and acrylonitrile (5.0 g.) was dissolved in glacial acetic acid (15 ml.) and sealed in a pyrex tube. Heating the tube to 150° for 4 hr. gave a crude product on evaporation. No identifiable products were obtained on chromatography using Woelm alumina and benzene as eluent.

Attempted preparation of ethyl 2-carbethoxy-2-(2'-quinolyl)-cyclopentylidene cyanoacetate (210).

a) Equimolar quantities of keto-ester (205a) and ethyl cyanoacetate containing a trace of piperidine were allowed to react by the procedure described by Kon and Nanji. The crude product showed a weak band at 2200 $cm.^{-1}$ in its infrared spectrum but distillation gave only starting material.

b) Equimolar quantities of keto-ester (205a) and ethyl cyanoacetate were boiled under a water separating device with benzene containing ammonium acetate and acetic acid for 40 hr. On evaporation of the benzene only starting material was observed.

c) Equimolar quantities of keto-ester (205a) and ethyl cyanoacetate containing a trace of piperidine and benzylamine were heated to 110° for 3 hr. Recovered starting material, as well as some N-benzyl-cyanoacetamide, were obtained.

d) When the above reactions were repeated using acetic anhydride as condensing agent none of the desired product was obtained.

2-Cyanocyclopentanone was obtained on hydrolysis of the enamine prepared by cyclisation of adiponitrile using potassium-t-butoxide in benzene as described by Thompson.[152]

2-Cyano-2-(2'-quinolyl)-cyclopentanone (211).

2-Cyanocyclopentanone (5.45 g., 0.05 mole) was added dropwise to a stirred solution of quinoline-1-oxide (7.25 g., 0.05 mole) in acetic

anhydride (10 ml.). An exothermic reaction took place which required cooling in an ice bath and the reaction was allowed to proceed for 1 hr. at room temperature. The mixture was then cooled to -5° until crystallisation took place. Filtration gave a yellow solid which was contaminated with an oil. The solid was extracted by warming with 60-80° petroleum ether to give the keto-nitrile (8.0 g., 68%). Recrystallisation from 60-80° petroleum ether gave the keto-nitrile (211) as pale yellow plates, m.p. 91-92°.

Found: C, 75.8; H, 4.97; N, 11.7%

$C_{15}H_{12}N_2O$ requires: C, 76.35; H, 5.12; N, 11.86%

ν_{max}(Nujol) 2242, 1768 cm.$^{-1}$

The n.m.r. spectrum ($CDCl_3$) showed six aromatic protons and six cyclopentanone protons.

5-Cyano-5-(2'-quinolyl)valeric acid (212).

The cyano-ketone (211) (0.50 g., 0.002 mole) was warmed gently with dilute aqueous sodium carbonate solution (15 ml.) until a solution occurred. The solution was neutralised with dilute hydrochloric acid and extracted with chloroform. Evaporation of the chloroform gave the acid (212) (0.52 g., 94%) as a white solid, m.p. 118-120°. Recrystallisation from 60-80° petroleum ether/ethanol mixture gave the acid (212) as colourless needles, m.p. 119-120°.

Found: C, 70.4 ; H, 5.40; N, 10.8%

$C_{15}H_{14}N_2O_2$ requires: C, 70.85; H, 5.55; N, 11.02%

ν_{max}(Nujol) 2240, 1722 cm.$^{-1}$.

The n.m.r. spectrum ($CDCl_3$) showed a four proton multiplet at approximately 2.1 p.p.m., a two proton triplet at 2.48 p.p.m. (methylene group α to COOH), a one proton triplet at 4.38 p.p.m. (proton α to CN), six aromatic protons, and a one proton singlet at 10.98 p.p.m.

2-Acetyl-cyclopentane-1,3-dione was prepared by the method of Merenyi and Nelson.[143]

2-(2'-Quinolylacetyl)-cyclopentane-1,3-dione (213).

A solution of 2-acetyl-cyclopentane-1,3-dione (3.2 g., 0.023 mole) in acetic anhydride (3 ml.) was added dropwise to a solution of quinoline-1-oxide (3.3 g., 0.023 mole) in acetic anhydride (5 ml.). An exothermic reaction took place with the immediate precipitation of an orange solid. The mixture was allowed to stand for 1 hr. and then filtered to give the triketone (213) (5.1 g., 73%). Recrystallisation from 100-120° petroleum ether gave the ketone as orange micro-needles, m.p. 240-242° with decomposition.

Found: C, 71.47; H, 4.78; N, 5.40%

$C_{16}H_{13}NO_3$ requires: C, 71.90; H, 4.90; N, 5.24%

ν_{max}(Nujol) 1680, 1640-1605(broad) $cm.^{-1}$.

The n.m.r. spectrum (T.F.A.) showed a four proton singlet at 3.02 p.p.m., a two proton singlet at 5.16 p.p.m., and six aromatic protons.

2-Imino-1-(2-quinolyl)-2-(2-cyclopentane-1,3-dione)-ethane (214).

A solution of ketone (213) (1.6 g.) in benzene (10 ml.) containing ethanol, an equivalent of malononitrile, and ammonium acetate (0.2 g.) was

heated under reflux for 12 hr. Evaporation of the mixture gave a solid residue which was recrystallised from 60-80° petroleum ether to give the imine (214) as colourless needles (1.1 g.) m.p. 185-186°.

Found: C, 71.77; H, 5.35; N, 10.42%

$C_{16}H_{13}N_2O_2$ requires: C, 72.16; H, 5.30; N, 10.52%

ν_{max}(Nujol) 3250, 1685, 1625 cm.$^{-1}$.

The n.m.r. spectrum ($CDCl_3$) showed a four proton singlet at 2.57 p.p.m., a two proton singlet at 4.87 p.p.m., and seven protons in the aromatic region.

Ethyl-2-(1-acetyl-1,4-dihydro-4-quinolyl)cyclopentanone-2-carboxylate (216).

Acetyl chloride (2.30 g., 0.030 mole) was added dropwise to a solution of quinoline (11.6 g., 0.09 mole) and 2-carbethoxycyclopentanone (4.7 g., 0.030 mole) in dry benzene (150 ml.), A precipitate of quinoline hydrochloride slowly formed and the reaction was allowed to stand at room temperature for 3 days until the smell of acetyl chloride disappeared. The quinoline hydrochloride was filtered and washed with ether. The combined filtrate and washings were washed with 2N hydrochloric acid (3 x 50 ml.), aqueous sodium carbonate solution, and the ether dried and evaporated. Trituration of the residue with petroleum ether gave the amide (216) (3.9 g., 40%) m.p. 132-140°. Recrystallisation from 60-80° petroleum ether gave colourless cubes, m.p. 138-140°.

Found: C, 70.0; H, 6.54; N, 4.2%

$C_{19}H_{21}NO_4$ requires: C, 69.70; H, 6.47; N, 4.28%

ν_{max}(CCl_4) 1750, 1720, 1690, and 1655 cm.$^{-1}$

The n.m.r. spectrum is shown facing p. 105.

2-Cyano-2-(1-acetyl-1,2-dihydro-2-quinolyl)-cyclopentanone (217).

Acetyl chloride (7.7 g., 0.10 mole) in dry benzene (10 ml.) was added dropwise to a stirred solution of quinoline (38.7 g., 0.3 mole) and 2-cyanocyclopentanone (10.9 g., 0.10 mole) in dry benzene (50 ml.). An exothermic reaction took place with the precipitation of quinoline hydrochloride. The mixture was stirred for an hour at room temperature and then the quinoline hydrochloride was filtered from the mixture. The quinoline hydrochloride was washed with ether and the combined filtrate and washings extracted with 3N hydrochloric acid (3 x 50 ml.). The organic layer was dried and evaporated to give a residue from which a solid was separated. The solid was filtered and recrystallised to give the amide (217) (8.0 g., 29%).

Found: C, 72.8 ; H, 5.56; N, 9.9%

$C_{17}H_{16}N_2O_2$ requires: C, 72.84; H, 5.75; N, 9.99%

$\nu_{max}(CCl_4)$ 2245, 1752, 1662, 1656 cm.$^{-1}$

The n.m.r. spectrum is shown facing p. 107.

The residue after filtration of the amide (217) was distilled giving 2-cyanocyclopentene-1-yl acetate (218, 5.3 g., 35%) as a colourless liquid, b.p. 70-72°/0.1 mm., and 2-cyanocyclopentanone (2.2 g.).

Found: C, 63.8; H, 5.78; N, 9.6%

$C_8H_9NO_2$ requires: C, 63.56; H, 6.00; N, 9.27%

ν_{max}(film) 2228, 1780, 1660 cm.$^{-1}$

The n.m.r. spectrum (CCl_4) showed a three proton singlet at 2.22 p.p.m. superimposed on a two proton multiplet, and a four proton multiplet at 2.6 p.p.m.

Attempted cyclisation of amide (217).

A solution of the amide (217) (2.80 g., 0.01 mole) in dry dimethoxyethane (50 ml.) was stirred and boiled under reflux with sodium hydride (0.24 g., 0.01 mole) for 2 hr. The mixture was cooled and acetic acid (1 ml.) added and the whole evaporated to a brown gum. The n.m.r. spectrum of this gum showed quinoline to be present with no sign of a vinyl proton characteristic of compound (219).

Chloroacetyl chloride was prepared by the action of phosphoryl chloride on chloroacetic acid.

Cyanoacetyl chloride was prepared from cyanoacetic acid and phosphorus pentachloride.[124]

Ethoxy-acetyl chloride was prepared from ethoxyacetic acid and benzoyl chloride.[146]

2-Carbethoxycyclopentene-1-yl chloroacetate (220).

Chloro-acetyl chloride (11.3 g., 0.1 mole) in dry benzene (10 ml.) was added dropwise to a solution of quinoline (38.7 g., 0.3 mole) and 2-carbethoxycyclopentanone (15.6 g., 0.1 mole) in dry benzene (50 ml.)

A precipitate of quinoline hydrochloride began to form and the mixture darkened. The mixture was stirred for 6 hr. and filtered, the filtrate being washed with ether. The filtrate and washings were extracted with 3N hydrochloric acid (3 x 100 ml.), aqueous sodium carbonate (1 x 50 ml.), and then dried and evaporated. No solid could be crystallised from the crude residue which was distilled giving recovered 2-carbethoxycyclopentanone (3.3 g.) and the ester (220) (14.3 g., 61%) as a colourless oil, b.p. 90-92°/0.05°.

Found: C, 51.1; H, 5.44%

$C_{10}H_{13}O_4Cl$ requires: C, 51.50; H, 5.59%

ν_{max}(film) 1790, 1728, 1663 cm.$^{-1}$

The n.m.r. spectrum (CCl_4) showed a triplet at 1.28 p.p.m. and quartet at 4.20 p.p.m. due to the ester protons, six cyclopentane protons, and a singlet at 4.35 p.p.m. due to the chloroacetyl protons.

2-Cyano-cyclopentene-1-yl chloroacetate (221).

Chloroacetyl chloride (22.6 g., 0.2 mole) in dry benzene (15 ml.) was added dropwise to a stirred solution of quinoline (77 g., 0.6 mole) and 2-cyano-cyclopentanone (22.0 g., 0.2 mole) in dry benzene (100 ml.). The reaction was allowed to proceed for 1 hr. and then worked up in a similar manner to the previous experiment. The residue was distilled giving 2-cyanocyclopentanone (10.4 g.), b.p. 95-100°/0.1 mm., and the ester (221, 18.6 g., 50%) as a colourless oil, b.p. 112-115°.

Found: C, 51.5 ; H, 4.37; N, 7.3%

$C_8H_8NO_2Cl$ requires: C, 51.76; H, 4.32; N, 7.55%

ν_{max}(film) 2230, 1790, 1662 cm.$^{-1}$.

The n.m.r. spectrum (CCl_4) showed six cyclopentanone protons and a two proton singlet at 4.36 p.p.m.

2-Carbethoxycyclopentene-1-yl ethoxyacetate (222).

Ethoxyacetyl chloride (6.2 g., 0.05 mole) was added dropwise to a solution of quinoline (20.0 g., 0.16 mole) and 2-carbethoxycyclopentanone (7.8 g., 0.05 mole) in dry benzene (50 ml.). The reaction was stirred for a further hour and worked up as in previous experiments. Distillation of the residue gave 2-carbethoxycyclopentanone (0.7 g.), b.p. 90-96°/0.1 mm., and the ester (222, 9.2 g., 76%) as a colourless oil, b.p. 102-105°/0.1 mm.

Found: C, 59.0; H, 7.52%

$C_{12}H_{18}O_5$ requires: C, 59.55; H, 7.44%

ν_{max}(film) 1788, 1730, 1658, 1108 cm.$^{-1}$

The n.m.r. spectrum (CCl_4) showed two superimposed triplets due to the ester and ether methyls, six cyclopentanone protons between 2 and 3 p.p.m., a quartet at 3.66 p.p.m. due to the ether protons, a quartet at 4.20 p.p.m. due to the ester protons and a singlet at 4.26 p.p.m.

2-Cyanocyclopentene-1-yl ethoxyacetate (223).

Ethoxyacetyl chloride (6.2 g., 0.05 mole) was added dropwise to a solution of 2-cyanocyclopentanone (5.5 g., 0.05 mole) and quinoline (19.5 g., 0.15 mole) in dry benzene (50 ml.). The reaction was allowed to proceed

for a further hour and worked up as in previous experiments. The residue was distilled giving the ester (9.0 g., 92%) as a colourless liquid, b.p. 98-100°/0.1 mm.

Found: C, 61.8 ; H, 6.57; N, 7.1%

$C_{10}H_{13}NO_3$ requires: C, 61.52; H, 6.71; N, 7.18%

ν_{max}(film) 2225, 1788, 1655, 1108 cm.$^{-1}$.

The n.m.r. spectrum (CCl_4) shows the ether protons as a quartet at 3.65 p.p.m. and a triplet at 1.23 p.p.m., six cyclopentanone protons, and a singlet at 4.26 p.p.m. due to CH_2 of the acetyl residue.

Reaction of quinoline and 2-cyanocyclopentanone in the presence of cyano-acetyl chloride.

Cyano-acetyl chloride (10.4 g., 0.10 mole) was added dropwise to a solution of quinoline (38.7 g., 0.30 mole) and 2-cyanocyclopentanone (11.0 g., 0.10 mole) in dry benzene (100 ml.). An exothermic reaction took place and the mixture became dark brown. The mixture was allowed to stir at room temperature for 1 hr. when a very crude product was obtained from which no identifiable products were obtained.

Ethyl 2-carbethoxy-cyclopentylidene cyanoacetate (224) was prepared by the method of Kon and Nanji.[141]

Ethyl 2-carbethoxy-2-(2'-quinolyl)-cyclopentylidene cyanoacetate (210).

The cyano-ester (224) (20.0 g., 0.080 mole) was added dropwise to a stirred solution of quinoline-1-oxide (11.8 g., 0.081 mole) in acetic anhydride (15 ml.). The solution darkened rapidly and was allowed to stir

at room temperature for 1 hr. Ethanol (10 ml.) was added to destroy the excess acetic anhydride and the whole evaporated to a dark residue. The residue was dissolved in ether and washed with aqueous sodium bicarbonate solution until free from acid and finally with water. The ether extracts were dried and the ether distilled. Chromatography on Woelm alumina, grade IV with 60/80° petroleum ether-benzene mixture gave a small amount of recovered cyano-ester (224, 1.2 g.) and the required addition compound (210, 19.6 g., 65%) as an orange oil which darkened rapidly on exposure to air.

Found: C, 68.5; H, 5.71; N, 7.1%

$C_{22}H_{22}N_2O_4$ requires C, 69.82; H, 5.86; N, 7.40%

ν_{max}(film) 2230, 1730, 1625 cm.$^{-1}$

The n.m.r. spectrum (CCl_4) showed three overlapping sets of ester peaks, two protons from 2.5 to 3.2 p.p.m. (protons α to double bond), and four protons from 1.7 to 2.4 p.p.m., and six aromatic protons.

Hydrogenation of the compound (210) in ethanol over 10% palladium on charcoal was slow and gave a crude mixture with no C≡N stretching in its infrared spectrum. Hydrogenation in ethanol or acetic acid using Adams' catalyst gave a crude product which showed loss of the C≡N group in its infrared spectrum. Sodium borohydride reduction in ethanol or isopropanol of compound (210) had no reaction on the exocyclic double bond.

Attempted hydrolysis of cyano-ketone (210).

a) The cyano-ketone (210, 2.0 g.) was boiled under reflux for 3 hr. with ethanol (25 ml.) containing water (0.5 ml.) which had been saturated with dry hydrogen chloride. Evaporation of the ethanol and neutralisation

of the product gave a product which still showed C≡N stretching in its infrared spectrum.

b) The cyano-ketone (210, 1.5 g.) was boiled under reflux for 3 hr. with ethanol (25 ml.) containing concentrated sulphuric acid, (1 ml.). Working up, as in the previous hydrolysis attempt, gave a crude product which still showed C≡N stretching in its infrared spectrum.

Hydrolysis of ethyl 2-carbethoxy-cyclopentylidene-cyanoacetate.

a) The cyano-ester (224, 5.0 g.) was boiled under reflux with ethanol (50 ml.) containing concentrated sulphuric acid (2 ml.) for 5 hr. To the cold solution, chloroform (150ml) and aqueous sodium bicarbonate solution were added. A precipitate formed which was filtered off and the chloroform layer dried and evaporated to give the cyano-ester (224) (2.1 g.). The precipitated sodium salt was acidified with dilute hydrochloric acid and extracted with chloroform. The chloroform was dried and evaporated to give the compound (225a, 1.9 g.). Recrystallisation from ethanol gave colourless needles, m.p. 220° (decomposition), (lit.[141] 238-240°).

Found: C, 59.6; H, 5.79; N, 6.3%

$C_{11}H_{13}NO_4$ requires: C, 59.18; H, 5.87; N, 6.28%

ν_{max}(Nujol) 3370, 3120, 2800, 2700, 1655, 1620 cm.$^{-1}$.

The n.m.r. spectrum (T.F.A.) is described in the discussion.

b) The cyano-ester (224, 6.0 g.), was boiled under reflux for 3 hr. with methanol (100 ml.) saturated with dry hydrogen chloride. Evaporation of the methanol gave a residue from which a solid separated. Filtration and recrystallisation of the solid from ethanol gave colourless needles,

m.p. 227-229° (decomposition) (225b) (1.8 g.).

Found: C, 57.2; H, 5.24; N, 6.6%

$C_{10}H_{11}NO_4$ requires: C, 57.41; H, 5.30; N, 6.70%

ν_{max}(Nujol) 3370, 3120, 2800, 2700, 1655, 1620 $cm.^{-1}$

The n.m.r. spectrum (T.F.A.) showed a two proton quartet at 2.30 p.p.m., a two proton triplet at 2.95 p.p.m., a two proton triplet at 3.40 p.p.m., and a three proton singlet at 4.14 p.p.m.

Recovered cyano-ester (224) and esters containing methyl groups were the only other products as shown by n.m.r. spectrum.

c) The cyano-ester (224) (8.1 g.) was boiled under reflux with ethanol (30 ml.) and water (30 ml.) containing potassium hydroxide (12 g.) for 8 hr. Evaporation of the mixture gave a solid which was dissolved in water (100 ml.) and acidified with 3N hydrochloric acid. The free acid was extracted with chloroform which was dried and evaporated giving the solid acid (4.2 g.). Methanol (50 ml.) and concentrated sulphuric acid (2 ml.) was added to the residue which was refluxed for 4 hr. The mixture was poured into benzene (50 ml.) and aqueous sodium bicarbonate solution. The organic extracts were dried and the benzene evaporated to give a colourless liquid (4.5 g.) which was distilled giving a fraction b.p. 80-82°/0.2 mm (3.8 g.) consisting mainly of the tri-ester (226). The n.m.r. spectrum (CCl_4) showed three methyl singlets at approximately 3.8 p.p.m. which did not correspond to the expected nine protons.

Dimethyl di-2-quinolylmalonate (227).

The impure tri-ester (226, 3.0 g.) was added dropwise to a solution of quinoline-1-oxide (2.2 g.) in acetic anhydride (3 ml.). No exothermic

reaction appeared to take place and the mixture was allowed to stand at 40-50° overnight when crystals separated. Filtration and recrystallisation of the solid gave the ester (227, 1.6 g.) as yellow prisms, m.p. 209-210°.

Found: C, 70.9; H, 4.63; N, 7.2%

$C_{23}H_{18}N_2O$ requires: C, 71.49; H, 4.70; N, 7.25%

ν_{max}(Nujol) 1750 cm.$^{-1}$

The n.m.r. spectrum showed a singlet (six protons) at 4.06 p.p.m. and six aromatic protons.

Di-2,2-quinolylmethane (228).

A suspension of the ester (227) (1.0 g.) in 20% hydrochloric acid (20 ml.) was heated under reflux for 2 hr. After removal of the aqueous hydrochloric acid the residue was basified with sodium carbonate solution and extracted with chloroform. The chloroform was dried and evaporated to give a solid which was recrystallised from 60/80 petroleum ether as light brown needles, m.p. 105-106° (lit.[123] 107°).

Isopropylidene malonic acid was prepared by the method of Meldrum.[147]

Attempted condensation of 2-carbethoxycyclopentanone with isopropylidene malonate.

a) The method of Corey[148] using pyridine as catalyst gave recovered starting material.

b) The method of Kon and Nanji[141] using piperidine as catalyst gave recovered starting material.

t-Butyl cyclopentylidene cyanoacetate (229)

A mixture of t-butyl cyanoacetate (70 g., 0.50 mole), 2-carbomethoxy-cyclopentanone (70 g., 0.50 mole) and a few drops of piperidine was allowed to stand at room temperature for 48 hr. and then refluxed for 4 hr. Distillation of the product gave starting material. The above mixture was then refluxed with xylene (200 ml.) for 12 hr., the xylene distilled and the residue distilled giving recovered starting materials and a solid which crystallised from the t-butyl cyanoacetate fraction. Filtration and recrystallisation of the solid from ethanol gave the cyano-ester (229, 14.2 g., 14%) as colourless needles, m.p. 87-88°.

Found: C, 69.4; H, 8.25; N, 6.8%

$C_{12}H_{17}NO_2$ requires: C, 69.54; H, 8.27; N, 6.76%

ν_{max}(Nujol) 2230, 1720 cm.$^{-1}$

The n.m.r. spectrum (CCl_4) showed the t-butyl peak at 1.58 p.p.m.

Cyclopentylidene-cyanoacetic acid (230).

The cyano-ester (229, 1.0 g.) was heated under water pump pressure at 220° until effervescence ceased. Recrystallisation of the residue gave the acid (230) as colourless needles, m.p. 132-133.5°.

Found: C, 63.0 ; H, 5.89; N, 9.1%

$C_8H_9NO_2$ requires: C, 63.60; H, 5.96; N, 9.28%

ν_{max}(Nujol) 2600 (broad), 2232, 1700 cm.$^{-1}$.

The n.m.r. spectrum ($CDCl_3$) showed eight cyclopentane protons and a singlet at 10.35 p.p.m. (acid proton).

Cyclopentylidene malononitrile (231).

A few drops of piperidine was added to a mixture of malonitrile (13.2 g., 0.20 mole) and cyclopentanone (16.8 g., 0.20 mole) in chloroform (50 ml.). An exothermic reaction took place and was allowed to proceed for 10 min. when the chloroform was extracted with 2N hydrochloric acid. The chloroform layer was dried and the chloroform distilled. Distillation of the residue gave some unreacted starting material and the nitrile (231, 22.0 g., 83%) as a colourless liquid, b.p. 80°/0.2 mm.

Found: C, 72.3; H, 6.05; N, 21.6%

$C_8H_8N_2$ requires: C, 72.7; H, 6.10; N, 21.2%

ν_{max}(film) 2240, 1615 cm.$^{-1}$

6-Amino-5,5,7-tricyano-3,3a,4,5-tetrahydro-2H-indene-4-spirocyclopentane (232).

A few drops of piperidine was added to a mixture of malononitrile (13.2 g., 0.20 mole) and cyclopentanone (16.8 g., 0.20 mole) in ethanol (40 ml.). An exothermic reaction took place and after about 10 min. a solid separated. The reaction was allowed to proceed for 30 min. and the solid filtered off. Recrystallisation from ethanol gave the compound (232, 16.6 g., 63%).

Found: C, 73.0; H, 6.05; N, 21.7%

$C_{16}H_{16}N_4$ requires: C, 72.7; H, 6.10; N, 21.2%

ν_{max}($CHCl_3$) 3465, 3385, 3200, 2220, 1632 cm.$^{-1}$.

Ethyl cyclopentylidene cyanoacetate (235) was prepared by the method of Vogel.[147]

Diethyl cyclopentylidene malonate (238) was prepared by hydrolysis of the condensation product (237) from cyclopentanone and isopropylidene malonate (236)[148] using refluxing ethanol containing a trace of dry hydrogen chloride. Evaporation of the ethanol gave the ester (238) as a colourless liquid.

The compounds (235), (237), and (238) were each added to a solution of quinoline-1-oxide in acetic anhydride producing, after a vigorous reaction, tarry products from which no identifiable material was obtained.

Attempted preparation of ethyl 2-(2'-quinolyl)-cyclopentylidene cyanoacetate (239).

Sodium hydride (2.4 g., 0.10 mole) was added to a stirred solution of ethyl cyclopentylidene cyanoacetate (235, 17.9 g., 0.10 mole) in dry benzene (300 ml.) and the mixture refluxed for 3 hr. To the yellow sodium salt was added 2-chloroquinoline (16.4 g., 0.10 mole) in dry benzene (25 ml.) over 15 min. The mixture was boiled under reflux for 3 hr., cooled, and extracted with water (100 ml.). The benzene layer was dried and evaporated giving starting material as the only identifiable material.

When toluene or xylene was used as solvent in the above experiment, 2-chloroquinoline was the only identifiable material from a crude reaction product.

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