SYNTHETIC APPROACHES TO 1,3-DIAZEPINES

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in part fulfilment of the requirements for
the Degree of Doctor of Philosophy

by

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To my Husband

The work in this thesis, unless otherwise stated, was carried out by the author under the supervision of Dr. G. Jones.

D. J. Tomkinson

Contents

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Abstract

A number of possible synthetic routes to monocyclic, fully unsaturated 1,3-diazepines are reported.

Diazabicycloheptanones were prepared from the addition of dimethylsulphoxonium methylide to alkylated pyrimidones and attempts were made to expand the products to 1,3-diazepines. An interesting byproduct from one reaction was a novel sulphoxonium ylid. Three bispyrimidonylethanes were isolated from the alkylation of 2-thiomethyl-4-(3H)-pyrimidone with dibromoethane.

Derivatives of cis-2-aminocyclopropane-carboxylic acid were synthesized as precursors for diazabicycloheptanones. Many reactions of these derivatives resulted in opening of the cyclopropane ring.

Photochemical 2 + 2 cycloadditions of various alkenes to 1,3-disubstituted-2-imidazolones were performed. No diazabicycloheptanones were obtained. When dichloroacetyl chloride or trichloroacetyl chloride (precursors to dichloroketene) were reacted with these imidazolones, the products formed were not the expected cyclobutanone derivatives, but C-acyl derivatives of the starting material.

Modification of existing 1,3-diazepines synthesized from 4-chloromethyltetrahydropyrimidines led to the isolation of methyl 2,3,6,7-tetrahydro-1-benzyl-4-methyl-2-oxo-1,3-diazepine-5-carboxylate. The silylated derivatives of the 4-chloromethyltetrahydropyrimidines were unstable.

The reaction of 1,2,3-triazolo[1,5-a]pyridine with bromine gave 2-dibromomethylpyridine which was subjected to flash vacuum pyrolysis and treated with strong base. No products characteristic of pyridyl carbene were formed but 1,2-bis-(2-pyridyl)ethylene was

obtained. A radical mechanism is proposed for this reaction. The proposed steric hindrance theory to explain the products obtained from the bromination of different triazolopyridines is described and tested.

Introduction

Interest in the 1,2- and 1,4-diazepine ring systems has escalated since the discovery in 1960 of the therapeutic activity of the latter compounds. However the 1,3-diazepine ring system and its benzofused derivatives have not been extensively studied. In fact monocyclic, unsaturated, unsubstituted 1,3-diazepines are unknown and the aim of this research has been to establish routes to provide these elusive compounds in satisfactory yields. Various precursors have been used in these attempts.

The literature on 1,3-diazepines spans fourteen years and is reviewed in the first chapter.

The second chapter reports the use of N-alkylated 4-pyrimidones in preparing bicyclic precursors in a form suitable for ring expansion into 1,3-diazepines. Alkylation methods and results are discussed and trial expansion experiments performed on the diazabicycloheptanones. The formation of a novel sulphoxonium ylid as a byproduct was noted.

Chapter three describes various attempts to prepare similar diazabicycloheptanones from cyclopropane starting materials.

A different approach can be found in Chapter 4 in which $[2\pi + 2\pi]$ cycloaddition reactions to imidazolones were attempted by both photochemical and chemical techniques.

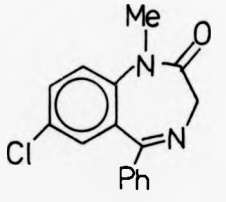
Modifications of existing 1,3-diazepines are described in Chapter 5 and the final chapter is an account of the synthesis of 2-dibromomethyl pyridines and the attempts made to generate pyridyl carbene either by flash vacuum pyrolysis or via anion formation.

CHAPTER ONE

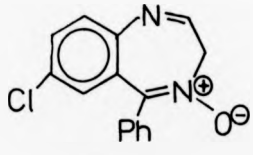
Historical review

REVIEW

Very little research has been directed towards the synthesis and reactions of 1,3-diazepines and their benzo-fused derivatives. In comparison, the 1,2 and 1,4-diazepines have been extensively studied. Large numbers of 1,4-diazepines have been synthesized since 1960 as a result of the discovery by workers at Hoffmann-LaRoche of the therapeutic activity of certain 1,4-benzodiazepines[1]. Notable examples of such compounds are the tranquillizers Valium (1) and Librium (2).



(1)



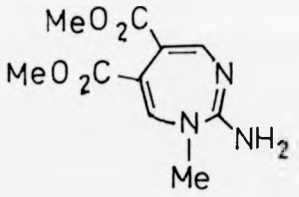
(2)

Reviews of monocyclic 1,3-diazepines[2-4] and benzodiazepines[5] can be found in the literature.

1.1 Monocyclic 1,3-diazepines

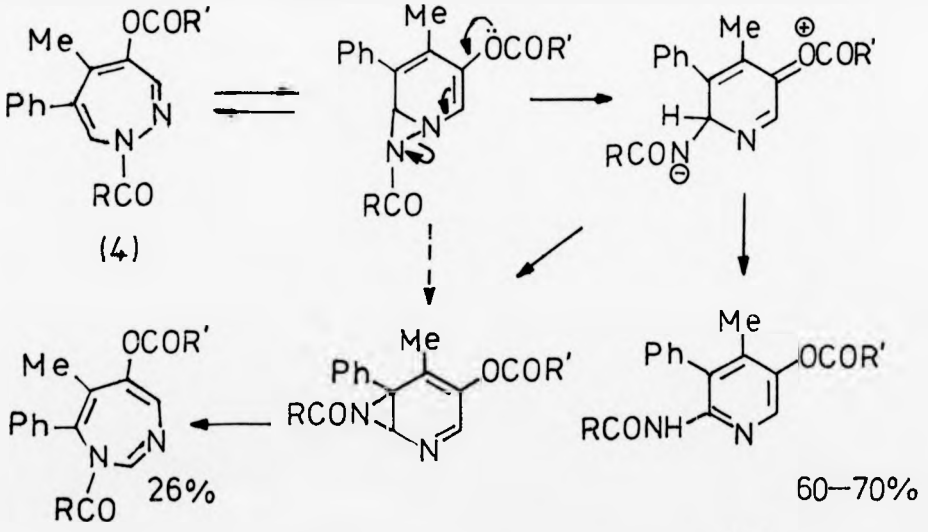
Fully unsaturated, unsubstituted, simple monocyclic 1,3-diazepines are unknown, and there are only four examples of the fully unsaturated type, with substituents, present in the literature[6-15].

The first method by Troxler and co-workers[6] involves the cycloaddition of dimethyl acetylenedicarboxylate with 2-amino-1-methyl imidazole producing the 1,3-diazepine (3) in very low yield as one of the products.



5% (3)

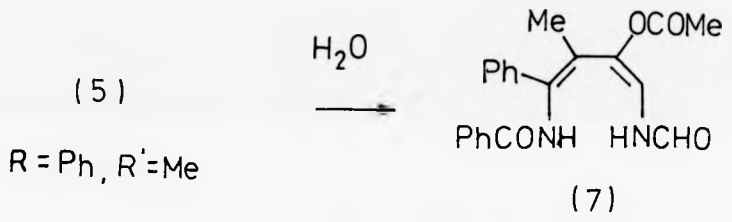
Moore et al.[7,8] observed that the thermal rearrangement of the substituted 1,2-diazepine (4) led to the isolation of the 1,3-diazepine (5) in 26% yield; the structure was determined by x-ray crystallography.



(4) (5) R=R'=Ph or Me (6)

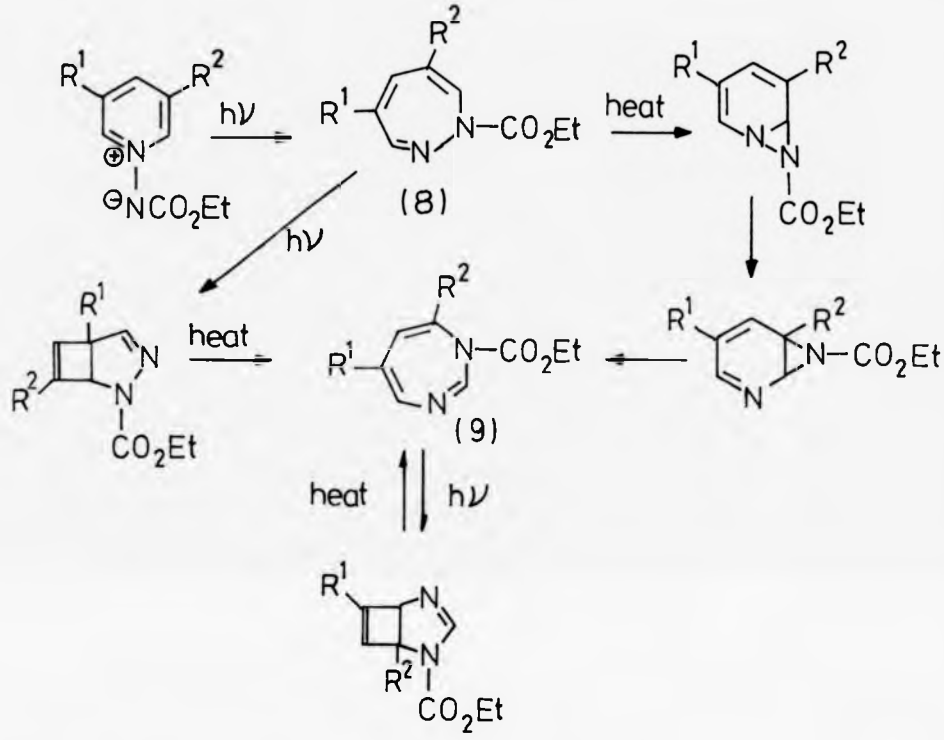
It was postulated that the mechanism proceeds with the initial formation of a bicyclic diaza-isomer. Electron release by the ester acyloxy group provides assistance for breaking the nitrogen--nitrogen bond forming a dipolar intermediate, which either cyclizes to the bicyclic aza-isomer followed by isomerisation to compound (5), or undergoes proton transfer forming the other product of reaction,

compound (6). This mechanism is supported by the fact that simple unsubstituted 1-acyl-1,2-diazepines do not show this reaction. The 1,3-diazepine (5) where R = C_6H_5 and R' = CH_3 was found to be thermally stable in boiling dry chlorobenzene, but reacted slowly with atmospheric moisture to give the acyclic compound (7).



Treatment of compound (5) with base caused ring contraction to the substituted benzamidopyridine (6) where R' = H.

A similar reaction pathway has been reported by Takashi Tsuchiya and his co-workers[9-14]. Thermolysis of 1H-1,2-diazepines (8) bearing electron donating substituents in the 4 or 6 positions produced 30-70% of the corresponding 1,3-diazepines (9).

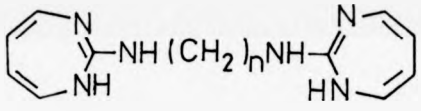


R^1 and R^2 are electron donating groups

The 1,2-diazepines (8) were prepared by irradiation of suitably substituted pyridine-N-imides, and the thermal rearrangement was thought to proceed by a similar mechanism to that of Moore[7,8], via a diaziridine intermediate followed by a thermal nitrogen-nitrogen bond fission. Further irradiation of the 1,2-diazepines (8) leads to the diazabicyclo[3:2:0]heptadienes shown in the above scheme, but these revert to 1,3-diazepines (8) on heating. Without electron donating substituents at position 4 or 6, 1,2-diazepines gave on thermolysis the parent N-imides and no 1,3-diazepines, which is in agreement with the arguments put forward by Moore. The 1,3-diazepines formed were unstable, being rapidly decomposed by water, acids,

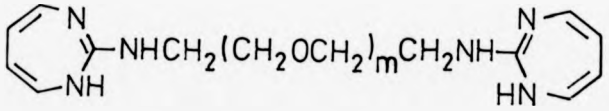
silica gel and alumina, and hence they were isolated by sephadex chromatography.

The polymers 4-polymethylene-bis(2-amino-1,3-diazepine) iodides (10) and 3-poly(oxyethylene)-bis(2-amino-1,3-diazepine) iodides (11) were prepared[15]. Their effects on neuromuscular transmission were studied in the end plate of a frog neuromuscular preparation.



$\cdot$ 2HI

n=2,4,6,8. (10)

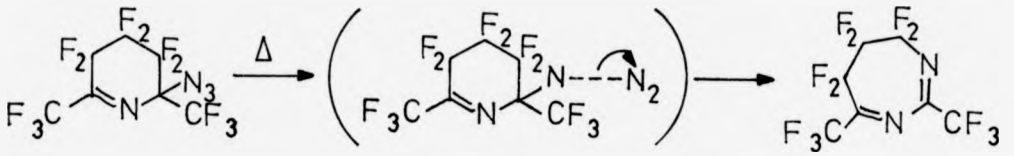


$\cdot$ 2HI

m=1,2,3. (11)

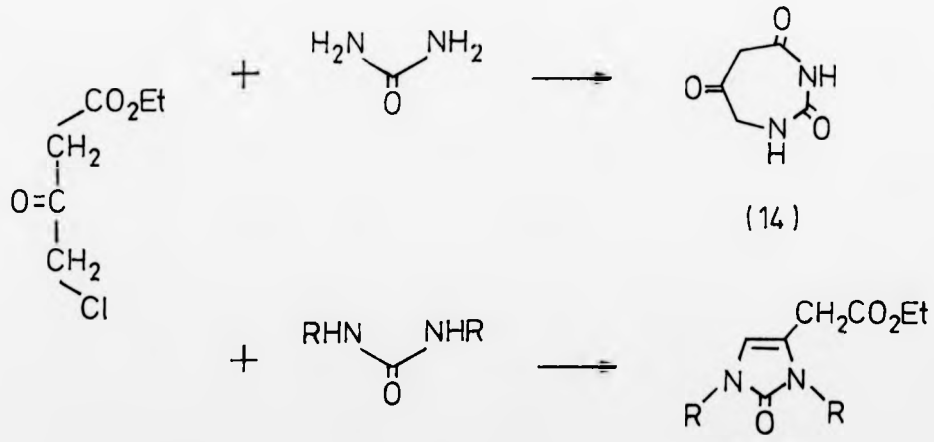
Work published by Kunieda and Witkop[16], Pandit et al.[17-20], Ashby and Griffiths[21], and by Gregory et al.[22], on partly unsaturated monocyclic 1,3-diazepines will be reviewed in subsequent chapters.

The fluorinated 1,3-diazepine (13) was formed[23] in very low yield when perfluoro-(6-azido-2,6-dimethyl-1-azacyclohexene) (12) underwent thermal ring expansion in a flow pyrolysis experiment at 380 °C and 1 mm Hg pressure. The molecular geometry has been determined by gas phase electron diffraction methods.



(12) (13)

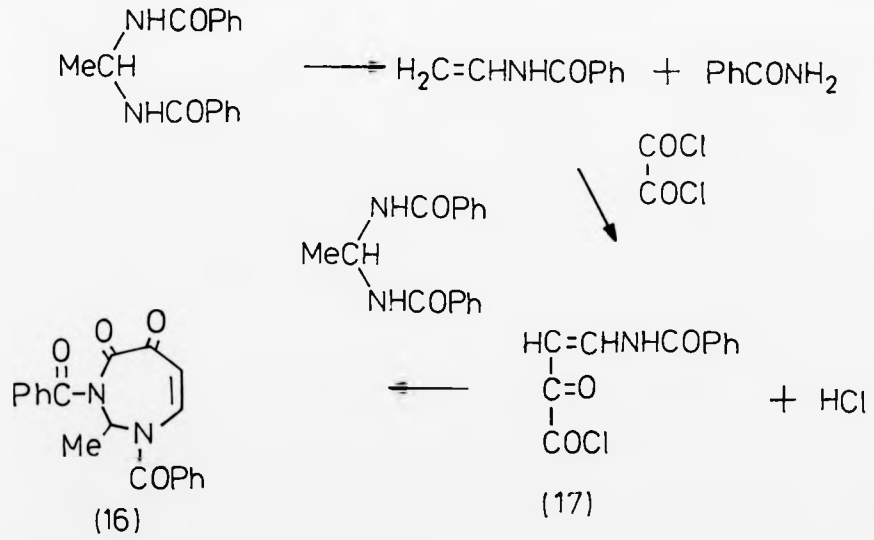
Breckenridge and Suckling[24] have reported an unusual cyclization reaction of ethyl 4-chloro-3-oxo-butanoate with urea, forming a novel diazepinetrione (14) in 66% yield. With 1,3-dimethyl-urea the same starting material gave an imidazolone (15) in 22% yield. The mechanism of formation of 1,7-dihydro-1,3-diazepine-2,4,6-trione (14) involves nucleophilic attack by urea at the carbonyl carbon of the ester followed by cyclization of the chloromethyl group.



(14)

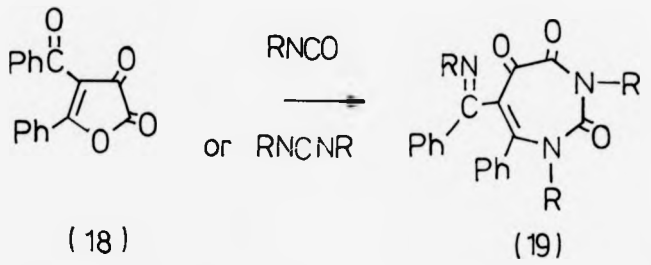
(15)

Another condensation route to 1,3-diazepines has been studied by Hanafin and Ben-Ishai[25] who have synthesized the N,N'-disubstituted--1,3-diazepine-3,4-dione (16) from ethylidene bisbenzamide and oxalyl chloride. The more usual products from methylene bisbenzamides and oxalyl chloride are imidazolidine-4,5-diones. The mechanism they propose to account for this irregularity with ethylidene bisbenzamide invokes intermediate formation of N-vinylbenzamide, which reacts further with oxalyl chloride forming the acid chloride (17). This acid chloride condenses with a second molecule of the bisadduct, and elimination of benzamide affords the product (16).



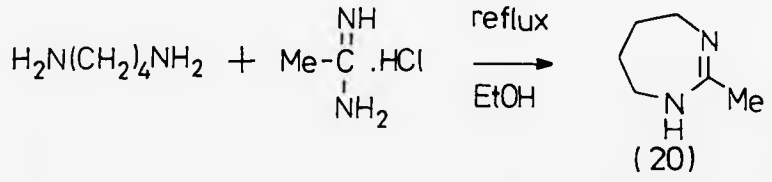
(16) (17)

1,3-Diazepinetriones have also been prepared by Kollenz and co-workers[26]. The acid catalyzed reaction of 4-benzoyl-5-phenyl-2,3-dihydro-2,3--furandione (18) with a large excess of aryl isocyanates or di-p-tolylcarbodiimide gave tetrahydro-1,3-diazepine-2,4,5-triones (19).



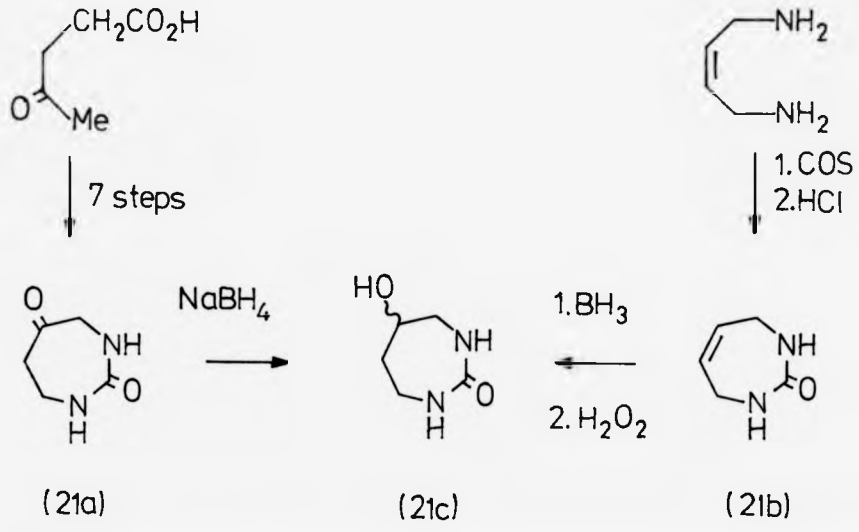
(18) (19)

A more generalized route to tetrahydro-1,3-diazepines has been developed by Desmarchalier et al.[27]. Treatment of 1,4-diaminobutane with acetamidine hydrochloride under mild conditions gave the 1,3-diazepines (20) in 47% yield.



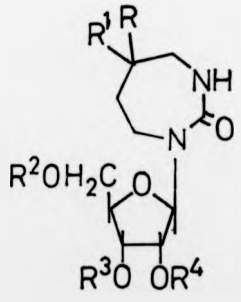
(20)

A great deal of recent research has been published on dihydro and tetrahydro-1,3-diazepinones and their nucleosides by Marquez and co-workers[28-34]. Two different routes were used in the synthesis of the hydroxyperhydro-1,3-diazepin-2-one (21c); firstly a seven stage synthesis of the ketone (21a) from levulinic acid with a final reduction step to the alcohol, and secondly a direct cyclization of cis-1,4-diamino-2-butene to the partly unsaturated 1,3-diazepinone (21b) which was hydrated to compound (21c) by a hydroboration-oxidation procedure.



(21a) (21c) (21b)

Diazepine nucleosides were then prepared from dione (21a) via the silyl ether modification of the Hillbert-Johnson reaction. This involved sequential trimethylsilylation, ribosylation with a ribofuranosyl bromide; separation of the N-1 and N-3 ribosylated compounds by chromatography, sodium borohydride reduction and deprotection afforded compound (22).

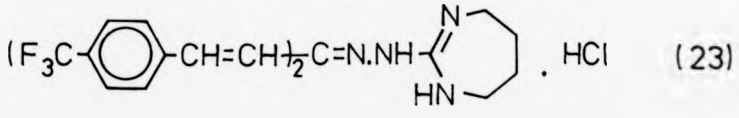


(22)

R=OH R^1=H
or R=R^1=H, O, OCH_2CH_2O, SCH_2CH_2S.
R^2=H, CH_2Ph, para $NO_2C_6H_4CO$, PO_3H_2, $P_3O_9H_4$.
R^3=H, CH_2Ph, para $NO_2C_6H_4CO$.
R^4=H, OR.

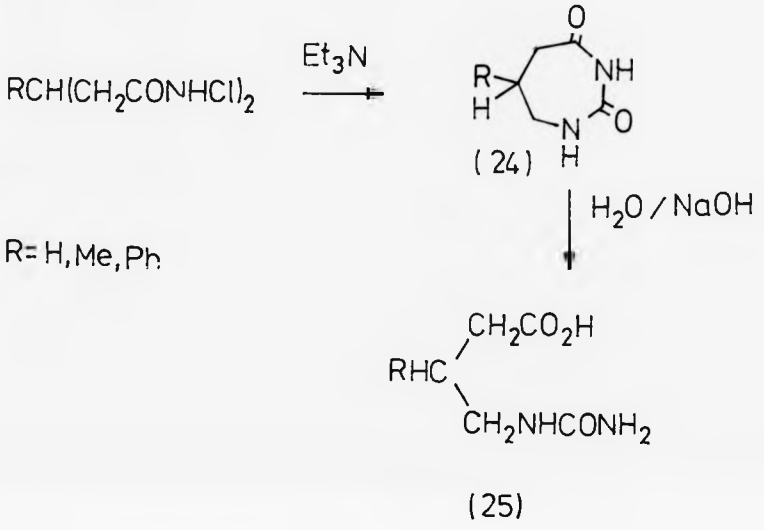
Compounds of this type are transition state inhibitors of cytidine deaminase. The most recent paper[34] presents evidence that diazepine nucleoside (22) ($R = R^1 = H$, $R^2 = R^3 = R^4 = C_6H_5CH_2$) arises from an oxygen to nitrogen transglycosylation rather than by a direct N-nucleosidation reaction.

A diazepine-hydrazone has been reported[35,36] having insecticidal properties. Reaction between 2-hydrazino-4,5,6,7--tetrahydro-1H-1,3-diazepine and $(4\text{-}CF_3.C_6H_4.CH=CH_2)_2CO$ gave the hydrazone (23) which was found to be very active against the larvae of three specific lepidopterous species, and extremely effective in fire ant control.



(23)

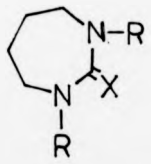
The saturated diazepinedione (24) was synthesized[37] by a cyclization reaction in moderate yield. Basic hydrolysis of compound (24) gave the ring opened material (25).



(24)

(25)

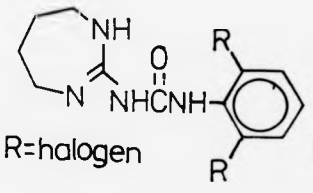
There are quite a number of references[38-52] in the literature to saturated 1,3-diazepines having the general structure of compound (26).



(26)

Some of these compounds[38-43] have been synthesized for their possible therapeutic activity. Ureas, including compound (27) have been prepared[38] as their pharmaceutically accepted salts and were found to possess antihypertensive, antidiarrhoea, and heart rate lowering properties, and relieved symptoms of irritable bowel syndrome. Compound (28) was found[39] to possess hypoglycaemic activity.

Another urea derivative (29) was found[40] to be an inducer of murine erythroleucaemia differentiation whilst compound (30) was evaluated[41] for its hypoglycaemic activity and its pKa and partition coefficient measured. Compounds with bulky substituents and a pKa of 8 - 11 were found to be the most active.



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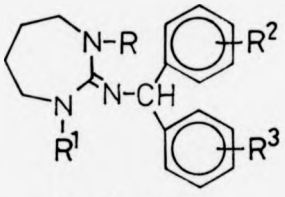
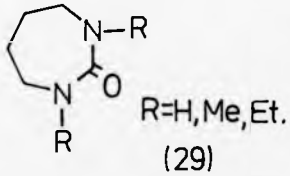


(28)

R=R¹=H,Me
R²=R³=H,R,RO,halogen



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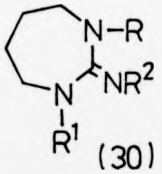
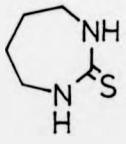


(30)

R=H,CHPh₂,Ac
R¹=H,alkyl,CONH₂
R²=H,CHPh₂

Ferrand[42] made use of the diazepine (31) in a cyclocondensation reaction to form a thiazolo[3,2-a]diazepine possessing vasodilating and hypotensive activity.



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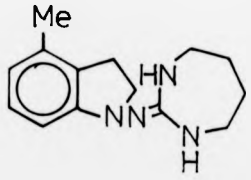
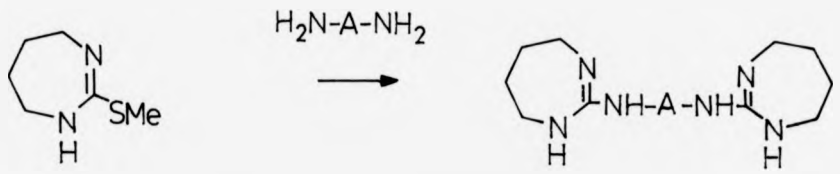


(32)

Compound (32) was prepared[43] together with a variety of aminoindolines and their salts for use as vasoconstrictors. Compound (31) has also been studied by Bogatski et al.[44-46],

who prepared from it the S-methyl derivative which with the appropriate diamine gave the diazepine dimer (33).



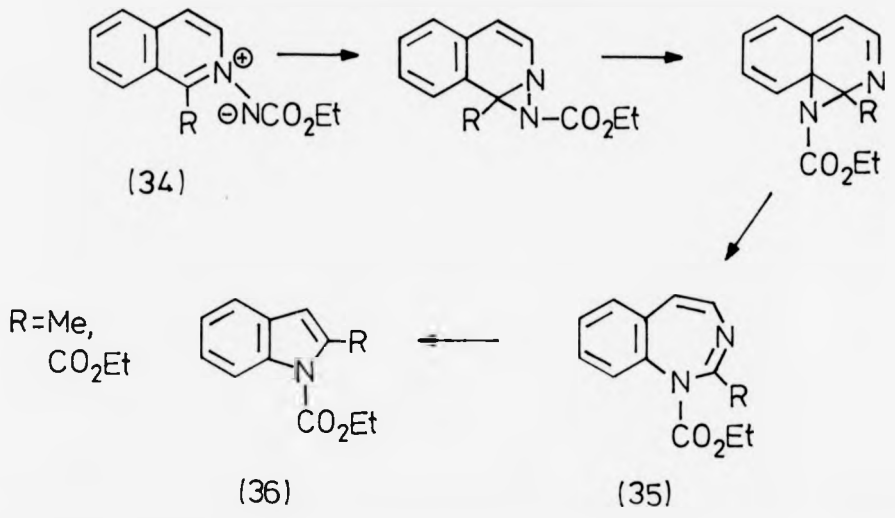
A= $(CH_2)_n$ n= 2-4,6,8 (33)

Other cyclic ureas and thioureas including seven membered rings have been mentioned[47-52] in the literature.

1.2 1,3-Benzodiazepines

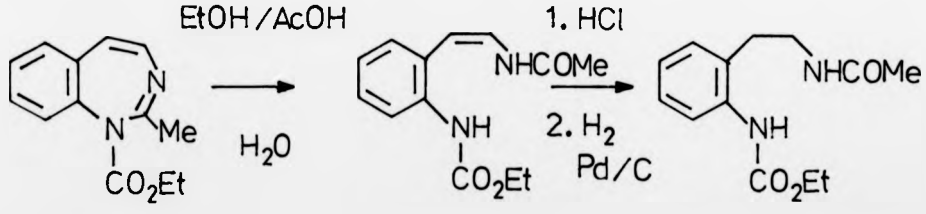
Fully unsaturated 1,3-benzodiazepines are as scarce as the monocyclic compounds, and only four examples have been reported in the literature.

Tsuchiya[53-57] has extended his work to the benzo-fused derivatives. Photolysis of isoquinoline-N-imides (34) gave the 1,3-benzodiazepines (35) in about 20% yield. Again the mechanism is thought to proceed via a diaziridine intermediate. A 1,5-sigmatropic shift gives an aziridine intermediate which undergoes ring expansion to the product (35).



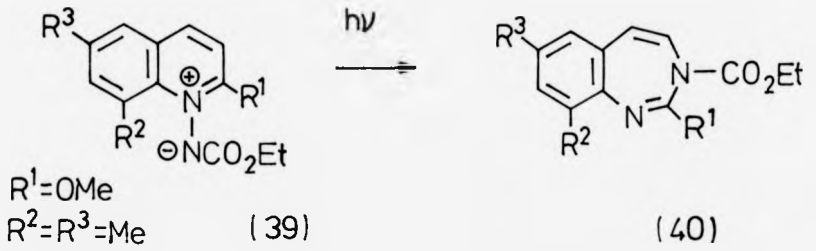
(34) (36) (35)

Further irradiation of compound (35) produces the 2-substituted indole (36) with elimination of hydrogen cyanide. Treatment of compound (35) with ethanol/acetic acid formed unstable adducts by addition to the imine double bond, and aqueous work up gave compound (37) in which the ring had been opened. Treatment with hydrogen chloride, followed by hydrogen with a palladium-charcoal catalyst gave the saturated compound (38).



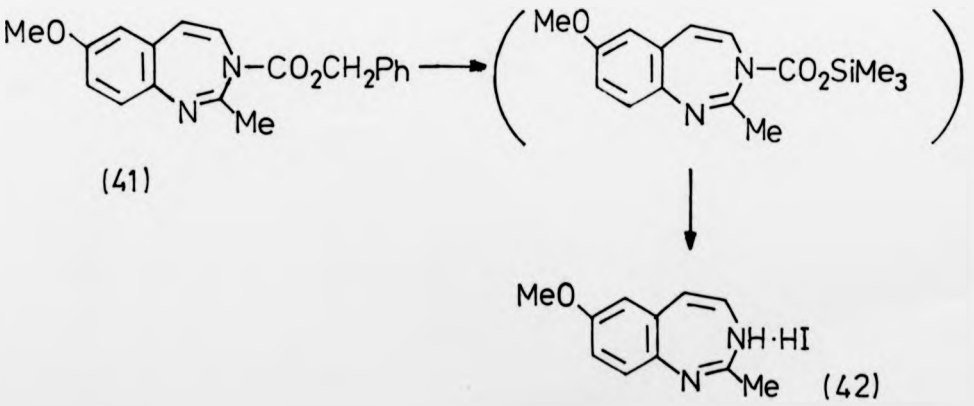
(35) (37) (38)

Irradiation of quinoline-N-imides (39) having electron donating substituents in the 6 or 8 position affords the corresponding 1,3-benzodiazepines (40), (possibly via a diaziridine intermediate[56]).



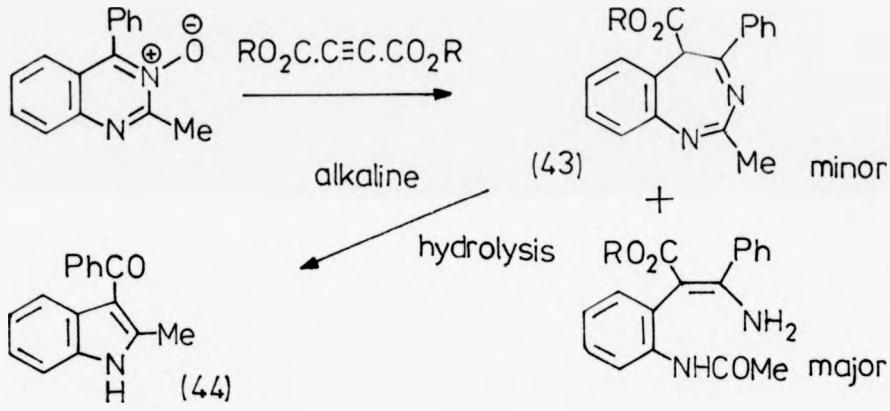
(39) (40)

A recent paper by Tsuchiya and co-workers[57] contains the synthesis of the first examples of N-unsubstituted 1,3-benzodiazepines. Treatment of the 3-benzyloxycarbonyl-3H-1,3-benzodiazepine (41) with trimethylsilyl iodide resulted in decarboxylation giving the N-unsubstituted-3H-1,3-benzodiazepine hydriodide (42) which on treatment with sodium bicarbonate produced the free base. Similar results were obtained from 1-benzyloxycarbonyl-1H-1,3-benzodiazepine and 1,3-thienodiazepines.

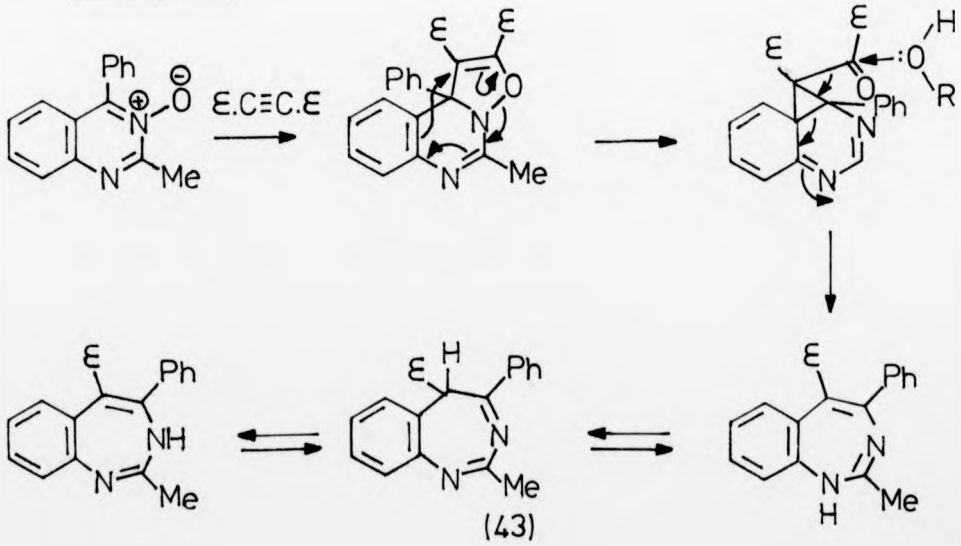


The free bases gradually decompose at room temperature but can be stabilized by N-acylation.

Stauss et al.[58], have isolated the substituted benzodiazepine (43) as a byproduct from the 1,3-dipolar cycloaddition of acetylene dicarboxylic esters to 2-methyl-4-phenyl-quinazoline-3-oxide. Ring contraction occurred on treatment with alkali forming the indole (44).

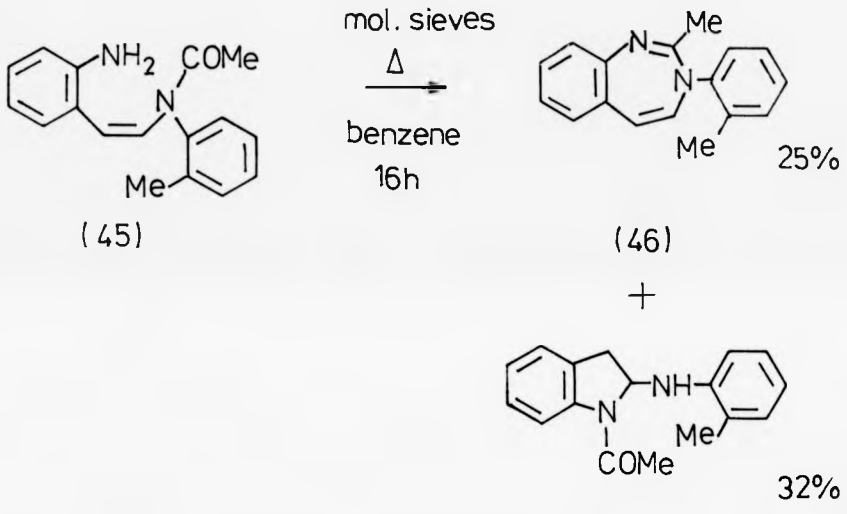


Mechanism

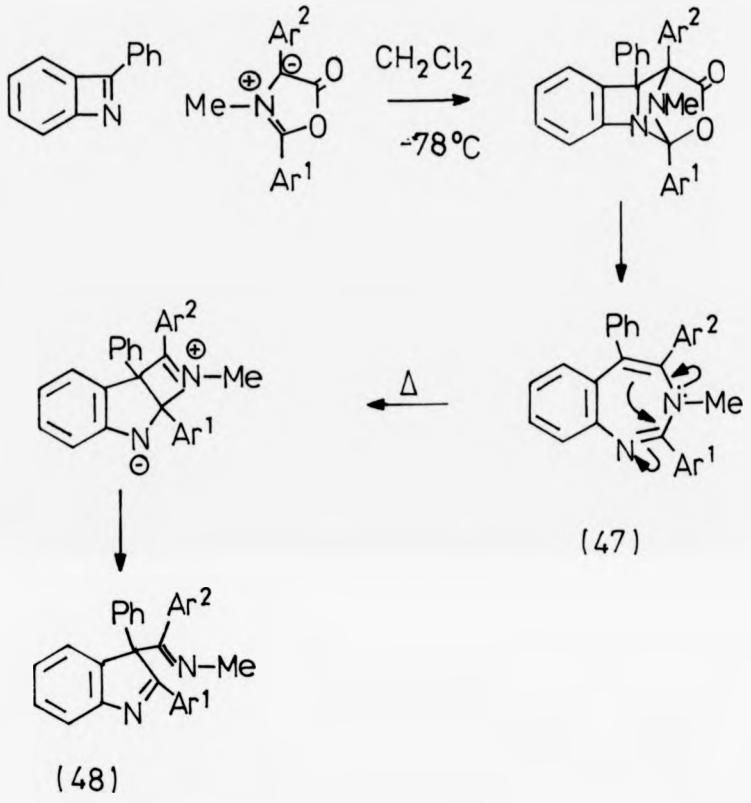


E=CO_2R

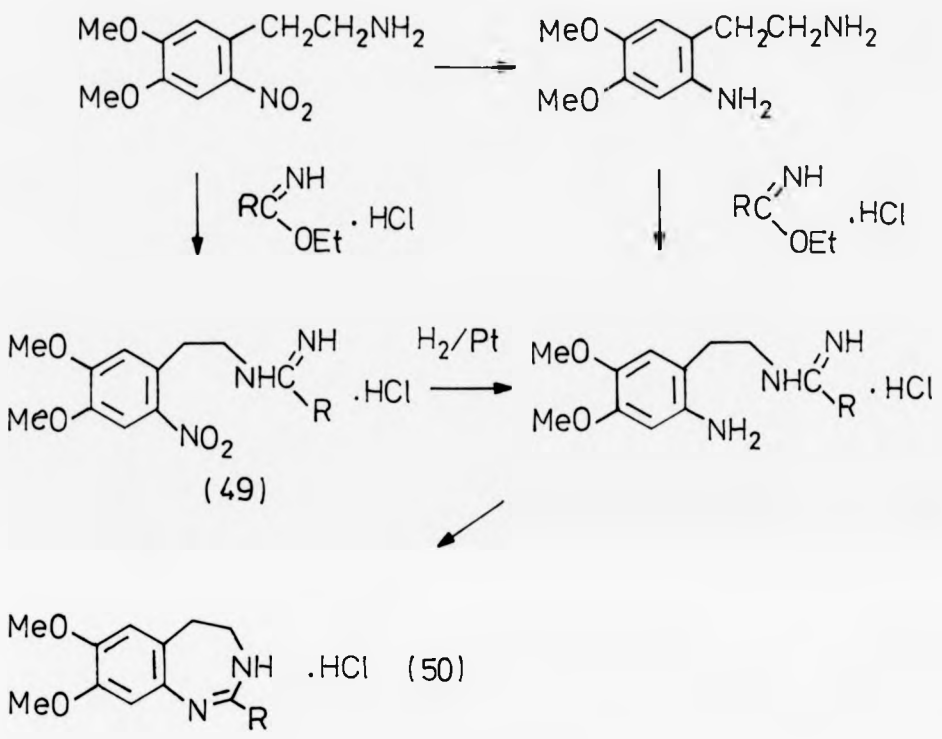
Molecular sieves have been successfully used by Chen and Forrest[59] to catalyze the cyclization of an aminostyrene derivative (45). The product (46) was unstable and rapidly hydrolysed to the starting material.



A fully unsaturated 1,3-benzodiazepine has been synthesized by Manley, Rees and Storr[60]. The flash vacuum pyrolysis of 4-phenylbenzotriazine gave 2-phenylbenzazete which was trapped at -78 °C and reacted with solid 3-methyl-2-p-tolyl-4-phenyl--1,3-oxazol-5-one in dichloromethane at -78 °C to give the benzodiazepine (47). Compound (47) undergoes thermal rearrangement at 76 °C in carbon tetrachloride to the 3H-indole (48).

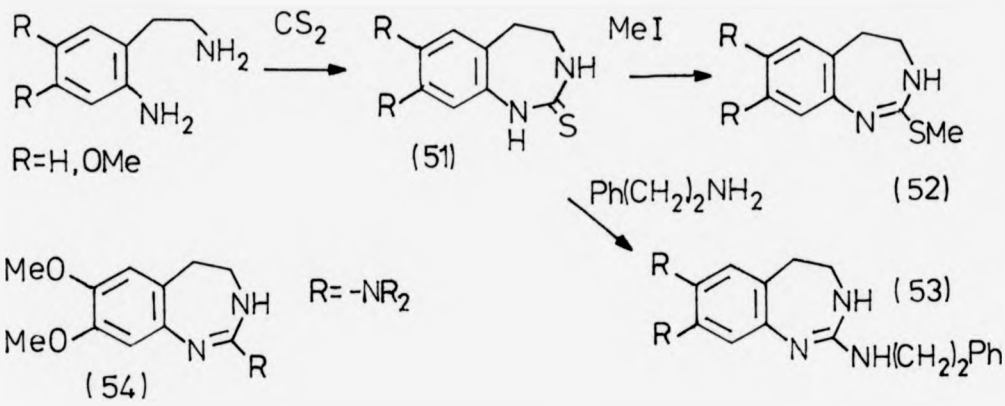


Various 1,3-benzodiazepines with lower levels of unsaturation have been synthesized by De Stevens et al.[61,62]. Intermediate amidines (49) were prepared from substituted phenylethylamines and imidate hydrochlorides and were cyclized to give 4,5-dihydro--1,3-benzodiazepines (50) in 34 - 86% yields. When R = aryl a better yield of benzodiazepine (50) is obtained if the intermediate amidine is reduced prior to cyclization. Yields are highest when the alkyl or aryl imidates bear electron withdrawing groups. The condensation reaction is inhibited by altering the nature of substitution on the basic amine function.

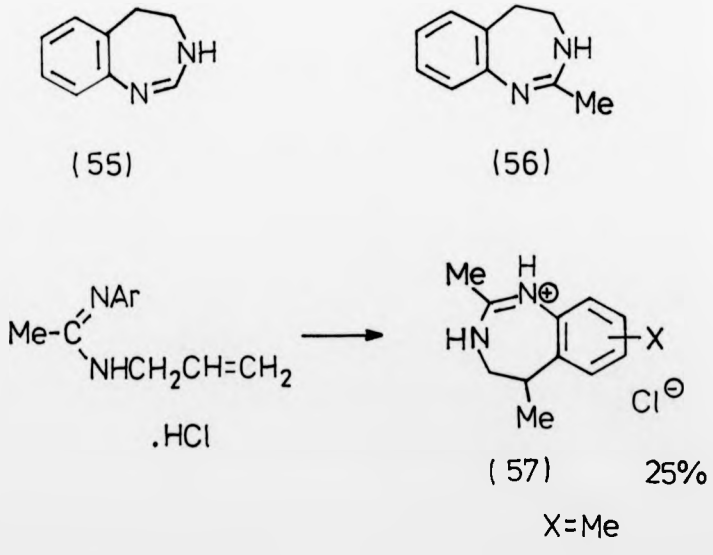


These 1,3-benzodiazepines have been found to have some therapeutic activity as analgesics and tranquillizers.

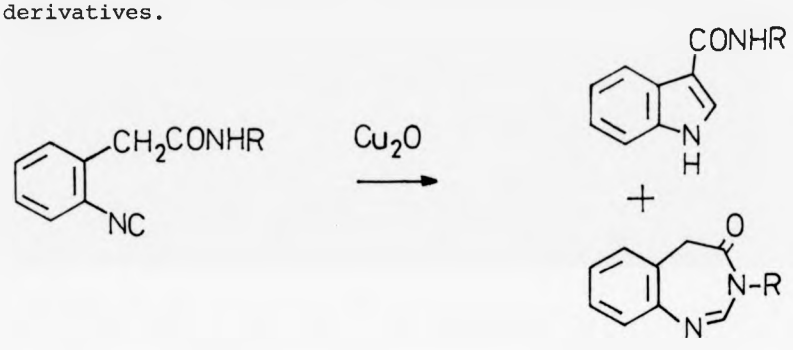
Similar routes to these compounds have been reported by Suh and Schnettler[63-68]. The treatment of phenylethylamines with carbon disulphide gave the 1,3-benzodiazepin-2-thiones (51) which were subsequently methylated to give the methylthio-benzodiazepines (52). Treatment of compound (51) with a variety of primary and secondary amines in a nucleophilic displacement reaction gave compounds (53) which were found to depress central nervous system activity. The products (54) formed when the amine was a piperazine had therapeutic activity as muscle relaxants and antihypertensives.



The unsubstituted 4,5-dihydro-3H-1,3-benzodiazepine (55) was synthesized by Benkovic and co-workers[70] from formamide acetate and β(o-aminophenyl)ethylamine. This route has previously been used by Desmarchalier[27] to prepare the 2-methyl derivative (56) from acetamidine hydrochloride and β(o-aminophenyl)ethylamine. When N-allyl-N'-aryl-acetamidine hydrochlorides are used[71] substituted 4,5-dihydro-1,3-benzodiazepines (57) are formed. The reaction is performed in polyphosphoric acid.

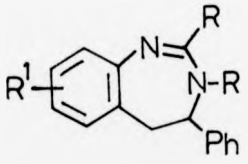


N-Substituted o-isocyanophenyl-acetamides have also been cyclized[72] using a copper II oxide catalyst producing N-substituted indole-3--carboxamides and N-substituted 4,5-dihydro-1,3-benzodiazepin-4-ones (58). It was observed that the less bulky the aryl substituent on the amide nitrogen, the greater the yield of 1,3-diazepine derivatives.



(58)

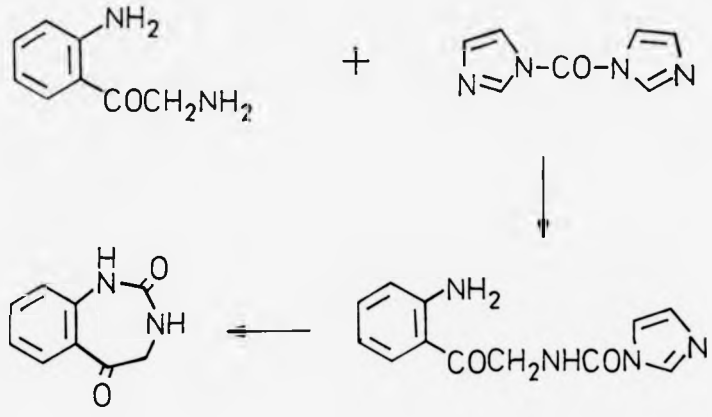
The synthesis of 4-phenyl-1,3-benzodiazepines (59) has been reported[73], and they have been found to possess some pharmaceutical activity.



R= H, alkyl
R^1= halogen, alkoxy, alkyl

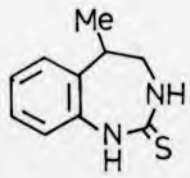
(59)

Taylor and Tully[74] have synthesized the 1,3-benzodiazepine--2,5-dione (61) from 1,1'-carbonyldi-imidazole and 2,2'-diamino-acetophenone. The intermediate imidazole N-carboxamide (60) cyclized in good yield to the diazepinedione (61).



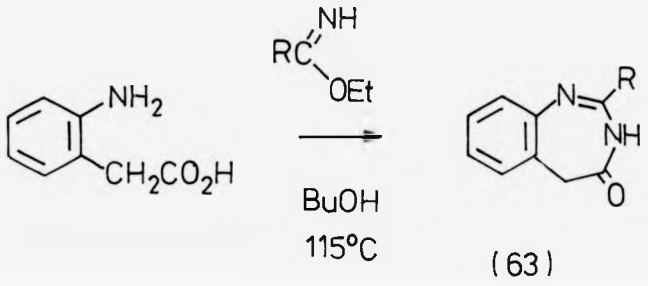
(61) (60)

Compound (61) reacted readily with hydroxylamine to form an oxime. Reduction with sodium borohydride produced secondary alcohols, and reaction with Grignard reagents gave carbinols. However the latter could not be dehydrated to introduce another double bond into the 4,5-position. Elslager[75] has used 4-methyl cinnoline in the preparation of diazepine (62). Different 1,3-benzodiazepines were formed including tricyclic and tetracyclic 1,3-diazepines.



(62)

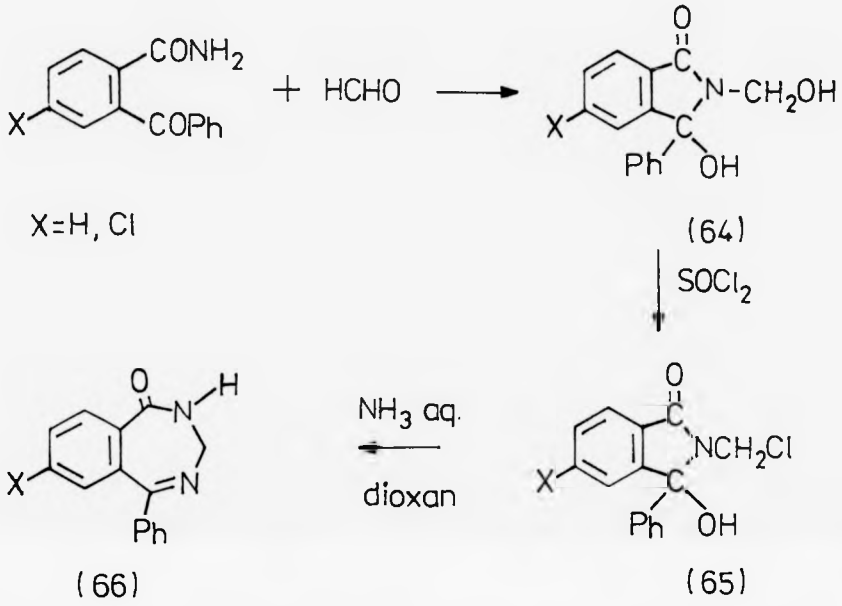
Another route to 1,3-benzodiazepin-4-ones (63) has been reported by Taub and Loeffler[76] via an imidate cyclization method. Compoundsof this type are psychosedatives, hypnotics and muscle relaxants.



(63)

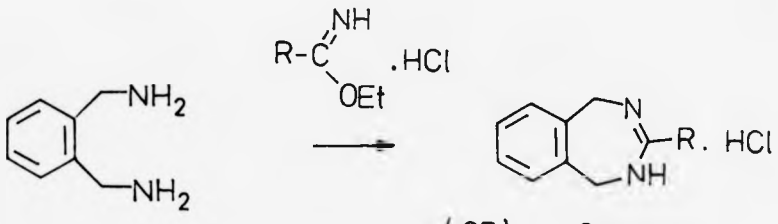
1.3 2,4-Benzodiazepines

There has been even less research directed towards the synthesis and chemistry of 2,4-benzodiazepines than to that of the 1,3-derivatives. A substantial amount of work however has been published by Golik and Taub[77-80]. The addition of formaldehyde to o-benzoylbenzamide under basic conditions gave the isoindole (64) which on treatment with thionyl chloride yields the chloromethyl derivative (65) in high yield. Reaction of this with aqueous ammonia in dioxan affords the 2,4-benzodiazepine (66) in 12% yield. Preliminary pharmacological assays revealed marked C.N.S. activity.



These pharmacological findings stimulated further work in this area. It was found that by converting the chloromethyl derivative (65) firstly to its azide and then to its amine, the yield of acid catalyzed cyclized material was increased to 60%. The structures of intermediates (64) and (65) were proved by ^{13}C n.m.r.. Preparation of the 7-chloro derivative (66) (X = Cl) was also accomplished and was found to have central nervous system activity similar to that of valium.

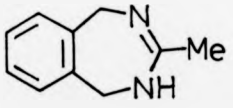
DeStevens[81] used a similar approach to that employed for his 1,3-benzodiazepine synthesis. Condensation of appropriate diamines with imidate hydrochlorides gave 4,5-dihydro-1H-2,4-benzodiazepines (67), the order of imidate reactivity resembling that of the isomeric 1,3- series (chloromethyl > alkyl > aryl).



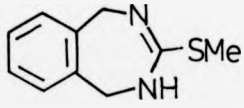
(67) 28-84%

R= alkyl or aryl

Similarly Desmarchalier[27] and Suh et al.[67] have extended their work on 1,3-benzodiazepines to cover the 2,4-isomers. Desmarchalier[27] synthesized the 2,4-benzodiazepine (68) from the condensation of o-xylenediamine with acetamidine hydrochloride. Suh and co-workers[67] substituted carbon disulphide for the amidine and obtained, after methylation, compound (69). Nucleophilic displacement of methyl sulphide by piperazine derivatives gave compounds with C.N.S. activity.

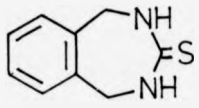


(68)



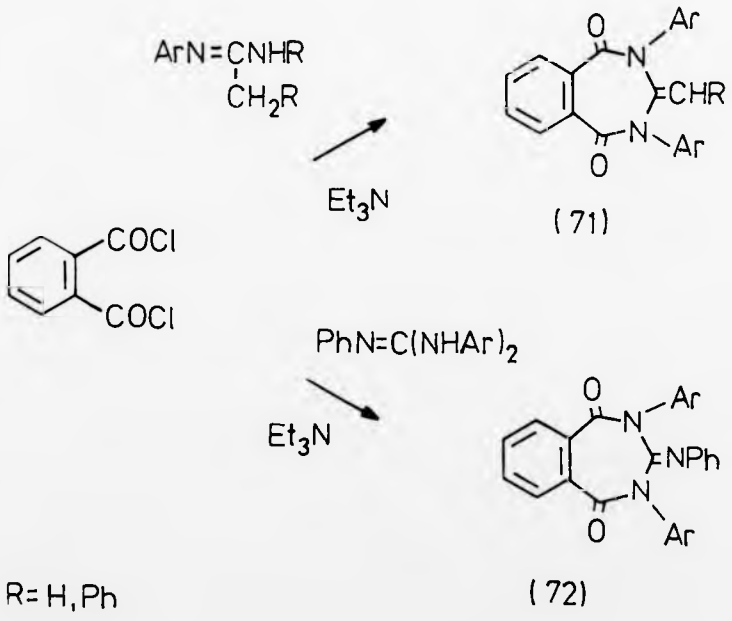
(69)

Elslager[82] prepared 1,2,4,5-tetrahydro-3H-2,4-benzodiazepine--3-thione (70) from phthalazine by a similar route to that used by Suh[67]. The 2,4-benzodiazepine was then converted into tricyclic and tetracyclic diazepines.



(70)

Heine et al.[83,84] have reported a general synthesis of 1H-2,4-benzodiazepine-1,5-diones. Substituted acetamidines were reacted with phthaloyl chloride in the presence of triethylamine. The respective 2,4-benzodiazepine-1,5-diones (71) and (72) were formed in high yields.



R= H, Ph

(71)

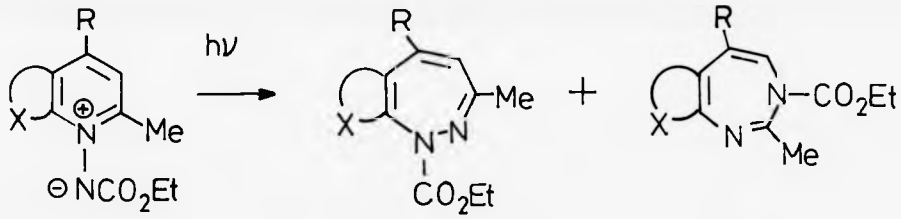
(72)

A variety of ring contraction and rearrangement reactions were observed.

1.4 Heterofused 1,3-diazepines

Much of the interest in heterofused 1,3-diazepines is of recent vintage.

Tsuchiya et al.[11-14,85,86] have extended their synthetic approach to include heterofused derivatives. Thus photolysis of pyridine-N-ethoxycarbonylimides condensed with thiophen, furan, pyrrole or pyridine rings, gave the corresponding novel 1H-1,2 and 3H-1,3-diazepines (73) and (74) respectively.

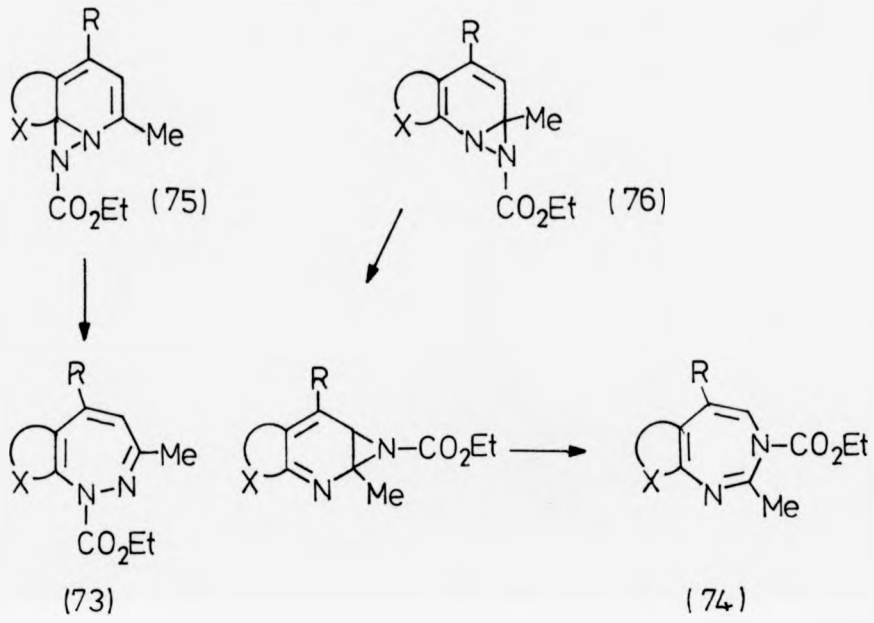


(73) (74)

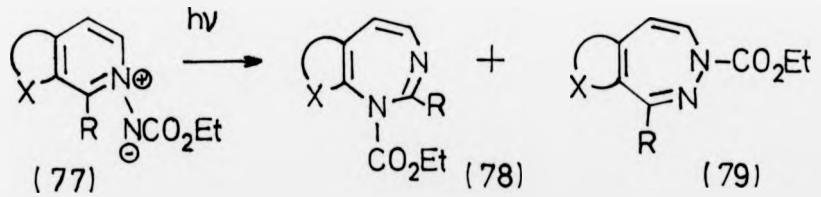
X = thiophen, furan, pyrrole, pyridine

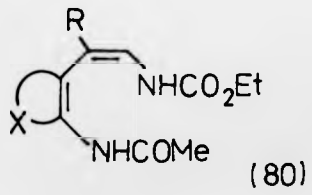
R=H, Me

In this ring expansion reaction the initial photoinduced rearrangement may take place on either side of the pyridine nitrogen giving two types of diaziridine intermediates (75) and (76).



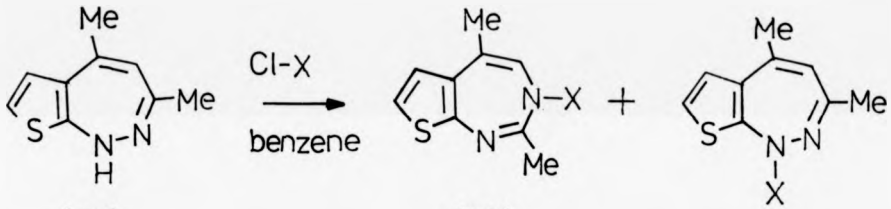
The former may give 1,2-diazepines directly, whereas the latter may rearrange further to an aziridine intermediate followed by ring expansion to the 1,3-diazepine. Ring expansion does not occur in the unsubstituted pyridine-N-imides. Substituent effects are discussed. Ring expansion of pyridine-N-acylimides (77) with a fused ring attached gives the corresponding fused 1H-1,3-diazepines and 3H-2,3-diazepines (78) and (79).





Treatment of compound (74) with hydrogen chloride in methanol gave the ring opened product (80).

Tsuchiya and his co-workers have recently reported[86] that treatment of N-unsubstituted-3-methyl-1H-1,2-thieno[2,3-c]diazepines (81) with ethyl chloroformate, acetyl chloride or benzoyl chloride, resulted in ring conversion to the corresponding 3-acyl-3H-1,3--thieno[2,3-d]diazepines (82).

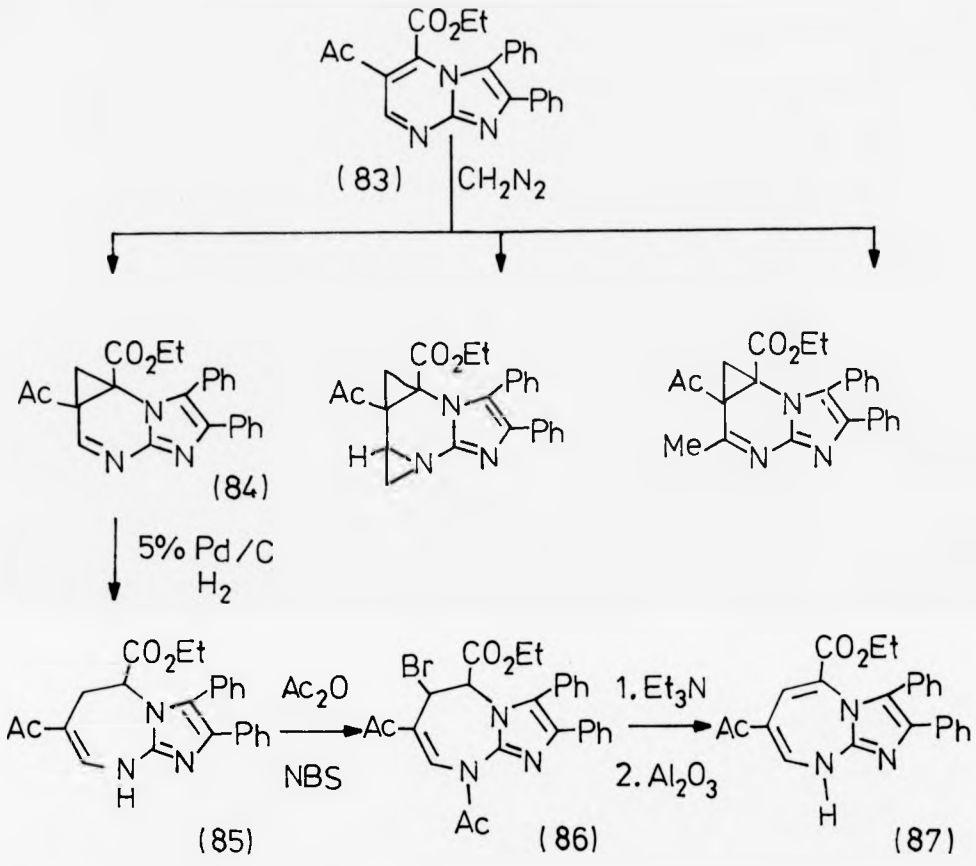


(81) (82)

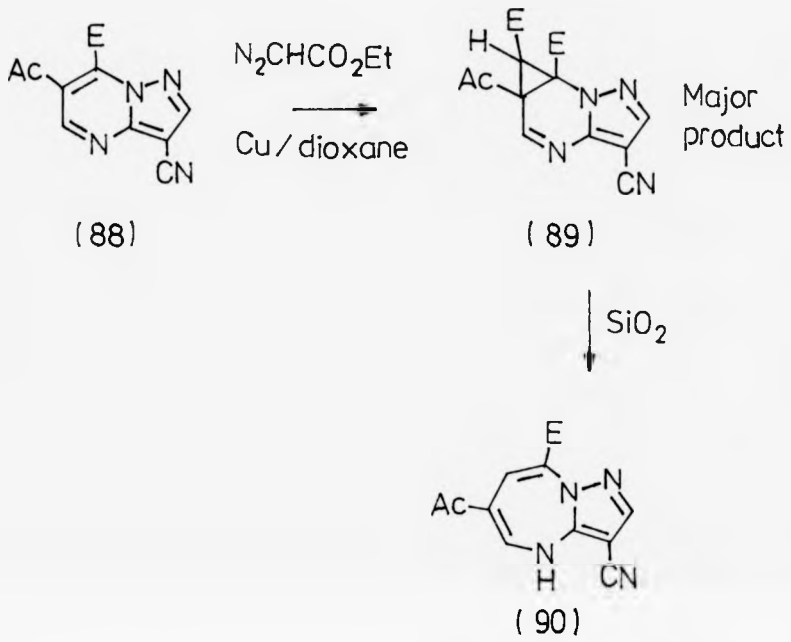
X	Yields	
CO_2Et	45%	—
CO_2CH_2Ph	40%	—
COMe	16%	20%
COPh	18%	12%

The acylation reactions were performed on a variety of similar compounds and the mechanisms were discussed.

The synthesis and reactions of ethyl 6-acetyl-2,3-diphenylimidazo-[1,2-a]pyrimidine-5-carboxylate (83) and related compounds have been studied by Kurihara and co-workers[87,88]. Reaction of compound (83) with diazomethane at room temperature gave a mixture of three products including the cyclopropa-imidazopyrimidinecarboxylate (84). Compound (84) was hydrogenated over 5% palladium charcoal giving ethyl 7-acetyl-5,6-dihydro-2,3-diphenyl-9H-imidazo[1,2-a]-[1,3]diazepine-5-carboxylate (85).

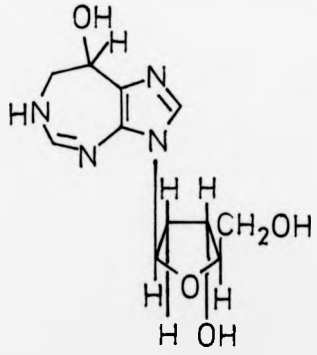


Subsequent treatment with acetic anhydride and pyridine produced the acetate which was brominated with N-bromosuccinimide. Dehydrobromination and hydrolysis gave the 9H-imidazo[1,2-a][1,3]-diazepine (87) in moderate yield. Similarly the cyclopropane derivative (89) was one of the products isolated from the reaction between the starting material (88) and ethyl diazoacetate. This was converted in high yield using silicic acid to the pyrazolo-1,3--diazepine (90).



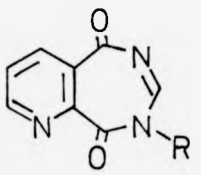
(88) (89) (90)

A potent deaminase inhibitor containing a hetero fused 1,3-diazepine ring has been reported[89]. The structure of the imidazo[4,5-d]diazepinol (91) was solved by single crystal x-ray diffraction.



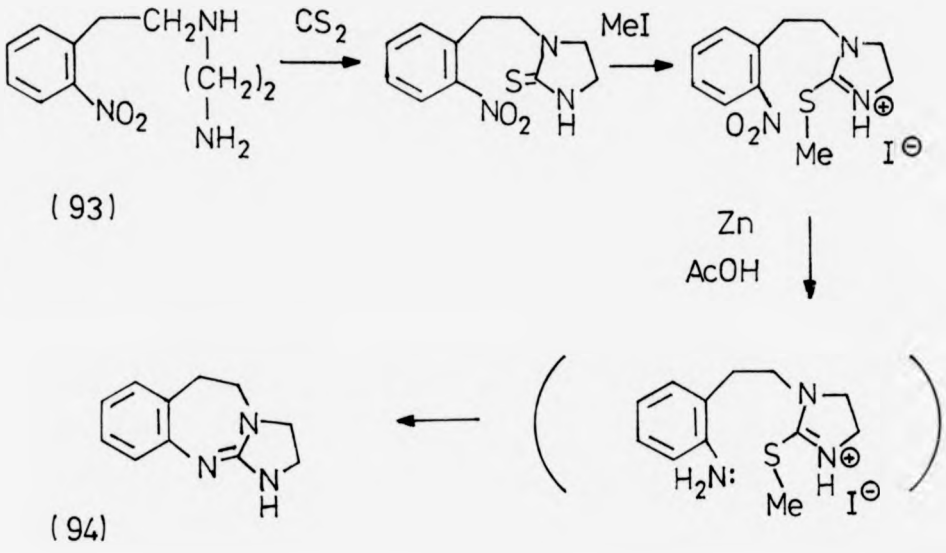
(91)

The compound 3H-4,9-dihydropyrido[2,3-e]-1,3-diazepine-4,9-dione (92) was prepared[90] by cyclizing a pyridine dicarboxamide with formic acid. The product was found to have weak hypotensive activity.



(92)

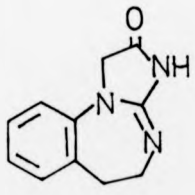
Jen et al.[91] have synthesized a series of tricyclic compounds, containing a guanidine moiety, to observe the influence of structural modification on the antihypertensive activity of 1,2,3,5-tetrahydroimidazo[2,1-b]quinazoline. Among the compounds prepared was the imidazo-benzo-1,3-diazepine (94). This synthesis involved treatment of the diamine (93) with carbon disulphide, followed by methylation, reduction, and subsequent intramolecular ring closure.



(93)

(94)

Imidazo-1,3- and-2,4-benzodiazepine derivatives (95) - (97) were prepared[92] as possible blood platelet aggregation inhibitors. Compound (95) was found to be an extremely potent inhibitor, but compounds (96) and (97) showed little or no activity.



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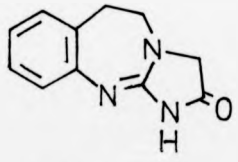

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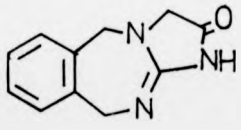
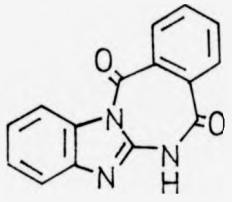


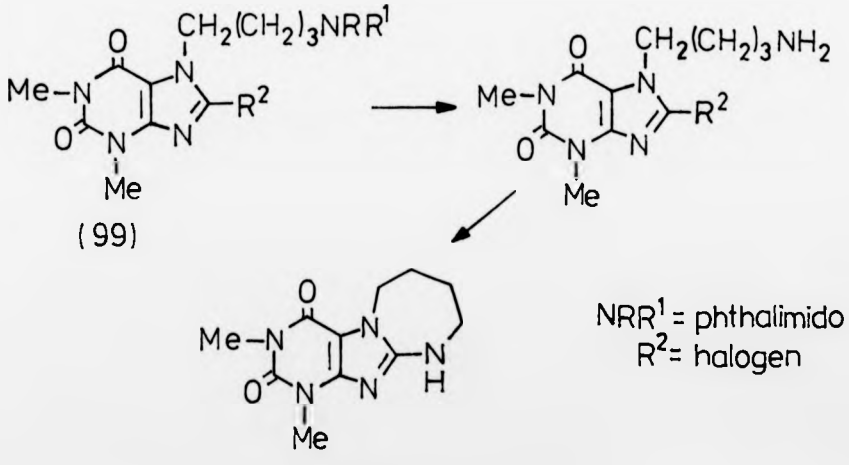
(97)

The heterofused 6H-benzimidazo[1,2-b][2,4]benzodiazepine--7,12-dione (98) was synthesized by Katritsky and Yates[93] by the condensation of 2-aminobenzimidazole and phthalic anhydride at 200 °C.



(98)

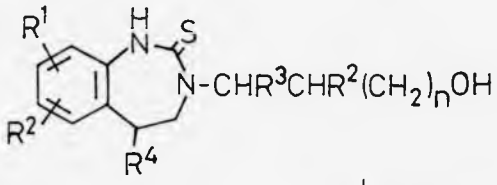
An unsaturated heterofused 1,3-diazepine was one of the products formed in a series of reactions designed[94] to prepare annelated xanthines. The xanthine (99) was converted in a two stage process into the diazepine (100). The first step involved hydrazinolysis and acid hydrolysis, the second step was a base induced cyclization.



(99)

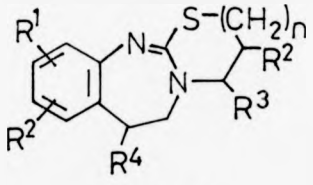
(100)

Finally, benzodiazepinethiones (101) were synthesized[95] for conversion to fused heterocycles (102) possessing antidepressant activity.



(101)

$MeSO_3H$ 100°C



(102)

n=0,1

$R=R^1=H, X, OR, OH, NO_2, NH_2$

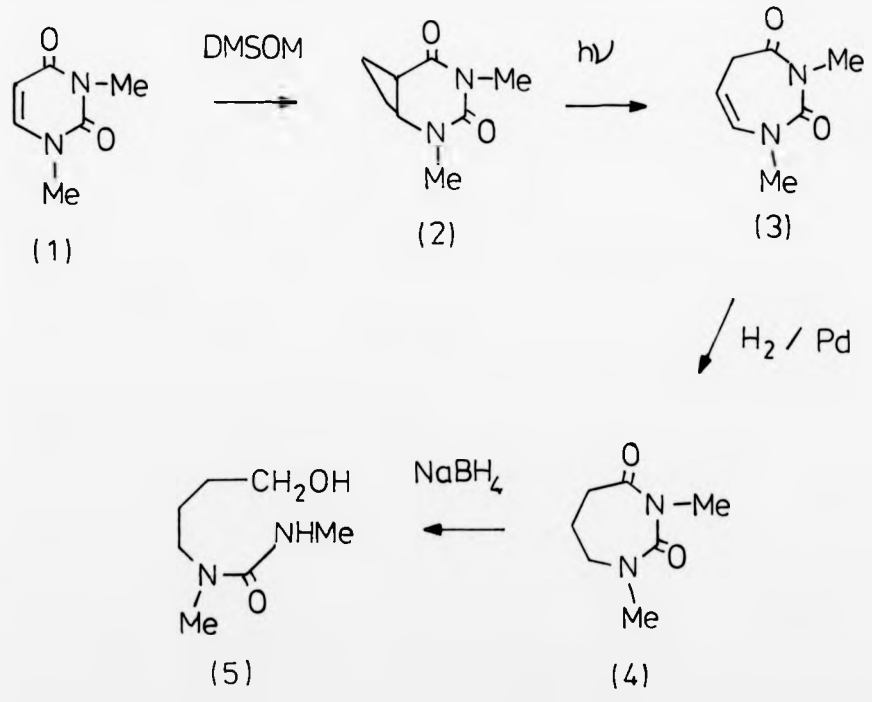
$R^2=R^3=R^4=H$, alkyl, Ph

CHAPTER TWO

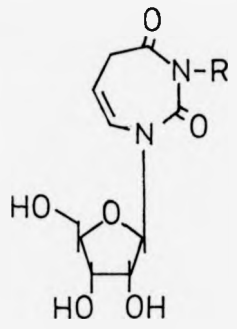
Cyclopropanation of pyrimidones

2.1 Introduction

The first approach to 1,3-diazepines investigated was based on that of Kunieda and Witkop[16]. This route involved the conversion of 1,3-dimethyluracil (1) into 2,4-dimethyl-2,4-diazabicyclo[4:1:0]-heptan-3,5-dione (2), by the addition of the ylide dimethylsulphoxonium methylide (DMSOM). On irradiation in water, ring expansion occurred to produce 1,3-dimethyl-1,5-dihydro-2H-1,3-diazepine-2,4-(3H)-dione (3) in 45% yield. The diazepine was catalytically reduced to the tetrahydro form (4) which with sodium borohydride gave compound (5).

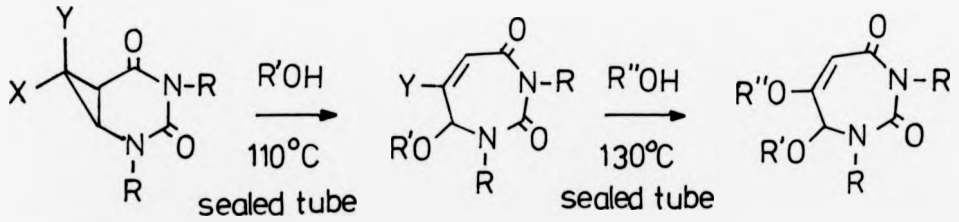


Nucleoside analogues (6) of the diazepine diones were also prepared by a similar sequence of reactions.



(6)

Pandit and his research group[17-20] have reported similar ring expansions of compound (7) derived from the addition of dihalocarbenes to 1,3-dibenzyluracil. Thus the diazabicyclo-heptadione (7) on treatment with alcohol in a sealed tube gave the 1,3-diazepine-3,5-dione (8).

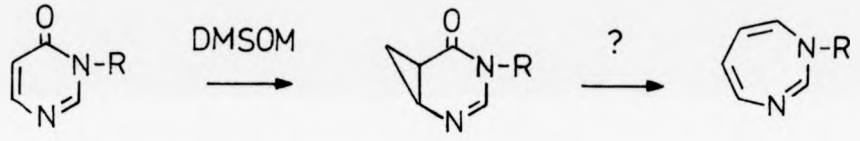


X=Y=Cl=Br

(7) (8) (9)

Further reaction of diazepine (8) with alcohol can occur if the temperature is raised and triethylamine included to trap the acid formed. Again similar experiments were conducted using nucleosides, forming novel 1,3-diazepine nucleosides. Reaction was shown to occur via a concerted disrotatory ring opening, followed by addition of alcohol.

There are no reports in the literature of attempts to produce a less substituted diazepine by modifying the bicyclic precursors. In this chapter are reported the use of 3-substituted-4-pyrimidones (14) instead of uracils in the reaction with DMSOM and other ylides. Methylide addition to the conjugated 5,6-double bond of these compounds should, in theory, give a diazepine into which a higher degree of unsaturation could be introduced.

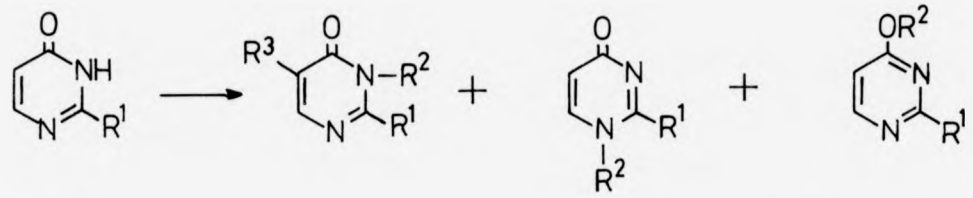


(14)

2.2 Alkylation of pyrimidones

The starting material, 4-(3H)-pyrimidone (10) which is commercially available, or may be synthesized[96-98] was used in the preparation of 3-substituted-4-pyrimidones, mainly by literature procedures although some are new compounds. The reagents and solvents used for these alkylations were varied and interesting differences in isomer distribution were observed (scheme 1)

Scheme 1



	R^1		R^1	R^2	R^3		R^1	R^2		R^1	R^2
10.	H	14a.	H	CH_3	H	15a.	H	CH_3	16a.	H	$CH_2C_6H_5$
11.	CH_3	b.	H	$CH_2C_6H_5$	H	b.	H	$CH_2C_6H_5$	b.	SCH_3	$CH_2C_6H_5$
12.	SCH_3	c.	H	CH_3	Br	c.	CH_3	CH_3			
13.	SH	d.	H	$CH_2C_6H_5$	Br	d.	SCH_3	$CH_2C_6H_5$			
		e.	CH_3	CH_3	H	e.	SCH_3	CH_3			
		f.	SCH_3	$CH_2C_6H_5$	H	f.	H	$CO_2C_2H_5$			
		g.	SCH_3	CH_3	H						

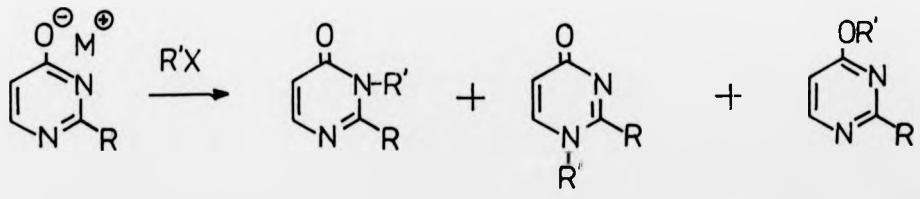
Starting material	Base	RX	Solvent	Total Yield (%)	%14	%15	%16	lit. Ref.
10	$NaOC_2H_5$	CH_3I	DMF*	50	50	-	-	88
10	$NaOC_2H_5$	CH_3I	CH_3OH	52	52	-	-	
10	$NaOC_2H_5$	CH_3I	THF$^{\Delta}$	11	-	11	-	88
10	$NaOC_2H_5$	$BrCH_2C_6H_5$	DMF	67	67	-	-	
10	$NaOC_2H_5$	$BrCH_2C_6H_5$	CH_3OH	73	35	37	1	90
11	KOH	CH_3I	CH_3OH	75	39	36	-	94
12	NaH	$BrCH_2C_6H_5$	DMF	79	25	26	28	96
12	$NaOC_2H_5$	$BrCH_2C_6H_5$	CH_3OH	20	9	-	11	
13	NaOH	$(CH_3)_2SO_4$	C_2H_5OH	90	35	55	-	89

(* dimethylformamide, $^{\Delta}$ tetrahydrofuran)

In alkylations using benzyl bromide in methanol as solvent, mixtures of 3-substituted and 1-substituted-4-pyrimidones (14b and 15b) were obtained together with trace quantities of O-alkylated material (16a). The two bromopyrimidones (14c and 14d) were prepared either by bromination of 4-(3H)-pyrimidone (10) and subsequent alkylation, or by direct bromination of the alkylated material. An alternative starting material was 2-thiouracil (13) which was either monomethylated using sodium hydroxide and methyl iodide to give 2-methylthiouracil (12) or dimethylated in both the 1- and 2- (15e) and 2- and 3- (14g) positions using sodium hydroxide and dimethyl sulphate. Alkylation of 2-methylthiouracil (12) in DMF gave three isomers (14f, 15d and 16b) whereas in methanol only isomers (14f) and (16b) were formed. Alkylation of 2-methyl-4-pyrimidone (11) gave both N-3 (14e) and N-1 (15c) isomers.

The site of alkylation of the sodium salts of 4-pyrimidones is determined by a combination of steric effects, solvent effects, charge distribution within the anion and polarizability. Jonak et al.[99] have discussed these effects in detail and the alkylation results in this chapter are comparable. A brief discussion of the factors affecting alkylation site is relevant.

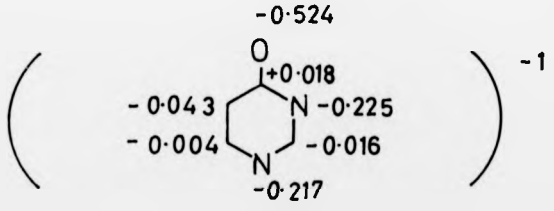
The three isomers obtained in alkylations of the sodium salts of pyrimidones are shown below.



Jonak et al.[99] have established the rate of alkylation (using alkyl iodides in methanol) as being second order. Consistent with their measurements is the fact that rates of alkylation decrease with increase in size of the alkyl halide or group R. In DMF increase in bulk of both alkylating reagent and substituent at C2, favours O-alkylation at the expense of N-3, perhaps because the rate of N-alkylation is decreased due to steric effects but the rate of O-alkylation remains constant.

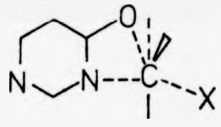
The site of alkylation is also dependant on the ionising power of the reaction media. As the ionising power of the solvent decreased (DMF > methanol > THF), N-1 alkylation increased. Thus it was found that 3-methyl-4-pyrimidone was formed in DMF and methanol whilst 1-methyl-4-pyrimidone was formed in THF. Also as the dielectric constant of the solvent decreased (methanol > THF) the sodium salts became more insoluble and the reaction became slower. Thus methylation of 4-pyrimidone in methanol was complete within 1h compared with three days for the same reaction in THF.

The charge distribution[99] on the anion of 4-(3H)-pyrimidone (shown below) indicates that 75% of the negative charge on the anion is distributed between N-3 and oxygen.



Although the oxygen atom has the greater amount of negative charge, factors other than steric hindrance must come into play to lead to the predominance of N-alkylation.

Nitrogen is more polarizable than oxygen, and the alkylating agent having little or no charge prefers to form covalent bonds with the more polarizable atom of the ambident system; therefore N-alkylation predominates. A transition state can be drawn as shown below:

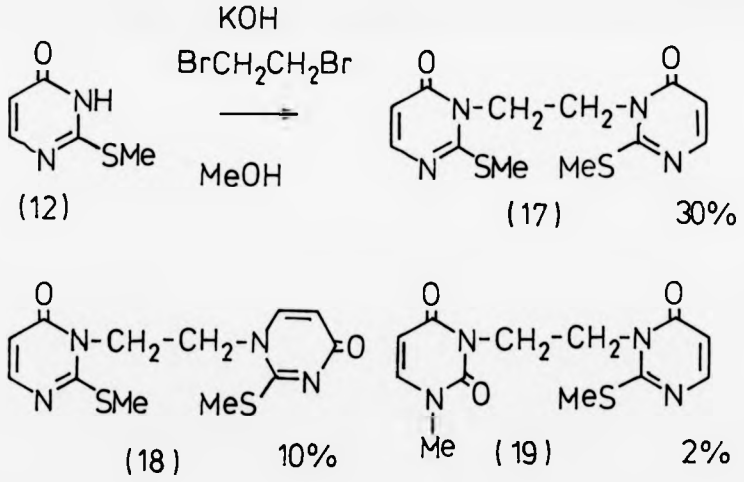


As the polarizability of N-3 is greater than O- then N-3 alkylation occurs.

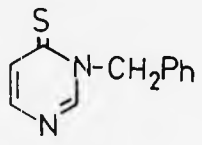
In DMF the anion is poorly solvated, therefore it is reasonable to assume that since 75% of the charge is distributed between O- and N-3 that interaction with the alkylating agent would be there and not at N-1. But if N-3 and O- are preferentially blocked by hydrogen bonded solvents then the N-1 position would become more important. It has been observed for some compounds that in methanol, hydrogen bonding increases, N-3 alkylation decreases and N-1 alkylation increases. The many factors controlling the site of alkylation indicate why the results obtained do not fall into any clear pattern.

On attempting to alkylate 2-methylthiouracil with dibromoethane only bispyrimidonylethanes were obtained. The symmetry of the major

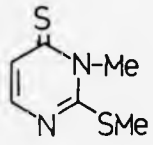
product (17) was reflected in the proton n.m.r. spectrum, and the relative shifts of the two doublets in the aromatic region clearly established it as the 3-3' isomer. By similar reasoning from the n.m.r. spectrum the second component, having two sets of doublet pairs was the 1,3' isomer (18). The third component, analysed for $C_{12}H_{14}N_4O_3S$ was shown, by n.m.r. to contain one N-methyl group and one S-methyl group. The most obvious structure is that of the uracil (19) presumably formed by an S to N thermal rearrangement with subsequent oxidation of thione to carbonyl.



Several references[101,109-111] were noted in the literature to alkyl-4-pyrimidinethiones, therefore two of the N-3 alkylated pyrimidones (14b) and (14f) were converted using Lawessons reagent[108] into their respective thiones (20) and (21) in the hope that the sulphur atom could possibly provide a better leaving group at a later stage in the synthesis.



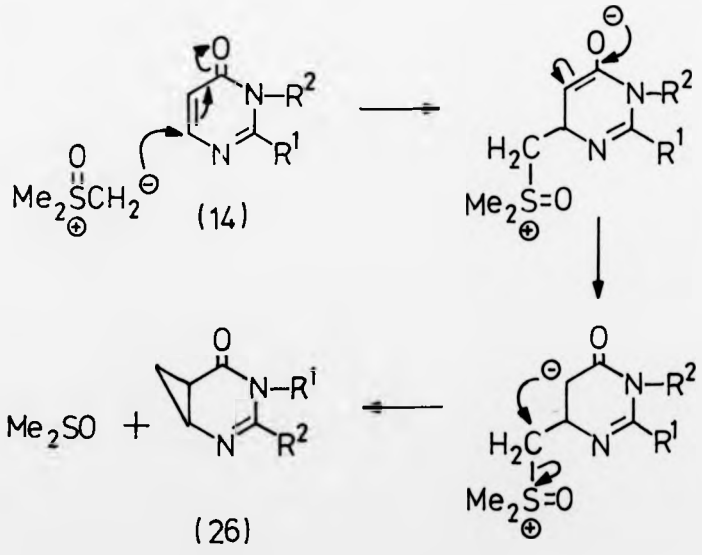
(20)



(21)

2.3 Cyclopropanation reactions

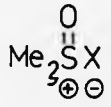
Formation of the 2,4-diazabicycloheptanones (26) was effected by the Michael addition of the anionic carbon atom of DMSOM to the conjugated 5,6-double bond of compound (14) followed by loss of dimethylsulphoxide.



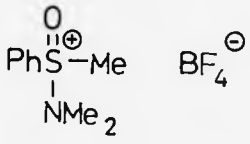
(14)

(26)

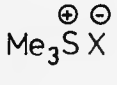
Proton abstraction from the salts (22)-(23) gave the sulphur ylides which were the source of the anionic carbon atoms in the previous reaction.



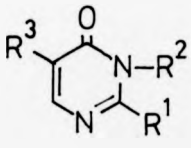
(22) X=I
(23) X=Cl



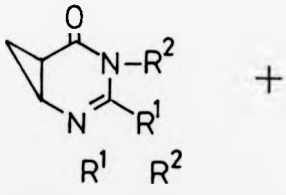
(24)



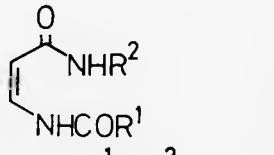
(25) X=I



(14) a-g



	R^1	R^2
(26) a	H	CH_3
b	H	$CH_2C_6H_5$
c	SCH_3	CH_3

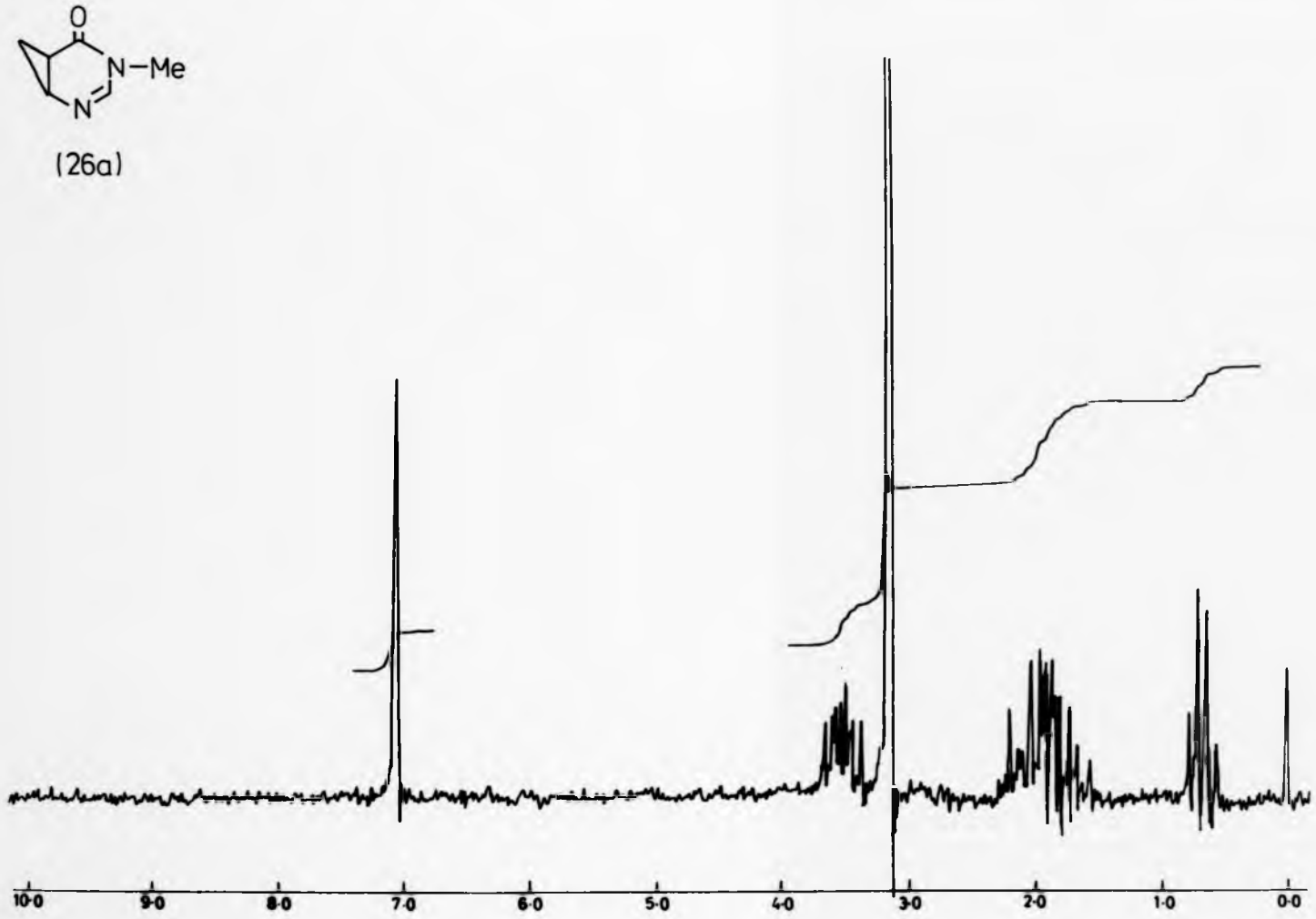


	R^1	R^2
(27) a	H	CH_3
b	H	$CH_2C_6H_5$

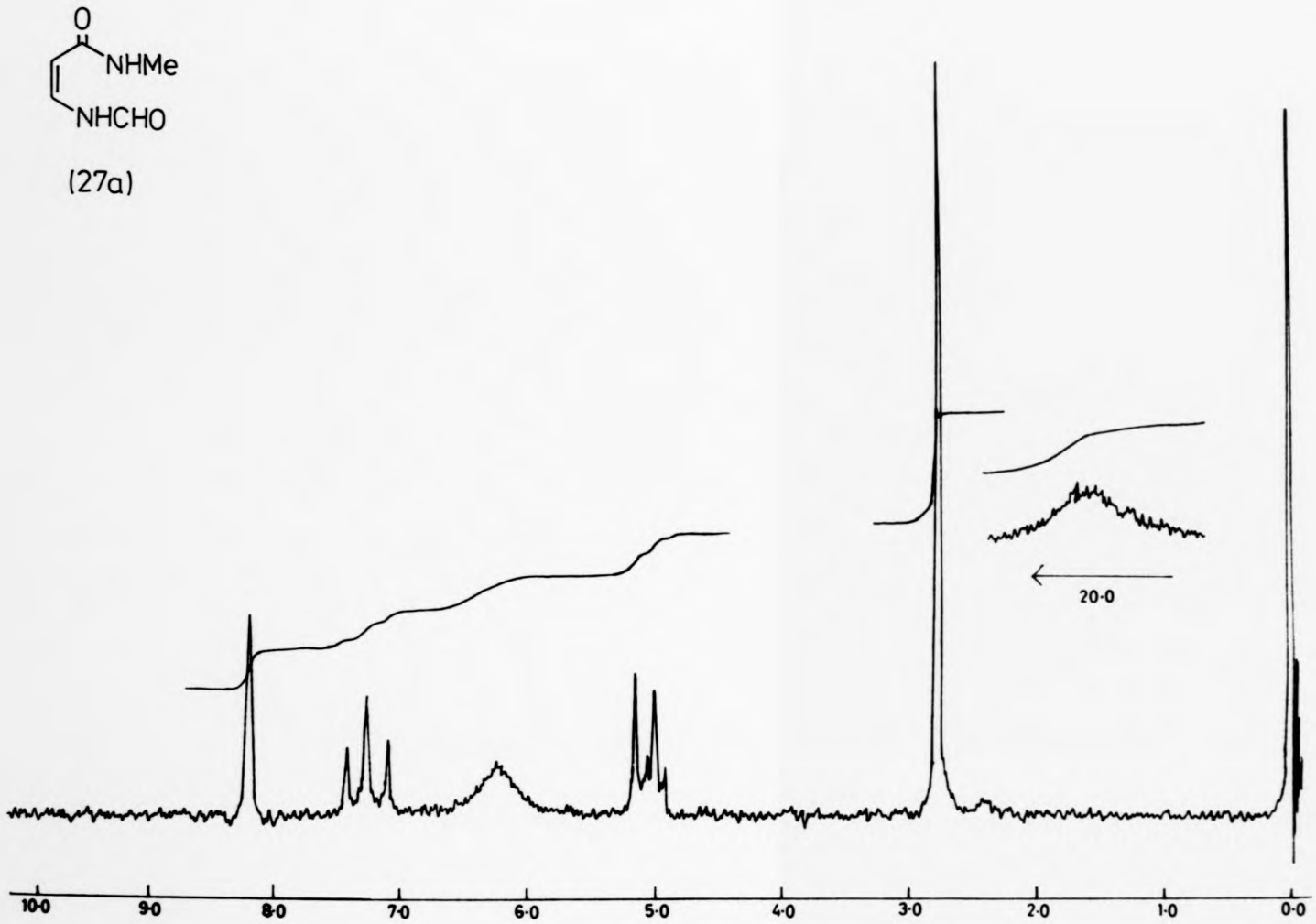
Preliminary experiments using 3-methyl-4-pyrimidone (14a) and DMSOM from the iodide salt (22)[112] in dimethyl sulphoxide as solvent gave a crude reaction mixture containing two new compounds and some unreacted starting material. The ^1H n.m.r. spectrum of this crude mixture indicated that a cyclopropane ring was present but attempts to separate the mixture by p.l.c. on silica[116] gave no product containing a cyclopropane. Chromatography on Florisil allowed isolation of the two products.

The first product off the column (in 8% yield) was shown by elemental analysis to have the formula $C_6H_8N_2O$ corresponding to the addition of a methylene group to pyrimidone (14a). A broad carbonyl absorption at 1650-1700 cm^{-1} and a ^1H n.m.r. spectrum consisting of complex absorptions due to four aliphatic protons in the region δ0.7 - 3.5 p.p.m. indicated the formation of the cyclopropapyrimidone (26a). The only other signals were at δ3.2 (3H, s, N-Me) and at δ7.05 (1H, s, H_2).

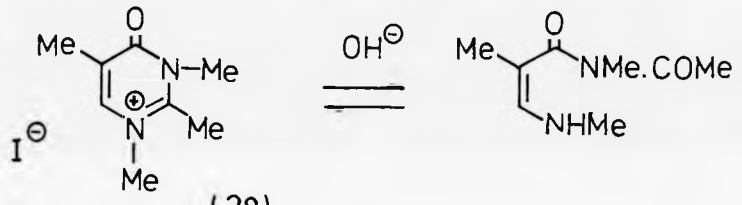
The second product eluted from the column in 32% yield showed i.r. absorptions at 3300, 1700, 1650 and 1626 cm^{-1}, and ^1H n.m.r. signals at δ2.8 (3H, s), 5.0 (1H, d, J = 8Hz), 6.0 (1H, br.s, exch. D_2O, NH), 7.3 (1H, dd, J = 8 and 8Hz), 8.3 (1H, s) and 11.0 (1H, br.s, exch. D_2O, NH). Elemental analysis gave the molecular formula as $C_5H_8N_2O_2$ indicating the addition of the elements of water to compound (14a), and this product of apparent hydrolytic ring opening is the 3-(N-formylamino)-cis-acrylamide (27a).



(26a)

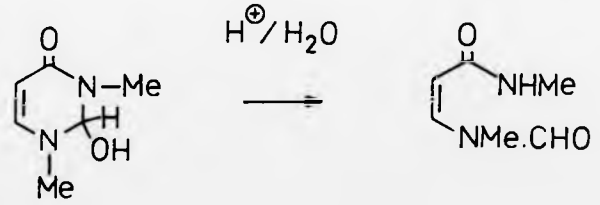

O
NHMe
NHCHO
(27a)
20·0
10·0
9·0
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0·0

The n.m.r. signals due to this compound (or some species with a closely similar spectrum) are clearly present in the crude reaction mixture where strictly anhydrous conditions have been maintained. A similar opening of the pyrimidone ring has been postulated in the literature by Hirschfeld[117] as a possible product in solution of the pyrimidinium salt (28).



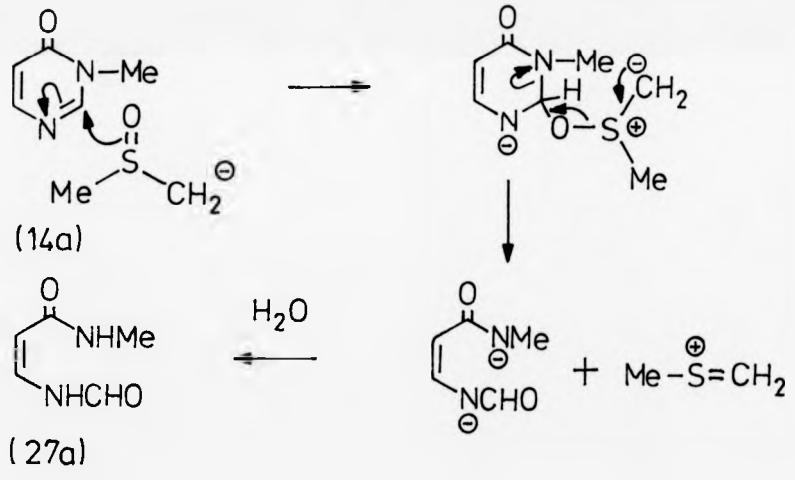
(28)

Tee and Paventi[118] also put forward u.v. evidence for the irreversible ring opening of the pseudo base (29) in alkaline media.

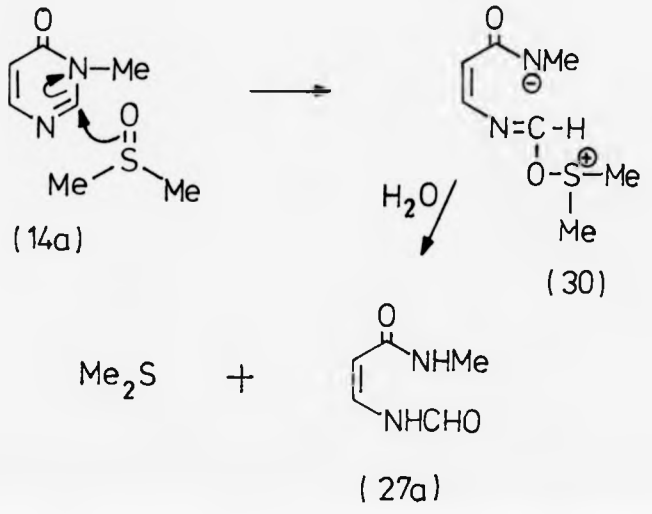


(29)

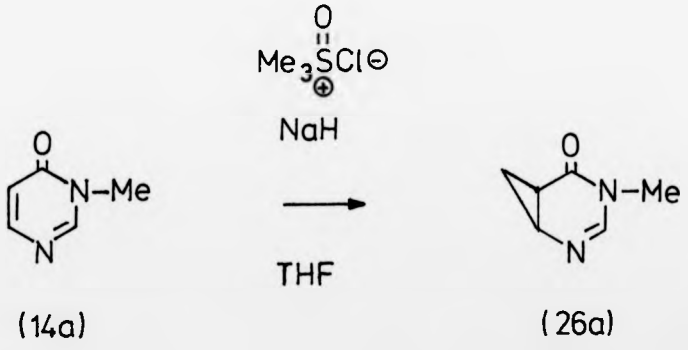
However in neither of these references is there a report of the isolation of these β-formamido-acrylamide derivatives. One possible explanation for the reaction is that the anion of dimethylsulphoxide was formed from the solvent and sodium hydride and reacted with the starting pyrimidone (14a) producing a charged intermediate which on rearrangement gave the aldehyde as shown in the attached scheme. After aqueous workup the cis acrylamide is formed.



Alternatively attack by the oxygen atom of a dimethyl sulphoxide molecule, opening the ring, could give an intermediate of structure (30) whose n.m.r. spectrum would only be slightly different from that of the product. Intermediate (30) could then be assumed to undergo attack by water (for example during column chromatography) to give the cis acrylamide.



It has been reported[113] that the use of THF as solvent and of trimethylsulphoxonium chloride (23) as the ylide precursor can give improved yields of 1,4 nucleophilic addition product. In the case of compound (14a) these conditions gave no improvement in the yield of compound (26a) but, significantly, no trace of the acrylamide (27a) was obtained.



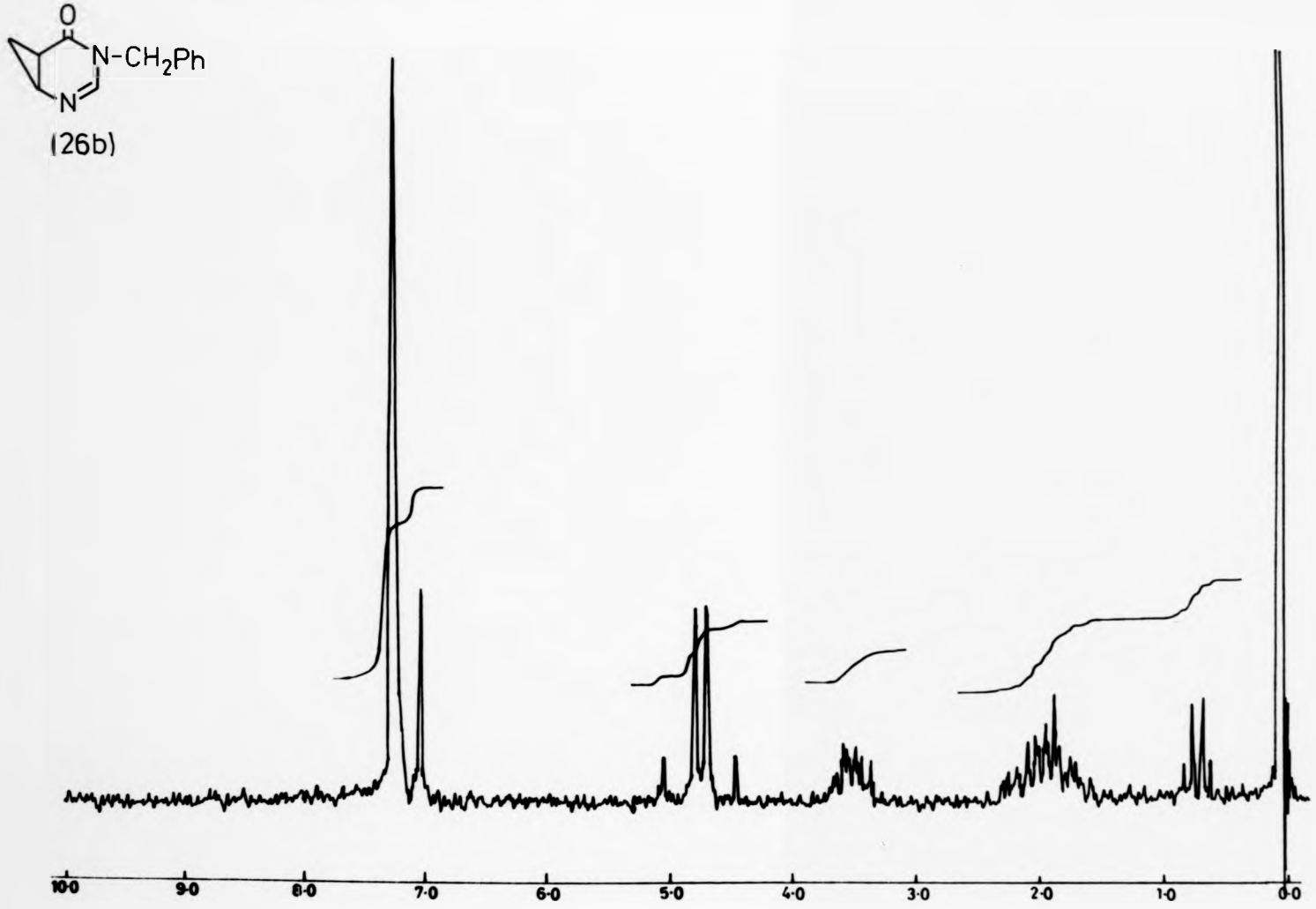
This rules out the possibility that the methylide ion causes ring opening and favours the two suggested mechanisms.

Further experiments were conducted with 3-benzyl-4-pyrimidone (14b) a potentially more useful starting material due to its readily removable alkyl group. In early experiments when DMSOM derived from the iodide (22) was used in dimethyl sulphoxide as solvent yields of compound (27b) and (26b) were 24% and 7% respectively. However in subsequent experiments using the iodide (22) the yield of the cyclopropapyrimidone (26b) was increased to 20% and by using the chloride (23) in THF a yield of 24% was obtained, but the reaction still remained inconsistent.

The spectral data of bicylic and ring opened benzyl substituted products resembled those of compounds (26a) and (27a) except that there was clear evidence of restricted rotation in compound (26b) due to the bulk of the N-alkyl group. The signal at δ4.7 p.p.m. due to the benzylic methylene protons appeared as a pair of doublets (J = 14Hz).

The ylides from salts (24)-(25), reportedly superior in some reactions, failed to react with pyrimidone (14b). The bromo-pyrimidones (14c) and (14d) both failed to react with DMSOM as did the bis-pyrimidonylethane (17) and the 1-substituted-4-pyrimidones (15a) and (15b).

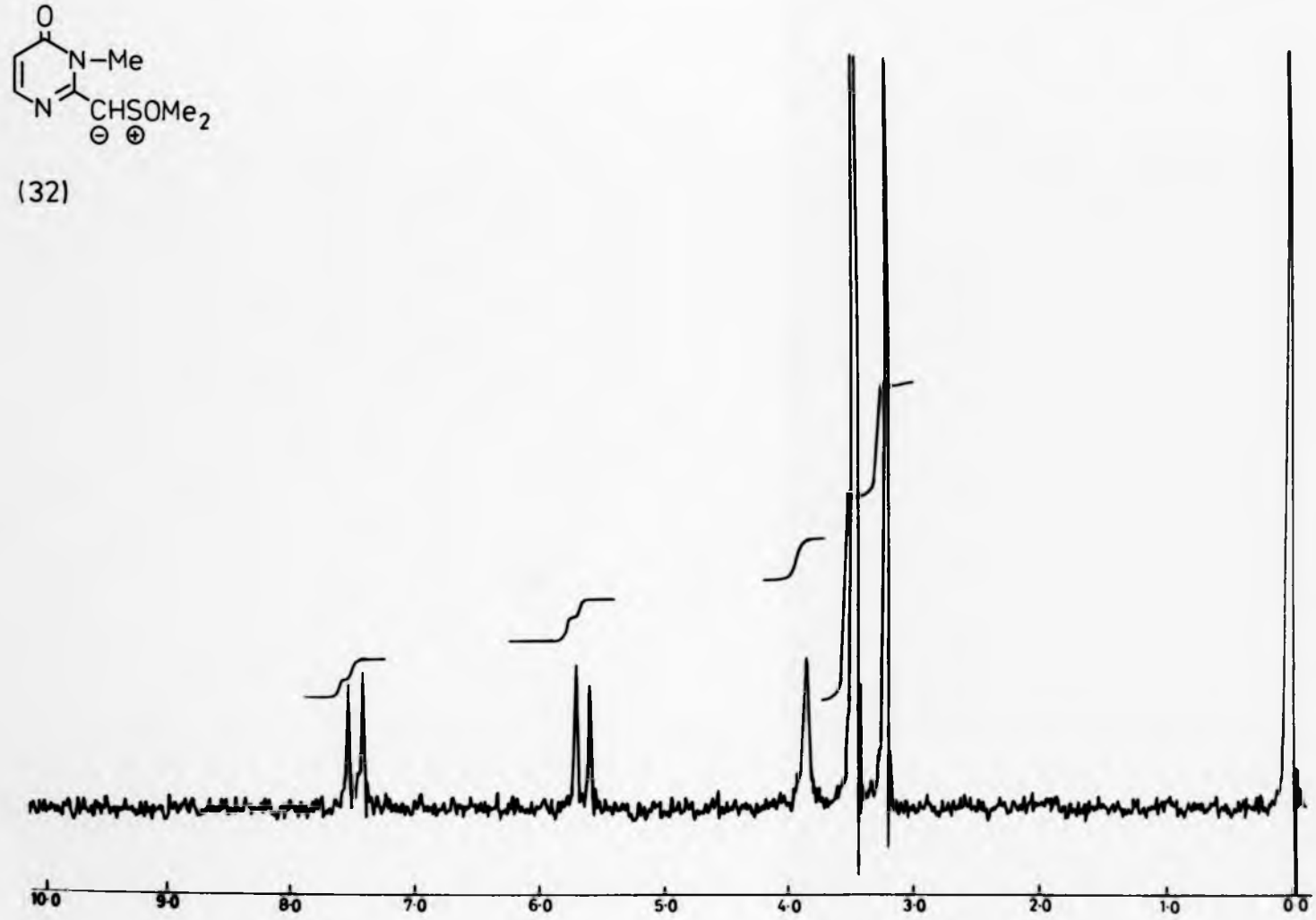
It was noted that Kunieda and Witkop[16] did not observe opening of the ring because of the carbonyl group at C2 in the ring, and, as opening of the ring appears to compete with, and in some cases dominate cyclopropanation, three 2,3-disubstituted pyrimidones (14e - g) were prepared in an attempt to inhibit ring opening.



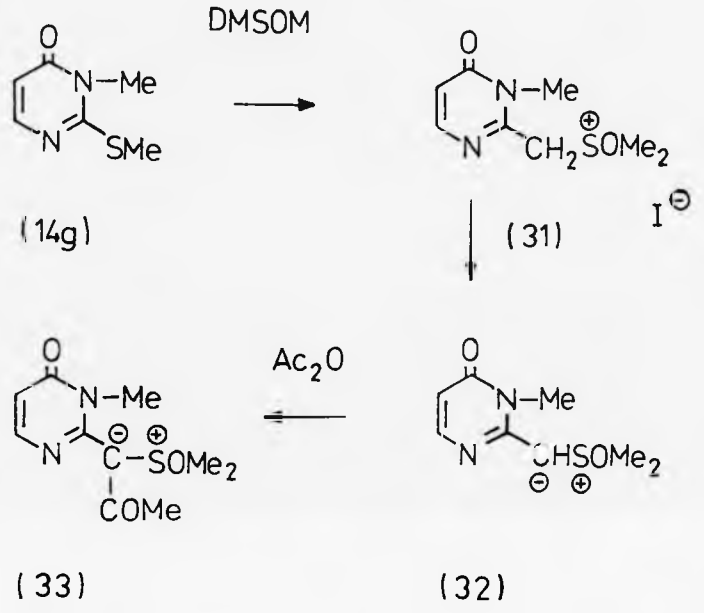
(26b)

There is no figure available for the pKa of the 2-methyl group in compound (14e). The failure to isolate any product, (except a trace of an acrylamide) from the reaction between (14e) and DMSOM in dimethyl sulphoxide may be due to equilibration of ylide with pyrimidonyl methyl anion and subsequent side reactions.

However it was established experimentally that a thiomethyl group at carbon 2 prevented opening of the pyrimidone ring. A thiomethyl group was used because of its ease of removal at a later stage with Raney nickel. The reaction between compound (14g) and DMSOM in dimethyl sulphoxide solvent gave on work up a small yield of cyclopropapyrimidone (26c). No further compounds were eluted from the Florisil column but careful examination of the aqueous washings showed the presence of at least one other major product which was isolated with difficulty as an iodide analysing for $C_8H_{13}N_2IOS$. Attempts to exchange iodide for perchlorate using an Amberlite ion exchange column loaded with ClO_4^- gave instead a neutral compound of formula $C_8H_{12}N_2OS$ which was water soluble and had i.r. absorption at 1670 cm^{-1}. The ^1H n.m.r. spectrum showed peaks at δ3.2 (3H, s, N-Me), 3.5 (6H, s, $^+SMe_2$), 3.9 (1H, s), 5.6 (1H, d, J = 6Hz) and 7.4 (1H, d, J = 6Hz). The ^{13}C n.m.r. spectrum was notable for a signal at δ62.2 p.p.m. (CH) which was assigned to the CH in the ylide (32). The iodide salt was therefore formulated as (31).



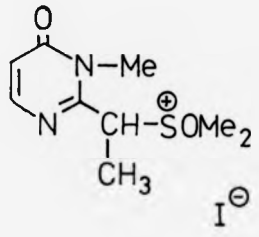
(32)



The ylide (32) was obviously formed by nucleophilic displacement of methyl sulphide anion from C2 of the starting material (14g). It was possible to raise the yield of compound (32) to 50% by adjusting the reaction conditions.

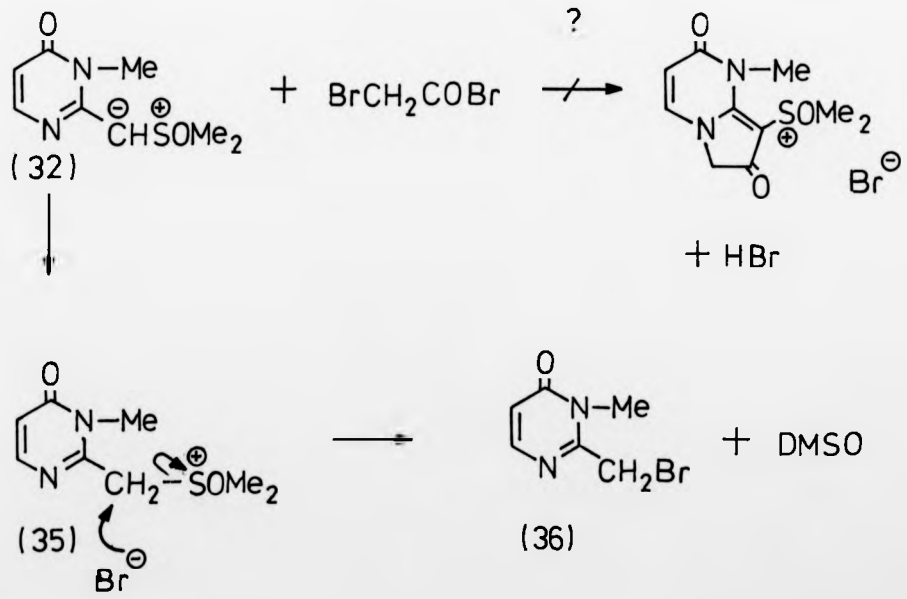
Similar replacements by DMSOM have been reported in the literature for 2-alkoxy-4-pyrimidones[69] and more recently for 2- and 4-chloropyrimidines[119].

The properties of the ylide (32) were briefly examined. It was acylated in excellent yield forming the acyl derivative (33). However in an attempt to prepare the iodide salt (34), exposure of ylide (32) to methyl iodide using DMF as solvent in a sealed tube at 100 °C resulted in an explosive reaction; no material was recovered.

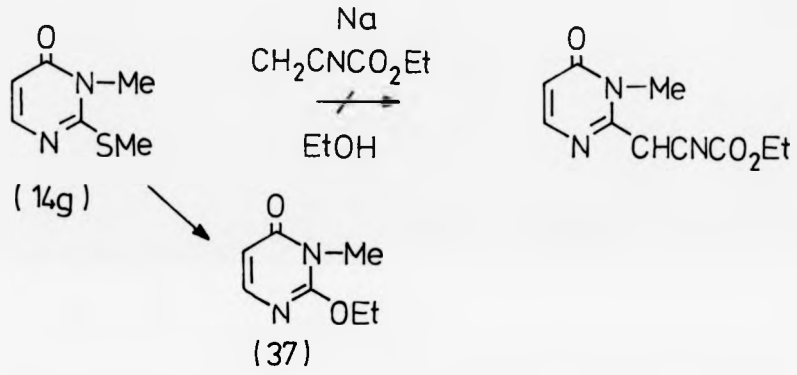


(34)

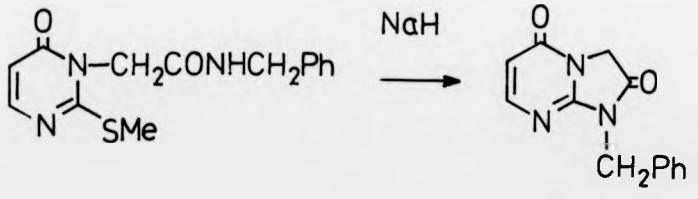
Noting the dipolar nature of the pyrimidone sulphoxonium ylide (32) the possibility of synthesizing novel heterocyclic systems was briefly investigated. On treating the ylide (32) with bromoacetyl bromide the only product isolated was 2-bromomethyl-3-methyl--4-pyrimidone (36). Presumably this was formed from the hydrobromide salt of the ylide (35). The bromide attacks the methylene group resulting in the expulsion of dimethylsulphoxide.



Reaction of 3-methyl-2-thiomethyl-4-pyrimidone (14g) with the sodium salt of ethyl cyanoacetate gave not the expected cyanoacetate derivative, but 2-ethoxy-3-methyl-4-pyrimidone (37). The mechanism involved a nucleophilic attack by ethoxide ion followed by displacement of methyl sulphide anion.

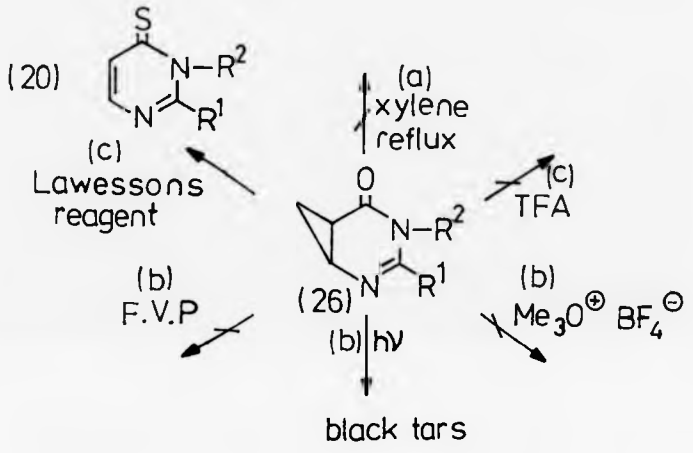


Research in this field is currently being studied by Abarca and Soriano[126] who have investigated different alkylating agents which can then undergo intramolecular expulsion of the methyl sulphide anion forming novel heterocyclic compounds. One example of such a compound was formed when the amide (shown below) was treated with sodium hydride.



2.4 Attempted ring expansions

Because of the poor yields from the cyclopropanation reactions few attempts have been made to cause ring expansion to the diazepines.



The compound (26a) was stable to boiling xylene (20h.) and compound (26c) was stable in solution to trifluoroacetic acid (24h.). In the latter case downfield shifts of two of the cyclopropane protons were observed and the full multiplicity seen for each signal. Compound (26b) was unchanged after treatment with trimethyloxonium tetrafluoroborate (38)[120]. Compound (26b) decomposed in aqueous methanol solution when irradiated at 240 nm using a medium pressure lamp through quartz. Separation of the resultant tar was attempted unsuccessfully by p.l.c.

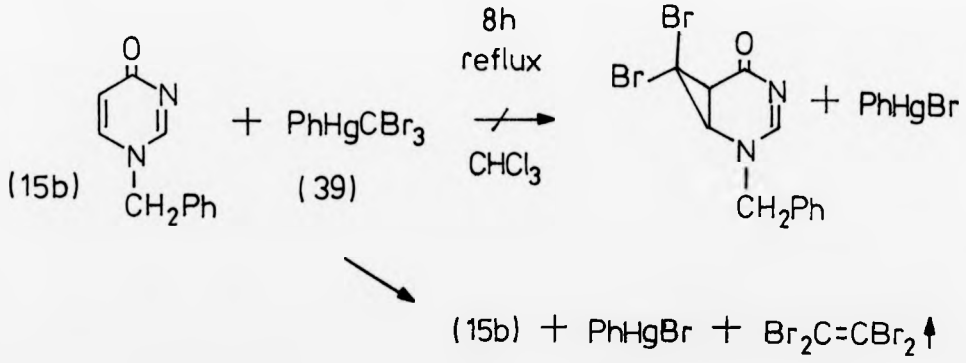
Flash vacuum pyrolysis of compound (26b) was performed at 500 °C and 2 x 10^{-2} mm Hg. The sample was vapourized at 60 °C. Purification of the pyrolyzate on a chromatotron using increasing amounts of ethyl acetate in light petroleum ether as eluant gave

mainly starting material and a small quantity of unidentified oil.

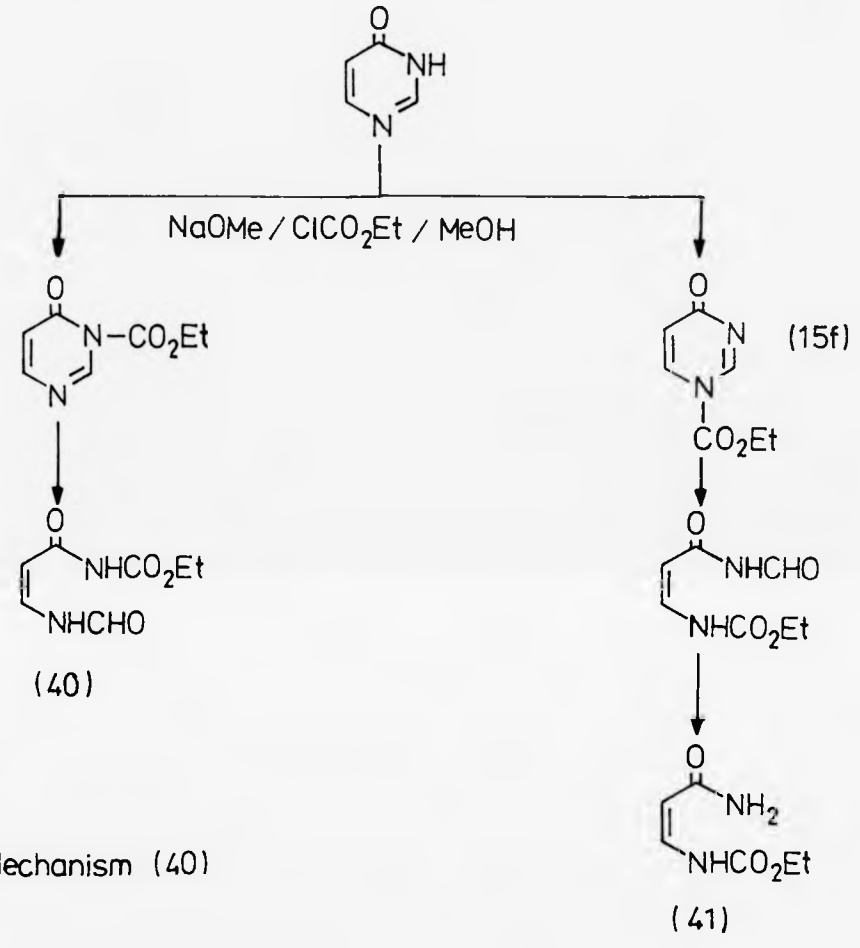
Treatment of compound (26c) with Lawesson's reagent gave the thione (20). No products characteristic of carbene insertion or addition were observed, so that there is no evidence of the fate of the methylene group from the diazabicycloheptanone (26c).

2.5 Alternative diazabicycloheptanones

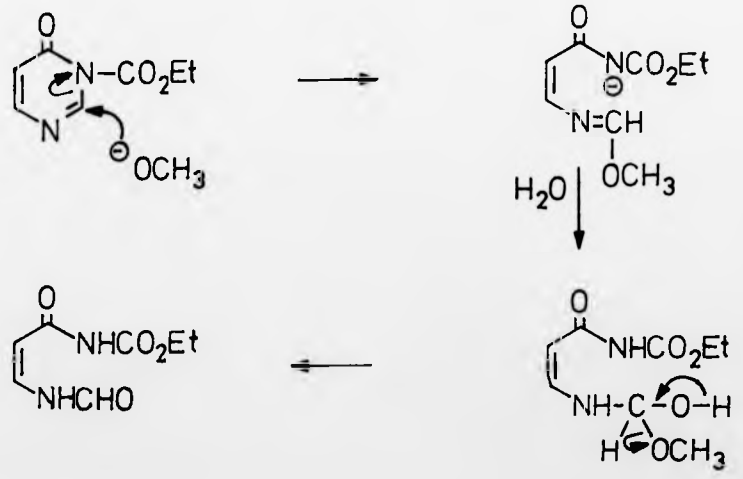
Previous workers[116] have attempted, without success, carbene additions to compound (14a). No carbene adducts were obtained from 1-benzyl-4-pyrimidone (15b) when it was refluxed with phenyltribromomethyl mercury (39)[121] in chloroform. Decomposition of phenyltribromomethyl mercury gave phenyl mercuric bromide and presumably tetrabromoethylene.



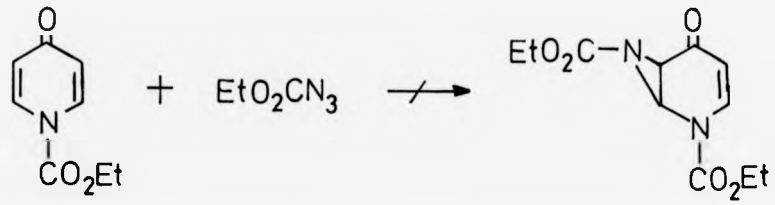
As DMSOM addition to alkylated pyrimidones gave very poor yields, compounds in which the charge balance differed were required. However attempts to synthesize ethyl 4-pyrimidone-1--carboxylate (15f) for cyclopropanation reactions gave only ring opened products (40) and (41). A similar mechanism can be written to that given (p. 51) for the previous ring opening of compounds (14a) and (14b), but using methoxide as the attacking species.



Mechanism (40)

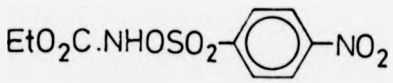


It seemed possible that bicyclic 1,3-diazepine precursors might be produced by reacting a nitrene with a 1-substituted-4--pyridone. However attempts to add the nitrene generated from ethylazidoformate (43) to N-ethoxycarbonyl-4-pyridone (42) failed and only 4-pyridone was isolated from the crude oil



(42) (43)

Carbethoxy nitrene may also be generated in situ from N-p-nitrobenzene sulphonyloxyurethan (NBSU) (44), but when reacted with compound (42) the only material recovered was a small quantity of 4-pyridone.



(44)

Experimental

Preliminary notes

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

Infrared absorption spectra were recorded on a Pye-Unicam SP2000 instrument and the ν_{max} values are quoted. Solids were recorded as solutions in chloroform and liquids as thin films.

Ultraviolet and visible absorption spectra were recorded on a Perkin-Elmer 257 spectrophotometer as solutions in 95% ethanol. The λ_{max} values are quoted with the extinction coefficient expressed as $\log_{10}\varepsilon$ in brackets.

Nuclear magnetic resonance spectra were routinely measured on a Hitachi Perkin-Elmer R24.B, as solutions in deuterochloroform unless otherwise stated.

Carbon 13 n.m.r. and proton n.m.r. at 100 mHz were recorded on a Jeol FX100 Fourier Transform instrument. Chemical shift values are quoted in delta (δ) values in p.p.m. with respect to tetramethylsilane as internal standard.

Microanalyses were carried out on a Perkin-Elmer 240 carbon/hydrogen/nitrogen analyser at the University of Keele.

Mass spectra were recorded on an A.E.I. M.S.I. 12 machine.

Column chromatography was carried out using deactived Woelm alumina, Florisil 100-200 mesh (Aldrich), or silica gel 60-120 mesh (B.D.H.).

Chromatotron plates were coated with silica gel PF-254 with $CaSO_4 . \frac{1}{2}H_2O$ type TLC (Merck). The components were visualized under ultraviolet light.

Thin layer chromatography was carried out on 20 x 5 cm glass plates coated with Kieselgel PF_{254} (Merck). The components were visualized under ultraviolet light or developed in iodine vapour.

Abbreviations used: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, exch = exchangeable, br = broad, and sh = shoulder.

EXPERIMENTAL

3-Methyl-4-pyrimidone (14a)

Prepared by the method of Jonak et al.[99] m.p. 122 °C (lit.,[100] m.p. 123-124 °C).

1-Methyl-4-pyrimidone (15a)

Prepared by the method of Jonak et al.[99] m.p. 153-156 °C (lit.,[99] m.p. 155-156 °C).

3-Benzyl-4-pyrimidone (14b)

Prepared by the same procedure in 67% yield, m.p. 104-105 °C (lit.,[101] m.p. 102-105 °C). The procedure of Bauer et al.[101] using methanol as solvent gave compound (16b) in 35% yield (reported[101] yield 13%).

1-Benzyl-4-pyrimidone (15b)

Prepared by the procedure of Bauer et al.[101] in 37% yield, m.p. 142-144 °C (lit.,[101] yield 12% m.p. 142-144 °C). The isomers (15b) and (16b) were separated by column chromatography using alumina (grade IV) and eluting with light petroleum containing increasing amounts of ethyl acetate.

5-Bromo-3-methyl-4-pyrimidone (14c)

Prepared by bromination of compound (15a) m.p. 153-154 °C (lit.,[102] m.p. 152-155 °C).

5-Bromo-3-benzyl-4-pyrimidone (14d)

Prepared by the benzylation in methanol of 5-bromo-4-pyrimidone in 10% yield. The product (14d) was purified by chromatography, on an alumina (grade IV) column, eluting with light petroleum containing increasing amounts of ethyl acetate, m.p. 140-142 °C

(from ethanol/light petroleum b.p. 40-60 °C).

Analysis found (%) C 49.95 H 3.35 H 10.6,

$C_{11}H_9BrN_2O$ required (%) C 49.85 H 3.4 N 10.55.

I.r. (cm^{-1}) 1660. ^1H N.m.r. (δ, p.p.m.) 5.15 (2H, s), 7.4 (5H, s), 8.2 (2H, d).

M/e mass units (%) 266, 264 (M^+ 100), 160 (20), 158 (18), 91 (87), 65 (85).

2-Methyl-4-pyrimidone (11)

Prepared by the procedure of den Hertog et al.[103]. The sodium salt of ethyl formylacetate prepared by either of the two published procedures[99,104] showed large peaks in the proton n.m.r. spectrum assigned to sodium ethoxide. If allowance is made for this in the condensation with acetamidine hydrochloride the yield reported can be improved to 26%. Compound (11) had m.p. 210-211 °C (lit.,[103] m.p. 212.5-213 °C).

2,3-Dimethyl-4-pyrimidone (14e)

Prepared by the method of Curd and Richardson[105] m.p. 65 °C (lit.,[99] m.p. 63-65 °C) in 36% yield (no yield reported).

2-Methylthio-4-pyrimidone (12)

Prepared by the method of Barrett et al.[106] m.p. 197-198 °C (lit.,[106] m.p. 198 °C).

3-Methyl-2-methylthio-4-pyrimidone (14g)

Prepared by the method of Brown et al.[100] m.p. 122-124 °C (lit.,[100] m.p. 122-123 °C).

3-Benzyl-2-methylthio-4-pyrimidone (14f)

Prepared by the benzylation of compound (12) using DMF as solvent and sodium hydride as base[107] m.p. 97-98 °C (lit.,[107] m.p. 97 °C).

1-Benzyl-2-methylthio-4-pyrimidone (15d)

Prepared in the same alkylation reaction as the 3-substituted isomer (14f) had m.p. 174 °C (lit.,[107] m.p. 176-177 °C). A quantity of 4-benzyloxy-2-methylthio-4-pyrimidine (16b) with spectral properties identical with those reported by Gacek and Undheim[107] was also obtained.

1,2-Di-(2-methylthio-4-pyrimidon-3-yl)ethane (17)

A solution of 1,2-dibromoethane (15 ml, 5 equiv.) in dry methanol (15 ml) was boiled vigorously under dry nitrogen while a solution of 2-methylthio-4-pyrimidone (12) (5g 0.035 mol) and potassium hydroxide (1.96 g, 0.035 mol) in methanol (25 ml) was added dropwise over 3h. The mixture was boiled (5h.), filtered, evaporated, and the residue chromatographed on alumina (grade IV). Three compounds were eluted by increasing quantities of ethyl acetate in light petroleum ether. The third was the dipyrimidonylethane (17) in 30% yield, m.p. 210 °C (from benzene).

Analysis found (%) C 46.2 H 4.3 N 17.9,

$C_{12}H_{14}N_4O_2S_2$ required (%) C 46.45 H 4.5 N 18.0.

I.r. (cm^{-1}) 1690. U.v., nm ($\log_{10}\varepsilon$) 227 (3.12), 290 (5.1), 313 sh.

^1H N.m.r. (δ, p.p.m.) 2.5 (6H, s), 4.4 (4H, s), 6.1 (2H, d,J = 6Hz).

M/e mass units (%) 310 (M^+ 16), 293 (16), 170 (10),
169 (100 $M-C_5H_5N_2OS$), 168 (77), 153 (74),
142 (36), 135 (16), 121 (27), 95 (23).

1-(2-Methylthio-4-pyrimidon-1-yl)-2-(2-methylthio-4-pyrimidon-3-yl)ethane (18)

First from the column described in the previous experiment was compound (18) in 12% yield, m.p. 77-78 °C (from cyclohexane).

Analysis found (%) C 46.8 H 4.7 N 18.1,

$C_{12}H_{14}N_4O_2S_2$ required (%) C 46.45 H 4.5 N 18.0.

I.r. (cm^{-1}) 1690. U.v., nm ($\log_{10}\varepsilon$) 248 (4.17), 285 (4.06), 298 sh, 310 sh.

^1H N.m.r. (δ, p.p.m.) 2.4 (6H, s), 4.1-4.7 (4H, m), 6.1 (1H, d, J = 6Hz), 6.3 (1H, d, J = 6Hz), 7.6 (1H, d, J = 6Hz), 8.1 (1H, d, J = 6Hz).

M/e mass units (%) 310 (M^+ 7), 169 (100, M-$C_5H_5N_2O_5$).

1-(1-Methyl-2,4-dioxopyrimidin-3-yl)-2-(2-methylthio-4--pyrimidon-3-yl)ethane (19)

Isolated as the second component from the column chromatography of compound (17) in 2% yield, m.p. 98-99 °C (from cyclohexane).

Analysis found (%) C 48.95 H 4.8 N 19.05,

$C_{12}H_{14}N_4O_2S_2$ required (%) C 48.95 H 4.75 N 19.05.

I.r. (cm^{-1}) 1700. U.v., nm ($\log_{10}\varepsilon$) 250 (4.16), 275 sh.

^1H N.m.r. (δ, p.p.m.) 2.4 (3H, s), 3.8 (3H, s), 4.2-4.7 (4H, m), 6.0 (1H, d, J = 6Hz), 6.3 (1H, d, J = 6Hz), 7.7 (1H, d, J = 6Hz), 8.1 (1H, d, J = 6Hz).

M/e mass units (%) 294 (M^+ 24), 168 (40), 154 (34),
153 (100 M-$C_5H_5N_2OS$), 127 (28),
96 (96), 84 (90), 70 (74).

3-Benzylpyrimidine-4-thione (20)

The pyrimidone (14b) (4g, 0.022 m) and Lawesson's reagent[108] (4.84 g, 0.012 mol) were dissolved in dry toluene (30 ml) and heated at 100 °C for 4h. The reaction mixture was applied to a silica gel column. Elution with benzene-ethylacetate mixtures gave the thione (20) in 65% yield, m.p. 104-106 °C (from cyclohexane).

Analysis found (%) C 65.6 H 4.75 N 13.73,

$C_{11}H_{10}N_2S$ required (%) C 65.35 H 5.0 N 13.85.

I.r. (cm^{-1}) 1400. U.V., nm ($\log_{10}\varepsilon$) 295 (4.05), 350 sh.

^1H N.m.r. (δ, p.p.m.) 5.65 (2H, s), 7.35 (5H, s), 7.5 (1H, d, J = 6Hz), 7.7 (1H, d, J = 6Hz), 8.3 (1H, s).

M/e mass units (%) 202 (M^+, 54), 169 (28), 91 (100).

3-Benzyl-2-methylthiopyrimidine-4-thione (21)

Prepared by the same method in 68% yield, m.p. 134-135 °C (from cyclohexane).

Analysis found (%) C 57.65 H 4.95 N 11.15,

$C_{12}H_{12}N_2N_2$ obtained (%) C 58.05 H 4.85 N 11.3.

I.r. (cm^{-1}) 1220 c=s. U.v., nm ($\log_{10}\varepsilon$) 238 (4.01), 295 (3.63), 360 (3.57),

^1H N.m.r. (δ p.p.m.) 2.4 (3H, s), 6.0 (2H, s), 7.3 (1H, d, J = 6Hz), 7.3 (5H, s), 7.5 (1H, d, J = 6Hz).

M/e mass units (%) 248 (M^+ 100), 233 (27), 215 (67), 201 (31, M-SMe), 128 (60), 91 (100, $PhCH_2^+$).

Trimethylsulphoxonium Iodide (22)

Prepared according to the procedure of Kuhn and Trischmann[112] m.p. 212-215 °C (lit.,[112] m.p. 214-215 °C).

Trimethylsulphoxonium Chloride (23)

Prepared according to the method of Corey and Chaykovsky[113] m.p. 222 °C (lit.,[113] m.p. 220-222 °C).

N,N-Dimethylamino-S-methyl-S-phenyl-sulphoxonium tetrafluoroborate (24)

Prepared according to the method of Shroek et al.[114] m.p. 118-120 °C (lit.,[114] m.p. 118-120 °C).

Trimethylsulphonium Iodide (25)

Prepared according to the method of Eméleus and Heal[115] m.p. 208-210 °C (no lit.,[115] value recorded).

Reactions between 4-pyrimidones and DMSOM

General method a

Sodium hydride (1.1 g, 0.022 mol, 50% dispersion in paraffin) was washed by decantation with dry light petroleum ether under a dry nitrogen atmosphere. Dry DMSO (30 ml) was added followed by trimethylsulphoxonium iodide (22)[112] (5 g, 0.0225 mol) in one portion, and the mixture stirred vigorously at room temperature until the evolution of hydrogen ceased (approx. 0.5h.). A solution of the pyrimidone (0.022 mol) in dry DMSO (10 ml) was added dropwise, the mixture stirred at room temperature (0.5h) and heated at 40-60 °C (4h.). Work up involved either evaporation of the reaction mixture at 60-70 °C and 0.01 mm Hg, the residue being extracted with chloroform, or dilution using three times its volume of water and extraction with chloroform.

In both cases the chloroform soluble material was purified by column chromatography on Florisil (150 g) in light petroleum ether (b.p. 40-60 °C), eluting with petroleum containing increasing percentages of ethyl acetate. First from the column was the cyclopropapyrimidone, then unreacted pyrimidone, and finally the aminoacrylamide.

General method b

Sodium hydride (1.1 g, 0.022 mol, 50% dispersion in paraffin) was washed as in (a) under a dry nitrogen atmosphere. Dry THF (30 ml) was added followed by trimethylsulphoxonium chloride (23)[113] (2.9 g, 0.0225 mol) in one portion and stirred (0.5h.).

A solution of the pyrimidone (0.022 mol) in dry THF (as required) was added dropwise and the reaction mixture refluxed (4h.). Filtration and washing of the filtered solid with more THF was followed by evaporation of the combined filtrates and separation of the products by column chromatography on Florisil (150 g) as in (a).

4-Methyl-2,4-diazabicyclo[4:1:0]heptan-5-one (26a) and Z-(3-formylamino)-N-methylacrylamide (27a)

Prepared from 3-methyl-4-pyrimidone (14a) by both methods (a) and (b). The diazabicycloheptanone (26a) was obtained in 8% yield and had m.p. 55-58 °C (from petroleum ether b.p. 40-60 °C).

Analysis found (%) C 57.65 H 6.45 N 22.75,

$C_6H_8N_2O$ required (%) C 58.05 H 6.45 N 22.6.

I.r. (cm^{-1}) 1680.

^1H N.m.r. (δ, p.p.m.) 0.7 (1H, q, H_7exo), 1.6-2.2 (2H, m, H_7endo, H_6) 3.2 (3H, s, NCH_3), 3.2-3.7 (1H, m, H_1), 7.05 (1H, s, H_3).

M/e mass units (%) 124 (M^+ 100), 110 (M-CH_2, 54), 95 (M-(CH_2+CH_3), 67 (82), 55 (62), 42 (98).

The cis-acrylamide (27a) was obtained in 32% yield and had m.p. 74-75 °C (from cyclohexane).

Analysis found (%) C 46.7 H 6.4 N 22.75,

$C_5H_8N_2O_2$ required (%) C 46.85 H 6.25 N 21.9.

I.r. (cm^{-1}) 3300, 1700, 1650, 1625.

^1H N.m.r. (δ, p.p.m.) 2.8 (3H, d), 5.0 (1H, d, J = 8Hz), 6.0 (1H, brs, exch D_2O, NH), 7.3 (1H, dd, J = 8 and 8Hz), 8.3 (1H, s) and 11.0 (1H, brs, exch D_2O, NH).

M/e mass units (%) 128 (M^+ 44), 110 (M-H_2O, 11), 100 (M-CO, 94), 98 (42), 96 (16), 71 (24), 70 (M-CH_3NHCO, 100), 58 (11), 42 (26).

4-Benzyl-2,4-diazabicyclo[4:1:0]heptan-5-one (26b) and Z-N-benzyl-3-formyl amino acrylamide (27b)

Prepared from 3-benzyl-4-pyrimidone (14b) by both methods (a) and (b). The maximum yield of diazabicycloheptanone (24%) was obtained by method (b) and had m.p. 61-63 °C (from light petroleum ether b.p. 40-60 °C).

Analysis found (%) C 71.8 H 5.95 N 14.1,

$C_{12}H_{12}N_2O$ requires (%) C 72.0 H 6.05 N 14.0.

I.r. (cm^{-1}) 1665. U.V., nm ($\log_{10}\varepsilon$) 265 (4.09).

^1H N.m.r. (δ, p.p.m.) 0.7 (1H, q, H_7exo), 1.6-2.2 (2H, m, H_7endo H_6), 3.4-3.6 (1H, m, H_1), 4.5-5.1 (2H, dd, J = 14Hz, CH_2), 7.0 (1H, s, Hz), 7.25 (5H, s, C_6H_5).

M/e mass units (%) 200 (M^+ 71), 173 (M-HCN 12), 110 (21), 95 (18), 93 (28), 92 (100).

The maximum yield of acrylamide (24%) was obtained by method (a) and had m.p. 83-85 °C (from benzene).

Analysis found (%) C 64.55 H 5.85 N 13.8,

$C_{11}H_{12}N_2O_2$ required (%) C 64.7 H 5.9 N 13.75.

I.r. (cm^{-1}) 3300, 1720, 1660, 1630.

^1H N.m.r. (δ, p.p.m.) 4.5 (2H, d), 5 (2H, dd), 6.0 (1H, br.s, exch. D_2O, NH), 7.3 (6H, s), 8.1 (1H, s), 11.2 (1H, br.s exch. D_2O, NH).

M/e mass units (%) 204 (M^+ 21), 186 (M-H_2O, 24), 159 (M-(H_2O+HCN) 36), 106 (100), 91 ($PhCH_2$, 66).

4-Methyl-3-methylthio-2,4-diazabicyclo[4:1:0]heptan-5-one (26c) and dimethylsulphoxonium(3-methyl-4-pyrimidon-2-yl)methylide (32)

(a) When 3-methyl-2-methylthio-4-pyrimidone (14f) was treated with dimethylsulphoxonium methylide in DMSO followed by aqueous workup and chloroform extraction, according to general method (a) the

diazabicycloheptanone (26c) was obtained in 7.5% yield, m.p. 79-81 °C (from benzene and light petroleum ether [b.p. 40-60 °C]).

Analysis found (%) C 49.55 H 5.8 N 16.65,

$C_7H_{10}N_2OS$ required (%) C 49.4 H 5.9 N 16.45.

I.r. (cm^{-1}) 1680. U.v., nm ($\log_{10}\varepsilon$) 213 (4.05).

^1H N.m.r. (δ, p.p.m.) 0.7 (1H,q, H_7exo), 1.5-2.0 (2H, m, H_7endo H_6), 2.3 (3H, s, SCH_3), 3.15 (3H, s, NCH_3), 3.5 (1H, m, H_1).

M/e mass units (%) 170 (M^+, 21), 156 (M-CH_2, 11), 125 (100), 98 (21), 95 (29).

Concentration of the aqueous layer gave the iodide (31) m.p. 181 °C (from absolute ethanol).

Analysis found (%) C 36.5 H 4.75 N 10.55,

$C_{18}H_{13}IN_2O$ required (%) C 36.4 H 4.9 N 10.6.

I.r. paraffin (cm^{-1}) 1660.

^1H N.m.r. (δ, p.p.m.) 3.0 (3H, s), 3.2 (1H, s), 3.5 (6H, s), 4.4 (1H, s), 5.4 (1H, d, J = 6Hz), 7.45 (1H, d, J = 6Hz).

(b) By using general method (b) the methylide (32) precipitated out of solution and was isolated by filtration. The yield by this method was 41%, m.p. 190 °C (from chloroform/benzene).

Analysis found (%) C 47.8 H 5.95 N 14.0,

$C_8H_{12}N_2O_2S$ required (%) C 48.0 H 6.0 N 14.0.

I.r. (cm^{-1}) 1670. U.v., nm ($\log_{10}\varepsilon$) 269 (385), 325 (4.31).

^1H N.m.r. (δ, p.p.m.) 3.2 (3H, s), 3.5 (6H, s), 3.9 (1H, s), 5.7 (1H, d, J = 6Hz), 7.5 (1H, d, J = 6Hz).

M/e mass units (%) 200 (M^+ 100), 123 (87), 103 (40), 95 (91), 69 (60), 43 (50).

Fully decoupled ^{13}C n.m.r. (p.p.m.) 28.5 (N-CH_3), 41.2 ($S(CH_3)_2$), 62.2 (CH), 99.5 and 152·5 (HC = CH), 159.7 (C_2), 161.1 (C_4).

Acetyl(3-methyl-4-pyrimidon-2-yl)dimethylsulphoxonium methylide (33)

The ylide (32) (1 g) was refluxed with acetic anhydride (5 ml, 10 equiv.) in dry chloroform (50 ml) for 2h. Removal of solvents and recrystallization of the residue from benzene gave the ylide (33) m.p. 186 °C in 87% yield.

Analysis found (%) C 49.65 H 5.55 N 11.75,

$C_{10}H_{14}N_2O_3S$ required (%) C 49.6 H 5.8 N 11.57.

I.r. (cm^{-1}) 1700. U.v., nm ($\log_{10}\varepsilon$) 250 (3.83), 325 sh.

^1H N.m.r. (δ, p.p.m.) 1.8 (3H, s), 3.6 (6H, s), 6.4 (1H, d, J = 6Hz), 7.8 (1H, d, J = 6 Hz).

M/e mass units (%) 242 (M^+ 42), 227 ($M-CH_3$, 55), 165 (60), 150 (36), 137 (75), 136 (100).

Attempted preparation of iodomethyl-(3-methyl-4-pyrimidon-2-yl)-dimethylsulphoxonium methylide (34)

The ylide (32) (0.2 g, 1×10^{-3} mol), methyl iodide (0.15 g, 1×10^{-3} mol) and dimethylformamide (10 ml) were heated at 100 °C for 16h. in a sealed tube. No material was recovered.

2-Bromomethyl-3-methyl-4-pyrimidone (36)

Bromoacetyl bromide (1 g, 5×10^{-3} mol) was added dropwise with stirring, via a syringe to a cooled solution of the ylide (32) (2 g, 0.01 mol) in dry chloroform (50 ml). Stirring was continued at room temperature 0.5h., then at reflux (3h.) during which time a solid precipitated out. The solid was removed by filtration (1.4 g) and the filtrate evaporated in vacuo to a yellow oil. The filtered solid was shown by ^1H n.m.r. in d_6 DMSO to be the hydrobromide salt (35) in 50% yield. The spectrum was rerun at regular intervals up to 12h. The singlet at δ2.6 due to DMSO

increased whilst the singlet at δ3.5 due to the dimethylsulphoxide group of compound (35) decreased. Intramolecular reaction was complete in 12h., the ^{1}H n.m.r. consisting of compound (36) and DMSO. A satisfactory analysis was not obtained for compound (35) due to its gradual degradation to compound (36).

The residue from the filtrate was applied to a Florisil column using increasing amounts of ethyl acetate in benzene as eluant. Compound (36) was the only product eluted in 33% yield. ^{1}H N.m.r. (δ, p.p.m.) 3.6 (3H, s), 4.2 (2H, s), 6.3-6.4(1H, d, J = 6Hz), 7.7-7.8 (1H, d, J = 8Hz).

2-Ethoxy-3-methyl-4-pyrimidone (37)

Ethyl cyanoacetate (1.5 g, 0.013 mol) in dry ethanol (10 ml) was added dropwise, with stirring to a solution of sodium (0.3 g, 0.013 mol) in dry ethanol (15 ml) under nitrogen. After stirring (0.5h.), a solution of 3-methyl-2-thiomethyl-4-pyrimidone (14 g) (2 g, 0.013 mol) in dry ethanol (50 ml) was added and the reaction mixture refluxed (3h.). The resultant solution was neutralized (glacial acetic acid), evaporated in vacuo to a yellow solid, extracted with diethyl ether, and the product sublimed at 65 °C and 0.01 mm Hg to give white crystals of compound (37), m.p. 57 °C, (lit.,[127] m.p. 59-60 °C).

Attempted thermal ring expansion of 4-methyl-2,4--diazabicyclo[4:1:0]heptan-5-one (26a)

Compound (26a) (50 mg, 3 x 10^{-4} mol) was refluxed in xylene at 140 °C under nitrogen for 20h. No change was observed in the ^{1}H n.m.r. spectrum.

Protonation of 4-methyl-3-thiomethyl-2,4-diazabicyclo[4:1:0]-heptan-5-one (26c)

Compound (26c) (10 mg) was dissolved in deuterated dichloromethane (0.5 ml) with trimethylsilane as internal standard. The ^1H n.m.r. was recorded at -10 °C. Trifluoroacetic acid (TFA) (0.5 ml) was added at -10 °C and the spectrum recorded again. The spectrum was rerun at 25 °C and again after 24h and was found to be the same.

^1H N.m.r. spectrum before the addition of TFA, CD_2Cl_2, (δ, p.p.m.) 0.6-0.75 (1H, q, H_7exo), 1.4-2.0 (2H, m, H_7endo H_6), 2.8 (3H, s, CH_3), 3.2 (3H, s, CH_3), 3.4-3.9 (1H, m, H_1).

^1H N.m.r. spectrum after the addition of TFA, CD_2Cl_2 (δ, p.p.m.) 1.3-1.4 (1H, q, H_7exo), 1.8-2.0 (1H, m, H_7endo), 2.4-2.6 (1H, m, H_6), 2.8 (3H, s, CH_3), 3.5 (3H, s, CH_3), 3.7-3.9 (1H, m, H_1).

Trimethyloxonium tetrafluoroborate (38)

Prepared according to the method of Curphey[120] m.p. 140-142 °C (lit.,[120] m.p. 176-180 °C with decomposition. Footnote states large variations found in the m.p. values of this compound).

Attempted ring expansion of compound (26c) using trimethyloxonium-tetrafluoroborate (38)[120]

Freshly prepared trimethyloxoniumtetrafluoroborate (180 mg, 0.0012 mol) was added with stirring to a solution of compound (26c) (200 mg, 0.0012 mol) in dry dichloromethane (25 ml) under dry nitrogen. Stirring was continued for 6h. The reaction mixture was filtered and the filtrate evaporated in vacuo to a white solid shown by ^1H n.m.r. to be starting material.

Irradiation of compound (26c)

A solution of compound (26c) (40 mg, 2.5×10^{-4} mol) in a methanol/water mixture (50%, 10 ml) was irradiated in a quartz tube at 240 nm for 6h. The solvent was removed in vacuo leaving a black tar. Attempts at separation by p.l.c. proved unsuccessful.

Flash Vacuum Pyrolysis of 4-benzyl-2,4-diazabicyclo[4:1:0]-heptan-5-one (26b)

The bicyclic compound (26b) (350 mg) was vapourized at 60 °C in a flash vacuum pyrolysis apparatus and pyrolyzed at 500 °C and 2×10^{-2} mm Hg. The pyrolyzate was collected on a nitrogen cooled finger. No products were identified.

Phenyltribromomethylmercury (39)

Prepared according to the method of Gillespie et al.[121] m.p. 118-120 °C (lit.,[121] decomp. 120 °C).

Attempted preparation 2-benzyl-7,7-dibromo-2,4-diazabicyclo-[4:1:0]heptan-5-one

A solution of 1-benzyl-4-pyrimidone (15b) (2.4 g, 0.01294 mol) in dry chloroform (50 ml) was stirred under nitrogen at room temperature. Compound (39)[121] (3.41 g, 0.00647 mol) was added and the reaction mixture refluxed for 2h., cooled, filtered, and the filtrate evaporated in vacuo. The filtered residue (2 g) m.p. 278-282 °C was phenyl mercuric bromide. The solid residue from the filtrate (3.8 g) was a mixture of 1-benzyl-4-pyrimidone (15b) and presumably tetrabromoethylene (m.p. 55 °C). Separatation was not attempted.

Z-N-Ethoxycarbonyl-3-formylaminoacrylamide (40) and 2-(3-ethoxycarbonylamino)-acrylamide (41)

A solution of sodium (0.46 g, 0.02 mol) in dry methanol (10 ml) was reacted with 4-(3H)-pyrimidone (2 g, 0.02 mol) under nitrogen. A solution of ethyl chloroformate (2 mls, 0.02 mol) in methanol (25 ml) was added dropwise, with cooling, and the reaction mixture was stirred at 40 °C (4h.). Filtration and evaporation of the filtrate left a yellow solid which was purified by column chromatography on Florisil (80 g) in light petroleum ether (b.p. 40-60 °C), eluting with petroleum containing increasing percentages of ethyl acetate. First from the column was Z-N-ethoxycarbonyl--3-formylaminoacrylamide (40) in 58% yield, m.p. 124 °C (from benzene).

Analysis found (%) C 45.38 H 5.58 N 14.97,

$C_7H_{10}O_4N_2$ required (%) C 45.16 H 5.38 N 15.05.

I.r. (cm^{-1}) 3320, 3000, 1750, 1680, 1630.

U.v., nm ($\log_{10}\varepsilon$) 278 (4.3).

^1H N.m.r. (δ, p.p.m.) 1.1-1.4 (3H, t), 4.0-4.3 (2H, q), 4.9-5.1 (1H, d, J = 10 Hz), 7.1-7.5 (1H, dd, J = 10Hz), 9.1 (1H, br.s, exch. D_2O, NH), 10.2-10.4 (1H, br.d. exch. D_2O, NH, J = 10Hz).

M/e mass units (%) 186 (M^+ 18), 158 (18), 142 (14), 115 (46), 114 (16), 96 (48), 86 (20), 82 (10), 70 (100), 69 (18), 68 (18), 56 (10).

Second from the column was starting material (1.2 g), and the third compound eluted was Z-(3-ethoxycarbonylamino)acrylamide (41) in 30% yield, m.p. 115-117 °C (from benzene).

Analysis found (%) C 45.32 H 6.13 N 17.64,

$C_6H_{10}N_2O_3$ required (%) C 45.50 H 6.33 N 17.72.

I.r. (cm^{-1}) 3500, 3400, 3300, 3000, 1750, 1680.

U.v., nm ($\log_{10}\varepsilon$) 253 (4.41).

^{1}H N.m.r. (δ, p.p.m.) 1.2-1.4 (3H, t), 4-4.3 (2H, q), 4.8-5 (1H, d, J = 10Hz), 5.7 (2H, br.s, exch. D_2O,NH_2), 6.9-7.3 (1H, dd, J = 10Hz), 10.3-10.6 (1H, br.d. exch. D_2O, NH, J = 10Hz).

M/e mass units (%) 158 (M^+ 12), 115 (6), 114 (6), 96 (18), 76 (21), 70 (100), 69 (12), 68 (12).

N-Carbethoxy-4-pyridone (42)

Prepared according to the method of Wyler et al.[122] m.p. 80 °C (lit.,[122] 85 °C).

N-[([4-nitrophenyl]-sulphonyl)oxy]urethan (NBSU) (44)

Prepared according to the method of Lwowski and Maricich[123] m.p. 111-112.5 °C (lit.,[123] 116.4-116.8 °C).

Ethyl azidoformate (43)

Prepared by the method of Forster and Fierz[124] b.p. 16 °C, 0.005 mm Hg (lit.,[124] b.p. 25 °C 2 mm Hg).

Attempted preparation 2,7-di-carbethoxy-2,7-diazabicyclo-[4:1:0]heptan-5-one

Ethylazidoformate (43)[124] (0.78 g, 6.8×10^{-3} mol) was added to a solution of N-carbethoxy-4-pyridone (42)[122] (1 g, 6.8×10^{-3} mol) in dry carbon tetrachloride (50 ml) and refluxed under nitrogen (7 days). Evaporation and column chromatography on Florisil (50 g) using petroleum ether (b.p. 40-60 °C), ethyl acetate solvent mixtures gave only 4-pyridone in 70% yield.

Reaction between N-carbethoxy-4-pyridone (42) and NBSU (44)

NBSU (1.39 g, 4.8×10^{-3} mol) was added as a solid, over 0.75 h. to a solution of N-carbethoxy-4-pyridone (42) (0.8 g, 4.8×10^{-3} mol) in dichloromethane (10 ml) containing triethyl-

amine (0.48 g, 0.0144 mol). The reaction mixture was stirred (2h.) at room temperature. Petroleum ether (b.p. 40-60 °C), was added and the precipitated solid filtered. The filtrate was evaporated in vacuo and applied to a Florisil column (25 g) eluting with petroleum/ethyl acetate solvent mixtures. 4-Pyridone was eluted in 33% yield. Other material eluted was unidentified.

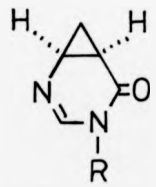
CHAPTER THREE

1,3-Diazepine precursors from cyclopropanes

3.1 Introduction

The synthesis of 2,4-diazabicyclo[4:1:0]heptanones by dimethylsulphoxonium methylide addition to 4-pyrimidones was unreliable and gave poor yields; therefore a more suitable synthetic route was required that would afford substantial quantities of these elusive compounds.

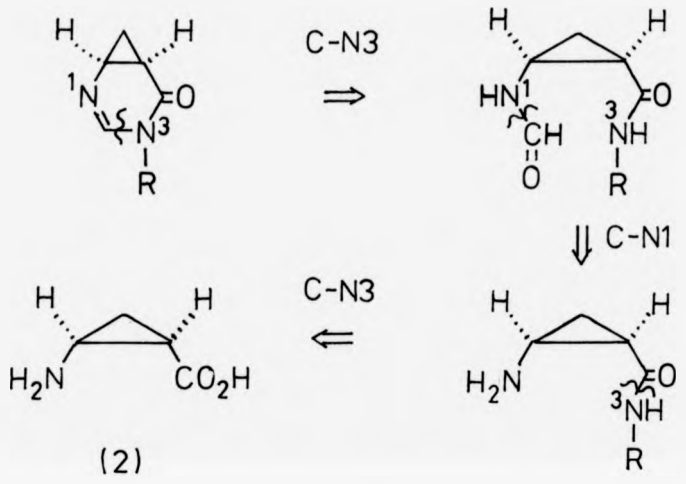
The problem was viewed as a retro synthesis, compound (1) being the 'target molecule' upon which suitable disconnections were performed. A disconnection is a reverse operation that will break a bond and convert the target molecule into a possible starting material. (The notation is that of Warren[126]).



(1)

Two different routes are shown in schemes (A) and (B). In the first scheme (A) compound (1) was treated as a cyclic enamine formed from an amine and a carbonyl compound in the same way as are ordinary enamines. The first disconnection was that of the C-N3 bond (shown by a curved line drawn through the bond being broken).

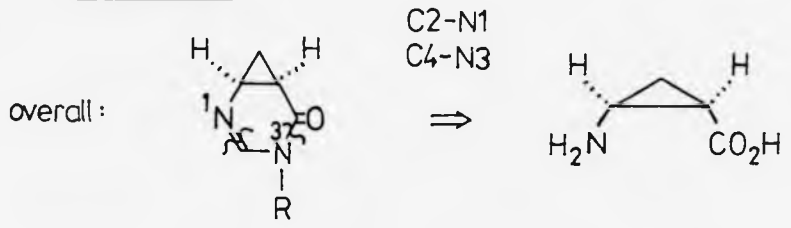
Scheme A

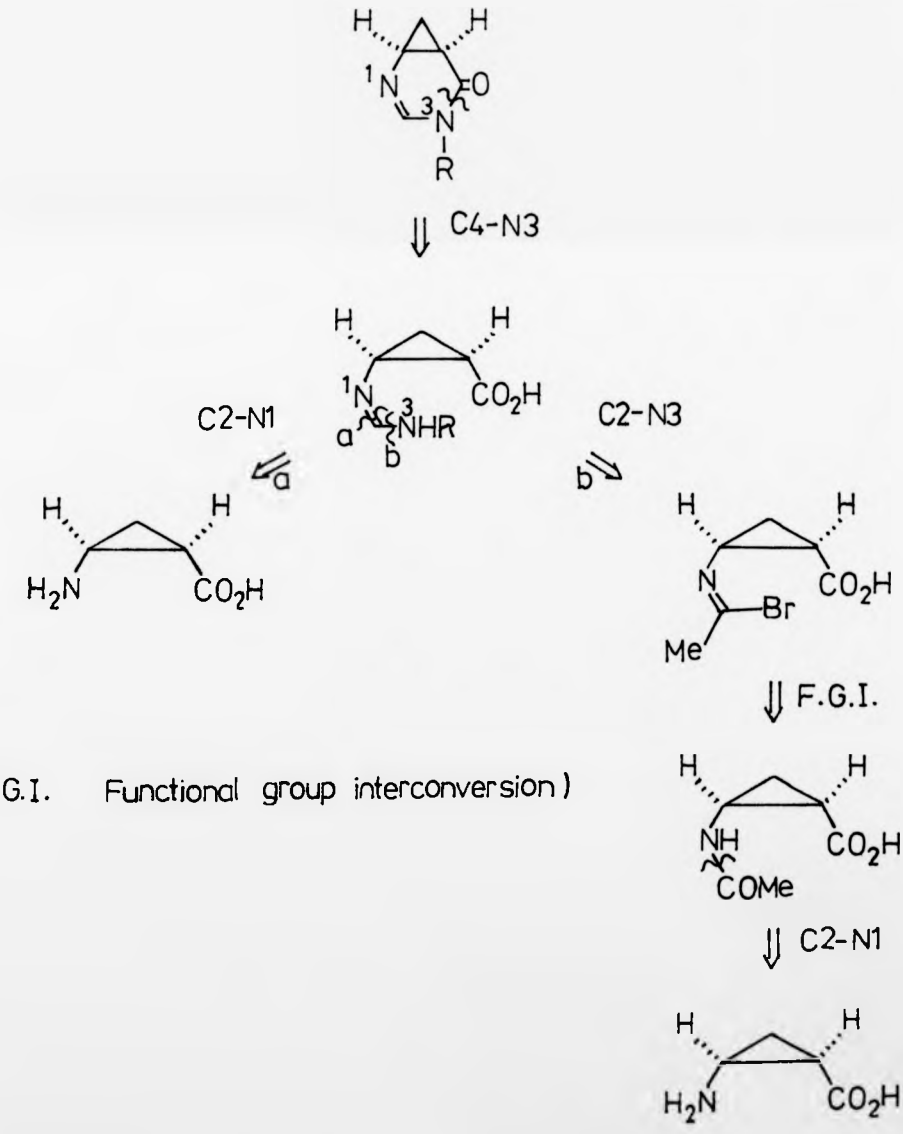


Further disconnections gave the structure of another compound, cis-2-aminocyclopropane-1-carboxylic acid (2) from which the target molecule might by synthesized.

In the second scheme (B) outlined below, two disconnections may be performed simultaneously or alternatively the problem could be approached in stages. The first disconnection involved breaking a C-N bond, this time between the carbonyl group and N3 nitrogen. There are two possible routes to this compound, one involved a disconnection at C-N3 (single bond), the other a disconnection at C-N1 (double bond). Both routes get back to the same starting material.

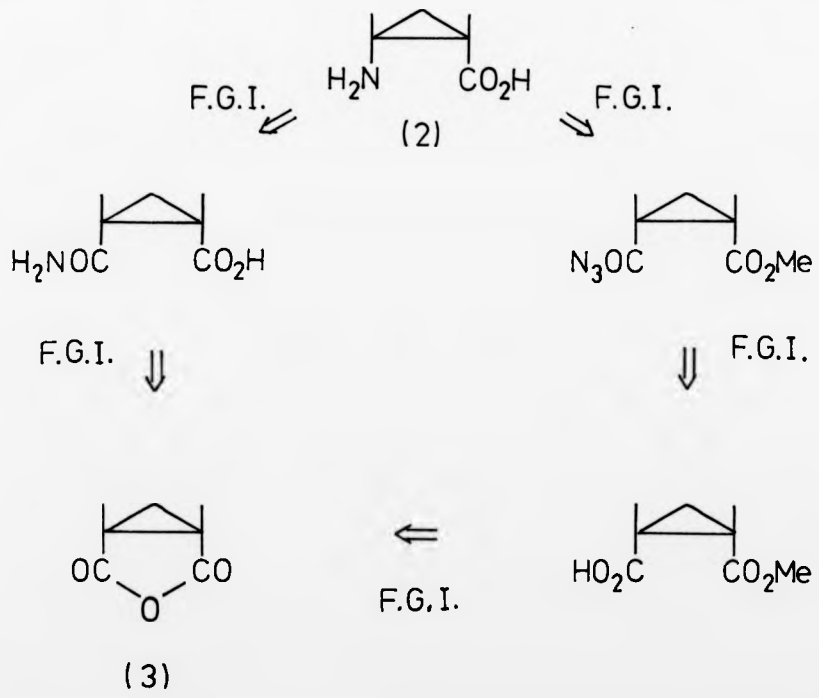
Scheme B





(F.G.I. Functional group interconversion)

Thus cis-2-aminocyclopropane-1-carboxylic acid (2) was a desirable starting material for the synthesis of diazabicyclo-heptanones. A C.A.S. on-line literature search revealed that this compound had not previously been synthesized. (Our thanks to I.C.I. Pharmaceuticals Division who made this service available). Further functional group interconversions of the amine group of compound (2) gave as the starting material cis-cyclopropane-1,2-dicarboxylic acid anhydride (3).



(3)

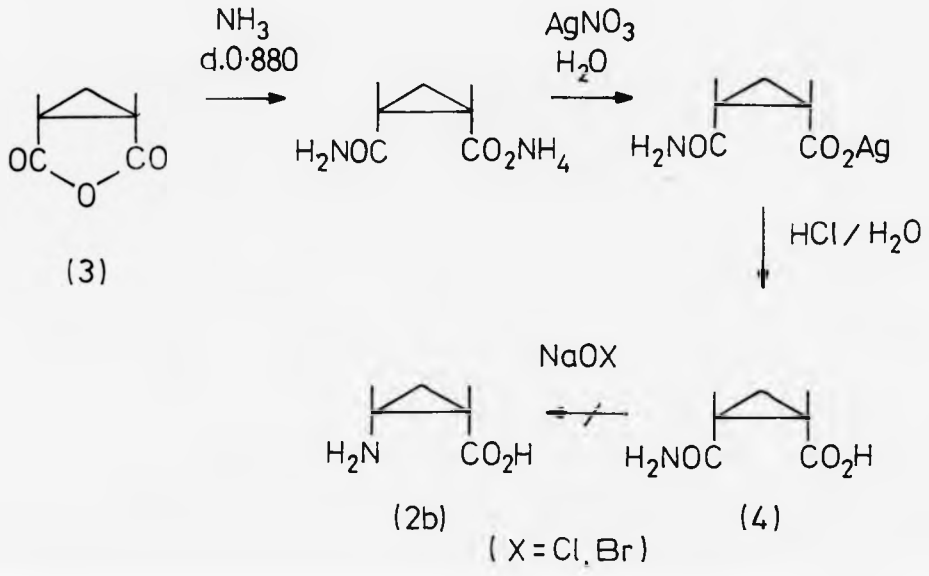
A weakness of the C.A.S. search programme used was revealed by a subsequent discovery of a paper by Cannon and Garst[127] recording the synthesis of some simple derivatives of methyl cis-2-aminocyclopropane-1-carboxylate.

This chapter is an account of the various attempts to synthesize cis-2-aminocyclopropane-1-carboxylic acid (2) and related compounds which appear in the retro synthesis of the target molecule (1).

3.2 Synthesis and reactions of cis-2-amidocyclopropane carboxylic acid (4)

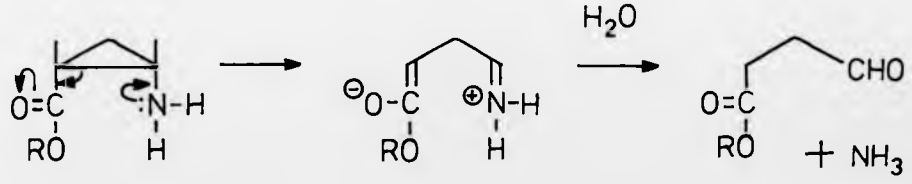
The starting material for this and the other reaction pathways in this chapter was cis-cyclopropane-1,2-dicarboxylic acid anhydride (3). This was prepared[128] in a series of sealed tube reactions using trans cyclopropane-1,2-dicarboxylic acid and acetic anhydride. With each successive run the cis:trans isomer ratio increased, until a 98% yield of the cis cyclopropane-1,2-dicarboxylic anhydride was obtained. Samples of the anhydride (3) were generously donated by I.C.I. Pharmaceuticals Division and Shell Biosciences.

The successful ring opening of compound (3) to the amide (4) was performed by standard procedures via an ammonium salt.

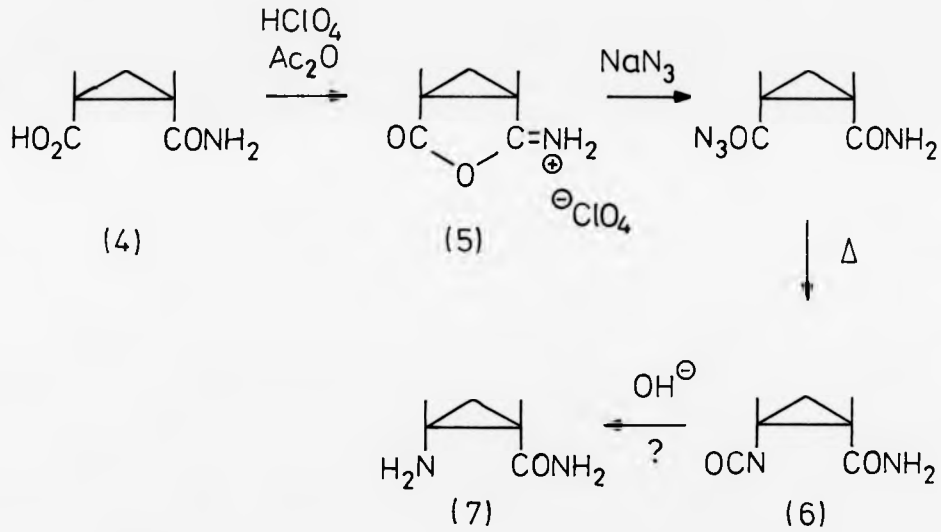


All subsequent attempts to convert the amide (4) into an amine by a Hofmann degradation reaction failed. These findings were in accord with those of Wheeler et al.[129]. These workers offered no explanation for this failure, but a later report[127] indicated that opening of the 3 membered ring had probably occurred.

The mechanism postulated[127] for this ring opening reaction (below) requires both a mobile pair of electrons on the amine nitrogen and a carbonyl group at C2.



An examination of the reactivity of the other functional group in the molecule suggested a Curtius reaction to convert the carboxylic acid into an amine. The method of Boyd et al.[130] was used with appropriate modification. This reaction sequence involved initial formation of a cyclic isoimidium salt (5) which in theory can be treated with sodium azide and heated to produce the isocyanate (6) hydrolysis of which leads to the amine (7).

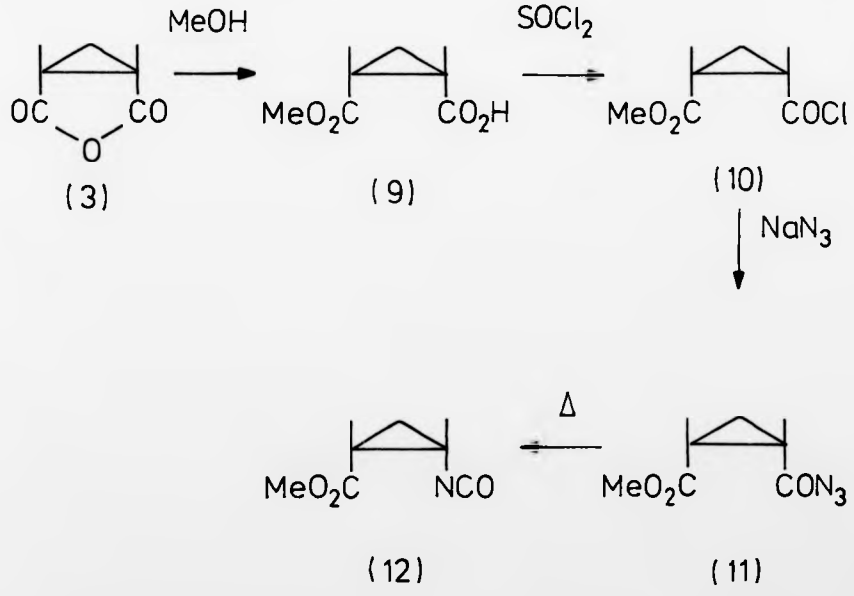


Careful addition of perchloric acid to an acetic anhydride suspension of cis-2-amidocyclopropane carboxylic acid (4) gave a viscous oil which solidified on trituration. Treatment with sodium azide gave a solid, the i.r. spectrum of which exhibited both azide and amide frequencies at 2150 and 1710 cm^{-1} respectively. Refluxing in benzene produced a small quantity of unidentified white solid, with a sharp absorption at 2280 cm^{-1} in the i.r. spectrum, but a satisfactory ^{1}H n.m.r. was not obtained. The reaction sequence was repeated on the N-benzyl derivative of cis-2-amidocyclopropane

carboxylic acid (8) formed from the anhydride (3) and benzylamine. As in the previous experiment i.r. spectra of the intermediates indicated that traces of azide and isocyanate were present, but the proton n.m.r. spectrum of the residue left after refluxing in benzene showed the presence of methyl and ethyl esters of the starting material (8). These were separated by chromatography, but no other material was obtained from the plate.

3.3 Synthesis and reactions of cis-2-carbomethyoxycyclopropyl-isocyanate (12)

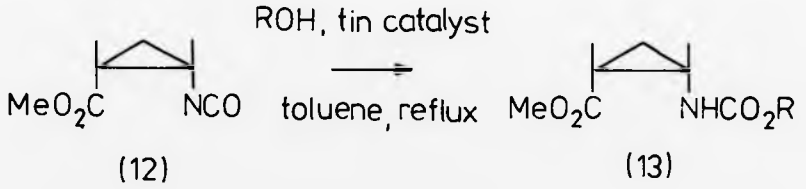
The isocyanate group, being suitable for functional group interconversion to an amine, led to the synthesis of compound (12) from cis-1,2-cyclopropane dicarboxylic acid anhydride (3) by route outlined below.



A Curtius reaction on cis-2-carbomethyoxycyclopropyl azide (11) gave cis-2-carbomethoxycyclopropylisocyanate (12) in overall 86% yield.

Proton n.m.r. spectra of the crude products from basic or acidic hydrolysis of isocyanate (12) indicated that ring opening and ester hydrolysis had occurred.

Various carbamate derivatives (13) of the isocyanate (12) were prepared by the general method of Francis and Thorne[131]. The isocyanate was refluxed with the respective alcohol in toluene, in the presence of a stannous octoate catalyst. The table lists the carbamates (13a - c) together with the overall yields from the anhydride (3).

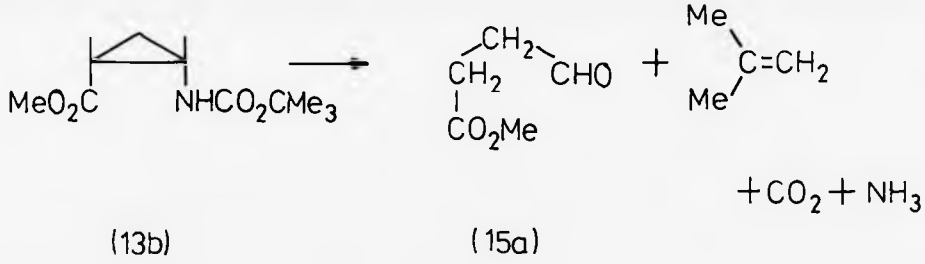


(12) (13)

	ROH	Carbamate R group	% yield
13a	CH_3OH	CH_3.	75.7
b	$(CH_3)_3COH$	$(CH_3)_3C$.	73
c	$(CH_3)_3SiCH_2CH_2OH$	$(CH_3)_3SiCH_2CH_2$.	63.6
d*	$C_6H_5CH_2OH$	$C_6H_5CH_2$.	45

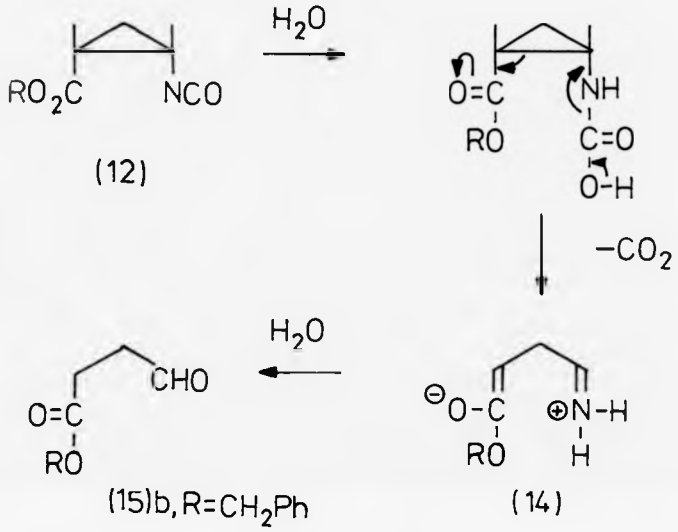
* taken from the literature[127].

The carbamate (13b) was subjected to hydrolysis using trifluoroacetic acid in benzene. Work up gave an oil having i.r. absorptions at 1750 and 1790 cm^{-1} and a ^{1}H n.m.r. spectrum consisting of a one proton singlet at δ9.85, a methyl singlet at δ3.7 and a multiplet at δ2.6 - 2.8 p.p.m., integrating for four protons. Further attempts to purify the oil failed, but a 2,4-dinitrophenylhydrazone (DNP) derivative was prepared, confirming the presence of an aldehyde group. The ring opened material was later identified as methyl-β-formylpropionate (15a).

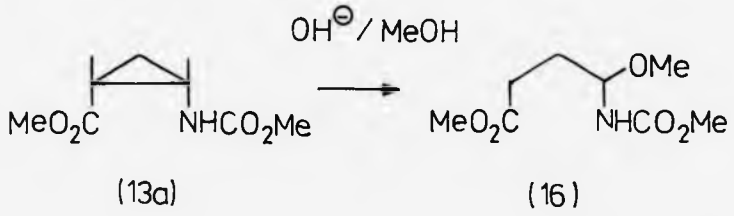


(13b) (15a)

The formation of this acylic product (15a) was similar to the hydrolytic ring opening of cyclopropylisocyanates proposed by Cannon and Garst[127]. Their mechanism involved initial hydration of the isocyanate group followed by decarboxylation and opening of the ring. Further hydrolysis converted the immonium intermediate (14) into the aldehyde (15b) which was isolated as its 2,4-DNP derivative.



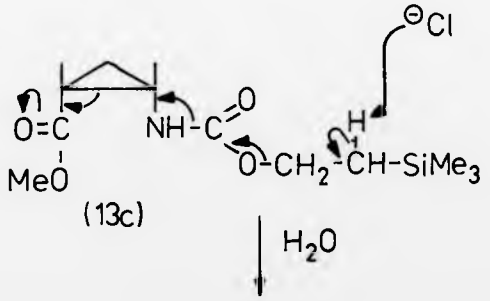
In an attempt to prevent opening of the ring the methyl carbamate (13a) was exposed to very mild hydrolysis conditions on an OH^- loaded Amberlite column in methanol. The oil eluted, after bulb to bulb distillation, gave in the i.r. spectrum two carbonyl absorptions at 1730 and 1770 and an NH absorption at 3480 cm^{-1}. The ^1H proton n.m.r. spectrum consisted of a broad singlet at δ5.2-5.5 integrating for one proton, a doublet of triplets at δ4.6-5.0 with a 6Hz chemical shift integrating for one proton, a sharp singlet of six protons at δ3.7, a three proton singlet at δ3.3 and two multiplets (of two protons each) at δ2.3-2.55 and δ1.7-2.1 p.p.m.. The mass spectrum had a molecular ion of 174, 31 mass units (CH_3O) less than the true M^+ and the elemental analysis was in agreement with a molecular formula of $C_8H_{15}O_5N$. The proposed structure (16) is shown below.



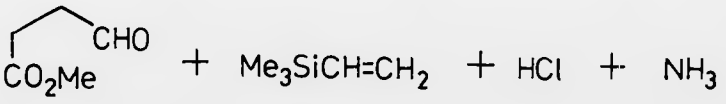
(13a) (16)

The product (16) corresponded to the reaction of methanol with the immonium intermediate in the hydrolytic ring opening of the cyclopropane ring.

In an attempt to hydrolyse trimethylsilylethyl carbamate (13c), stirring with zinc chloride in nitromethane followed by aqueous work up gave an oil which was shown by i.r., ^{1}H n.m.r., and b.p. to be methyl β-formylpropionate (15a).

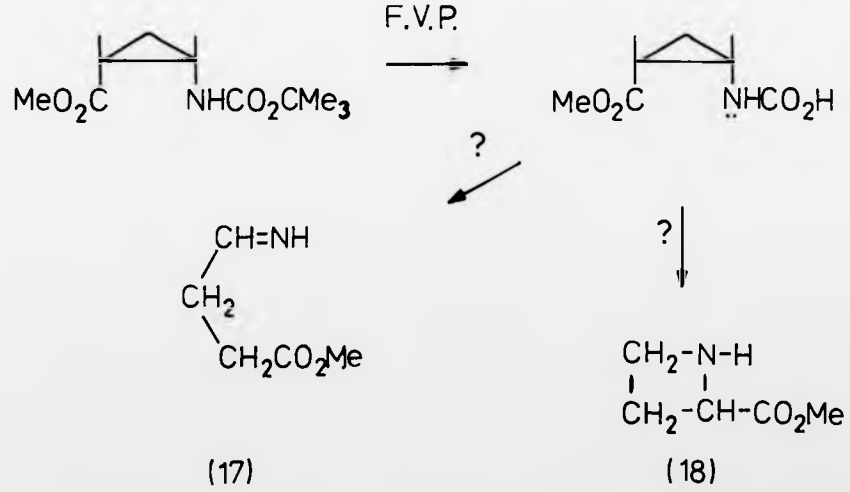


(13c)



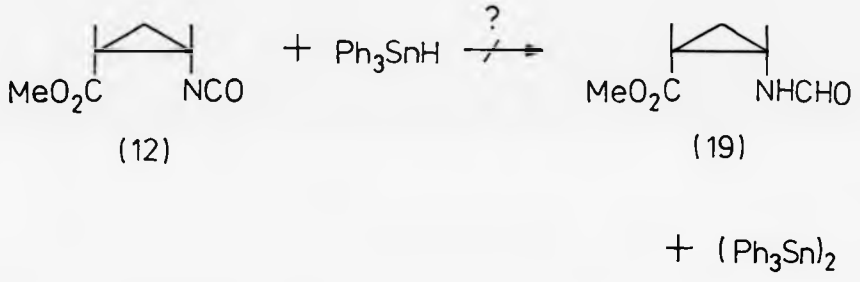
(15a)

It is apparent that ring opening poses a major problem and that it would occur whenever a mobile electron pair was present on a cyclopropylamine bearing a carbonyl group at C2. Flash vacuum pyrolysis of the t-butyl carbamate (13b) gave some interesting results. The crude pyrolyzate had a molecular ion of 115 mass units and a proton n.m.r. spectrum consisting of a sharp singlet at δ3.7 integrating for three protons, a pair of broad triplets at δ1.7-1.95 and δ2.3-2.6 p.p.m. integrating for approximately two and three protons respectively and a broad one proton singlet at δ1.3 p.p.m. Attempted bulb distillation resulted in decomposition and in another attempt at purification using a Florisil column, no identifiable material was eluted. Assuming ring opening to have occurred the available data on this product suggests two possible structures, methyl 4-imino butanoate (17) or an azetidine aminoacid ester (18); however no further structural evidence was obtained.



(17) (18)

An attempt was also made to convert the isocyanate into a suitable functional group other than the amino group. When cis-2-carbomethoxycyclopropylisocyanate (12) was treated with triphenyl tin hydride no trace of the expected product (19) was isolated. After chromatography of the crude reaction mixture the only material recovered was a very small amount of the methyl carbamate (13a).

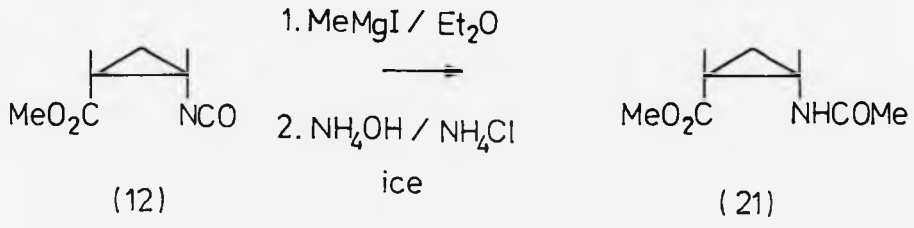


(12) (19)

3.4 Synthesis and reactions of cis-2-carbomethoxy-(N-acetyl)-cyclopropylamine (21)

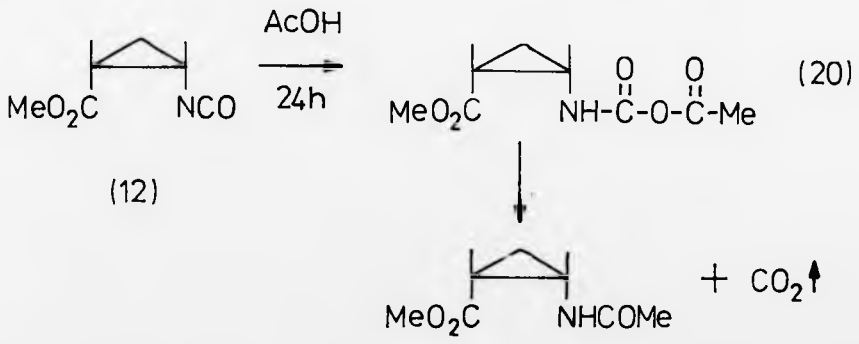
The isocyanate (12) provided the basic framework for the target molecule but it had now become necessary to avoid the primary cyclopropylamine (2) or any other related structure prone to ring opening. One general reaction of isocyanates involves their treatment with alkyl magnesium reagents forming N-substituted amides[135]. A Grignard reaction on cis-2-carbomethoxy cyclopropylisocyanate (12) gave, after column chromatography, a product which was shown by elemental analysis to have the formula $C_7H_{11}NO_3$. The proton n.m.r. spectrum contained in addition to the cyclopropane ring protons and ester protons, a three proton singlet at δ1.4, and a broad

one proton signal at δ6.5 p.p.m. The mass spectrum and i.r. spectrum confirmed the structure of cis-2-carbomethoxy-(N-acetyl)-cyclopropylamine (21).



(12) (21)

The N-substituted amide (21) was also produced when the isocyanate (12) was stirred in glacial acetic acid at room temperature for 24h. A slow evolution of carbon dioxide was observed, presumably from the anhydride intermediate (20).

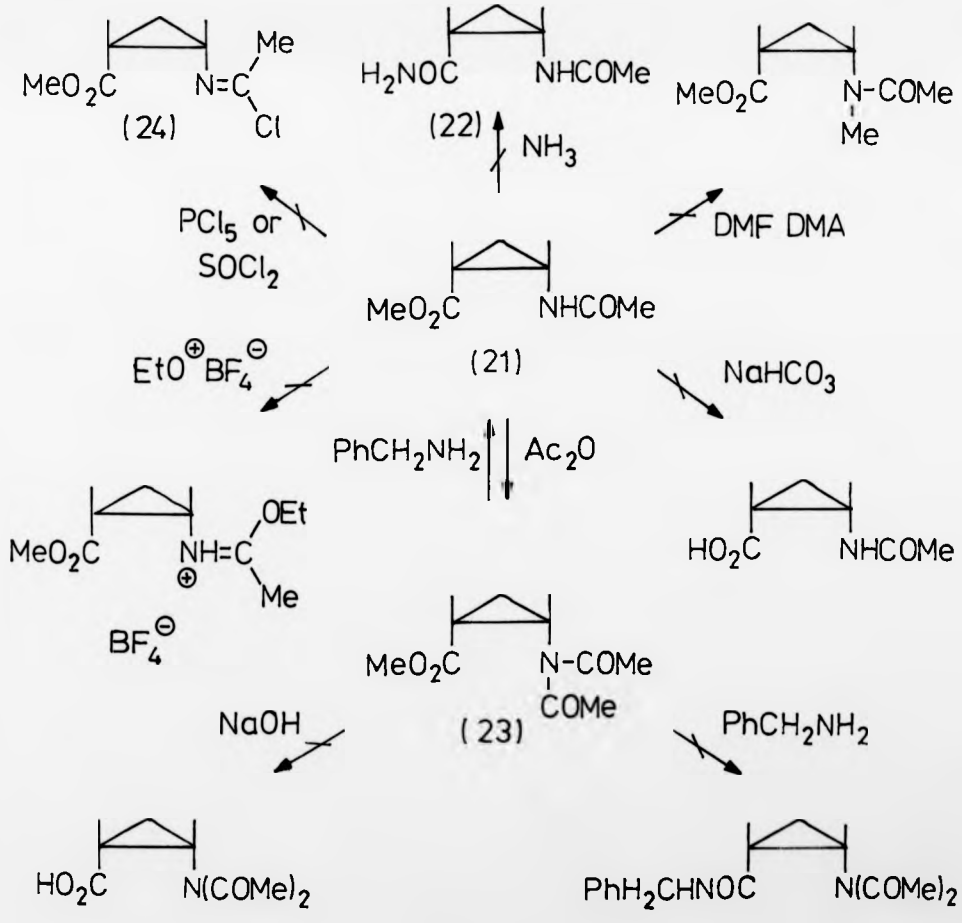


(12) (21)

The reactions attempted using compound (21) are summarized in scheme C.

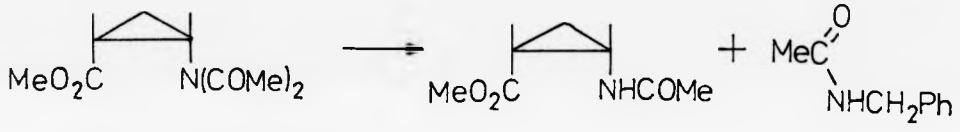
The N-substituted amide (21) was treated with a saturated solution of ammonia in methanol at 0 °C in an unsuccessful attempt to convert the ester into an amide (22). Proton n.m.r. evidence indicated that the cyclopropane ring had opened but no identifiable products were isolated when the residue was chromatographed.

Alkylation of compound (21) using dimethylformamide dimethylacetal (see scheme C) was unsuccessful, but acetylation with acetic anhydride gave the N,N-diacetyl derivative (23).



Scheme C

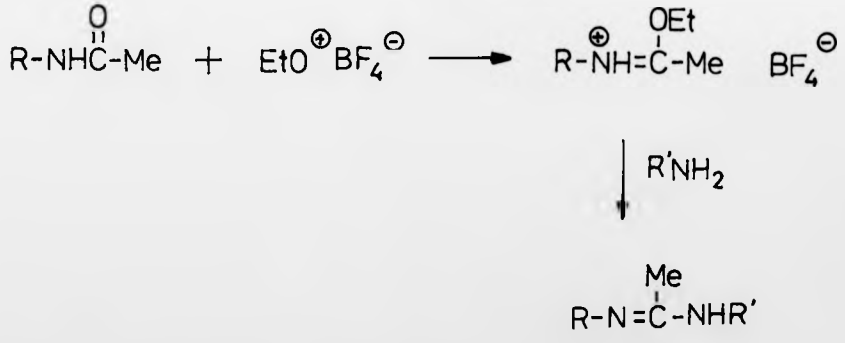
Treatment of compound (23) with dilute alkali hydrolysed the ester group and resulted in opening of the ring presumably as a result of deprotection of the amine. When cis-2-carbomethoxy--(N,N-diacetyl)cyclopropylamine (23) was refluxed with benzylamine in an attempt to convert the ester into an amide which was suitable for ring closure transamidation occurred. The only product isolated was cis-2-carbomethoxy-(N-acetyl)-cyclopropylamine (21).



(23) (21)

Hydrolysis of the methyl ester (21) was not accomplished with saturated sodium bicarbonate solution.

The oxygen atom of amides can be alkylated by oxonium salts to give salts of N-alkylimino esters[136]. These ions can then be treated with amines forming amidines as shown below.

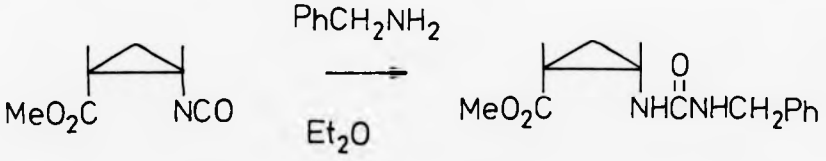


Unfortunately cis-2-carbomethoxy-(N-acetyl)cyclopropylamine (21) was unreactive towards triethyloxonium tetrafluoroborate.

Attempts to prepare the imidoyl chloride (24) of compound (21) using either thionyl chloride or phosphorus pentachloride gave only black tars.

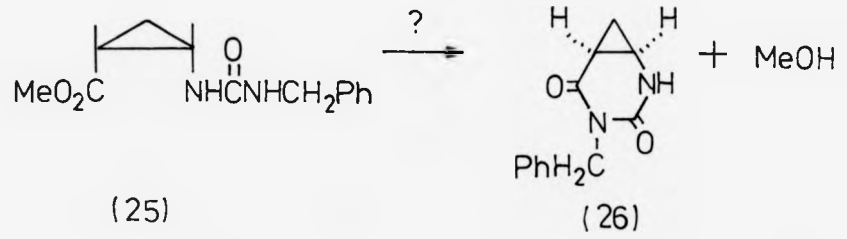
3.5 Synthesis and reactions of N-benzyl-N'-(2-methoxycarbonyl-cyclopropyl)urea (25)

On addition of benzylamine to cis-2-carbomethoxycyclopropyl-isocyanate (12) a vigorous reaction occurred, resulting in the formation of a white precipitate which on recrystallization, analysed for $C_{13}H_{16}N_2O_3$. ^1H N.m.r., i.r. and mass spectral data confirmed the product as the urea (25).



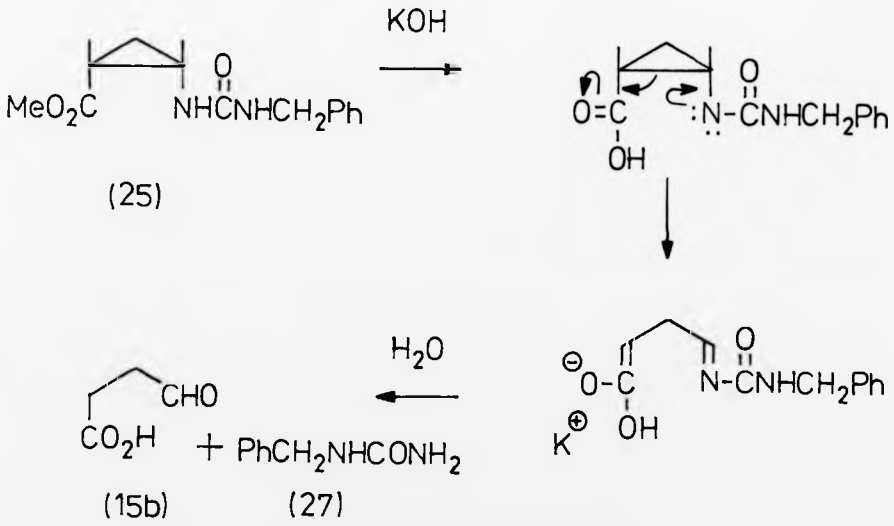
(12) (25)

Compound (25) possessed an ester and an amino function suitably placed for closure to a six membered ring. The product (26) from such an internal condensation would possess a structure similar to that of the target molecule.



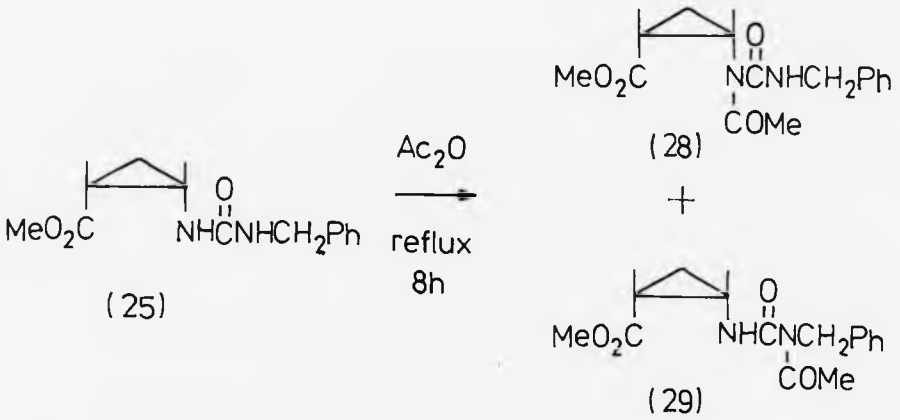
(25) (26)

No reaction was observed when thermal cyclization of compound (25) was attempted. Reaction with base led not to cyclization but to ring opening, the products of reaction being N-benzyl urea (27) and β-formylpropionic acid (15b).



(25) (15b) (27)

When compound (25) was subjected to prolonged (8h.) boiling in acetic anhydride only trace quantities of acylated material were obtained. Proton n.m.r. indicated that a mixture of monoacylated derivatives (28 and 29) had been formed.



No further attempts to prepare cyclopropapyrimidones were made.

EXPERIMENTAL

cis-Cyclopropane-1,2-dicarboxylic acid anhydride (3)

Prepared according to the method of Le Count et al.[128] b.p. 71-74 °C, 0.1 mm Hg (lit.,[128] b.p. 88-92 °C, 0.9 mm Hg.).

cis-2-Amidocyclopropane carboxylic acid (4)

cis-Cyclopropane-1,2-dicarboxylic acid anhydride (2 g, 0.018 mol), was stirred (5 min) with aqueous ammonia (5 ml,d. 0.880). The reaction mixture was evaporated to dryness, redissolved in water (10 ml) and treated with a solution of silver nitrate (3.5 g, 0.02 mol) in water (10 ml). The silver salt was collected by filtration and dissolved in hot water (100 ml). Hydrochloric acid (0.018 mol, 1M solution) was added dropwise with stirring, the reaction mixture cooled and the precipitate collected using a centrifuge. Evaporation of the filtrate gave cis-2-amidocyclopropane carboxylic acid in 91% yield, m.p. 175-177 °C (from water) (lit.,[129] m.p. 179-180 °C, yield 50%).

Attempted preparation of cis-2-aminocyclopropane carboxylic acid (2b)

To a mixture of sodium hydroxide (2.4 g, 0.06 mol) and compound (4) (1.29 g, 0.01 mol) in an ice/water mixture, was added bromine (1 ml, 0.02 mol) dropwise with stirring. After heating the reaction mixture at 75 °C until it was clear, dilute hydrochloric acid was added dropwise to neutralize the solution, which was extracted with ether (3 x 100 ml). Removal of the ether in vacuo left a negligible residue as did continuous extraction of the aqueous layer.

Attempted preparation of cis-2-amidocyclopropylisocyanate (6)

A suspension of cis-2-amidocyclopropane carboxylic acid (4) (1.3 g, 0.01 mol) in acetic anhydride (5 ml) was treated dropwise with perchloric acid (1.3 ml of 62% solution) with swirling and occasional cooling. The oil was pipetted from the reaction mixture and triturated with ether to give a white solid, compound (5), which was added in small portions to a stirred solution of sodium azide (1.34 g, o.o2 mol) in a mixture of water (6 ml) and acetone (11 ml). The acetone was removed in vacuo at room temperature and the oil extracted with ether (3 x 20 mls); the combined extracts were dried ($MgSO_4$) and the ether removed in vacuo leaving the crude azide, i.r. (cm^{-1}) 3430, 3010, 2150, 1740 and 1700.

cis-2-Benzylamidocyclopropane carboxylic acid (8)

Benzylamine (5.45 ml, 0.05 mol) was added dropwise with stirring to a suspension of cis-1,2-cyclopropane dicarboxylic acid anhydride (5.6 g, 0.05 mol) in chloroform (50 ml). The reaction mixture was refluxed (0.2h.), cooled, and the solvent removed in vacuo. Trituration with diethyl ether gave the product (8) in 96.5% yield, m.p. 90 °C (from diethyl ether/chloroform).

Analysis found (%) C 65.92 H 5.94 N 6.42,

$C_{12}H_{13}NO_3$ required (%) C 65.75 H 5.94 N 6.39.

I.r. (cm^{-1}) 3460, 3320, 1730.

^1H N.m.r. (δ, p.p.m.) 1.3-1.7 (2H, m), 1.8-2.1 (2H, m), 4.3-4.4 (2H, d, J = 6Hz), 7.25 (5H, s), 7.5 (1H, broad s, exch. D_2O), 8.0 (1H, broad t, exch. D_2O).

M/e mass units (%) 219 (M^+ 1.9), 201 (5.2), 174 (10.8 $M^+ - CO_2H$), 131 (1.3), 128 (1.2 $M^+ - CH_2Ph$), 107 (10.7), 106 (43.2), 91 (30.4 CH_2Ph), 79 (13.4), 77 (9.1 Ph), 69 (10.2), 68 (12.4), 55 (10.7), 45 (2.5 CO_2H), 41 (9.1), 40 (12.1).

Attempted preparation of cis-2-benzylamidocyclopropylisocyanate

To a suspension of the amide (4) (2.05 g, 0.01 mol) in acetic anhydride (10 ml) was added perchloric acid (1.2 ml of 62% solution) dropwise, with swirling and ice cooling. Trituration with diethyl ether produced a thick oil which was dissolved in acetone (15 ml) and added dropwise to a solution of sodium azide (0.98 g, 0.015 mol) in water (8 ml). After 10 min. the acetone was removed in vacuo at room temperature, the aqueous solution extracted with ether, dried ($MgSO_4$) and evaporated to give the azide, i.r. (cm^{-1}) 3440, 3010, 2140, 1720 and 1675. The azide was dissolved in benzene (30 ml) and refluxed (4h.). Evaporation of the solvent gave an oil (0.7 g), i.r. (cm^{-1}) 3460, 3340 (broad), 3020, 2270, 1730 and 1690, shown by t.l.c. to contain two main components. The oil was applied to a chromatotron using 50% ethyl acetate in petroleum ether (b.p. 40-60 °C) as eluant. First from the plate was the ethyl ester of the starting material identified by its ^1H n.m.r. spectrum; (δ, p.p.m.) 1.1-1.3 (3H, t), 1.2-1.7 (2H, m), 1.85-2.1 (2H, m), 3.9-4.2 (2H, q), 4.3-4.4 (2H,d), 6.4 (1H, br.s, exch. D_2O), 7.3 (5H, s). The second product was the methyl ester of the starting material; ^1H n.m.r.(δ, p.p.m.) 1.1-1.7 (2H, m), 1.8-2.1 (2H, m), 3.6 (3H, s), 4.3-4.4 (2H, d), 6.4 (1H, br.s, exch. D_2O), 7.3 (5H, s). These products were obtained in trace quantities and were not purified any further.

cis-2-Carbomethoxycyclopropanecarboxylic acid (9)

Prepared according to the procedure of Wheeler et al.[129] m.p. 42-44 °C (lit.,[129] m.p. 51-52 °C).

cis-2-Carbomethoxycyclopropanecarbonyl chloride (10)

Prepared according to the method of Cannon and Garst[127] b.p. 68 °C, 0.7 mm Hg(lit.,[127] b.p. 52-53 °C, 0.35 mm Hg).

cis-2-Carbomethoxycyclopropyl isocyanate (12)

To a cold solution of the acid chloride (10) (12.7 g, 0.078 mol) in acetone (200 ml) was added sodium azide (5.5 g, 0.085 mol) in water (12 ml). The reaction mixture was vigorously stirred throughout the addition. After 0.25h., water (300 ml) was added and the solution extracted with dichloromethane (3 x 100 ml), dried ($MgSO_4$), filtered and evaporated to give crude azide (11) in 93% yield. The azide (12.3 g, 0.073 mol) was refluxed in dry benzene (50 ml, 4h.) then the solvent was removed in vacuo leaving the isocyanate (12) in quantitative yield. Distillation did not improve the purity of compound (12) and chromatography led to ring opening with formation of compound (15a) therefore a satisfactory analysis was not obtained.

I.r. (cm^{-1}) 2300, 1750.

^1H N.m.r. (δ, p.p.m.) 1.1-1.5 (2H, m), 1.7-2.1 (1H, m), 2.8-3.1 (1H, m), 3.7 (3H, m).

M/e mass units (%) 141 (M^+, 22), 98 (43, M^+ - HCNO), 86 (100, M^+ - CHNCO), 82 (72, M^+ - CO_2Me), 59 (45), 55 (48), 54 (47), 27 (50).

Hydrolysis of cis-2-carbomethoxycyclopropyl isocyanate

An aqueous solution of potassium hydroxide (1.25 g in 2.5 ml) was stirred vigorously with a solution of the isocyanate (0.5 g) in benzene (5 ml) for 0.5h. The organic layer was separated, dried ($MgSO_4$) and evaporated in vacuo leaving a negligible residue. Neutralization of the aqueous layer and further extraction did not yield any further material.

cis-2-Carbomethoxy-(N-carbomethoxy)cyclopropylamine (13a)

A solution of isocyanate (12) (2.5 g, 0.018 mol), methanol (0.8 ml, 0.018 mol) and stannous 2-ethylhexanoate catalyst (3 drops) in dry toluene (15 ml) was heated at 90 °C (1h.) with stirring. Removal of the solvent in vacuo left a yellow oil which solidified on trituration with light petroleum ether (b.p. 40-6o °C) giving cis-2-carbomethoxy-(N-carbomethoxy)cyclopropylamine (13a) in 96% yield, m.p. 56 °C (from cyclohexane)

Analysis found (%) C 48.66 H 6.19 N 8.29,

$C_7H_{11}NO_4$ required (%) C 48.55 H 6.36 N 8.09.

I.r. (cm^{-1}), 3460, 1750.

^1H N.m.r. (δ, p.p.m.) 1.1-1.5 (2H, dt, J = 6Hz), 1.7-2.1 (1H, q, J = 6Hz), 3.1-3.5 (1H, q, J = 6Hz), 3.7 (6H, s), 5.3 (1H, br.s, exch. D_2O).

M/e mass units (%) 173 (M^+ 17.6), 142 (11.8), 141 (64.7), 114 (82), 98 (41.2), 82 (100), 59 (76.5), 55 (58.8), 42 (53).

cis-2-Carbomethoxy-(N-carbo-t-butyloxy)cyclopropylamine (13b)

A solution of isocyanate (12) (2.5 g, 0.018 mol), t-butanol (1.7 ml, 0.018 mol) and stannous-2-ethyl hexanoate (3 drops) in dry toluene (15 ml) was heated at 90 °C (1h.). Work up gave the product (13b) in 92% yield, m.p. 68 °C (from cyclohexane).

Analysis found (%) C 55.79 H 8.21 N 6.48,

$C_{10}H_{17}O_4N$ required (%) C 55.81 H 7.91 N 6.51.

I.r. (cm^{-1}) 3430, 1720.

^1H N.m.r. (δ, p.p.m.) 1.1-1.4 (2H, m), 1.5 (9H, s), 1.7-2.0 (1H, m), 3.1-3.4 (1H, m), 3.7 (3H, s), 5.2 (1H, br.s, exch. D_2O).

M/e mass units (%) 215 (M^+ 9.3), 159 (46.3), 142 (44.4), 128 (27.7), 115 (76), 110 (70.4), 100 (92.6), 98 (79.6), 87 (22.2), 84 (85.2), 83 (92.6), 82 (66.6), 66 (37.0), 59 (79.6), 58 (87.0), 57 (100.0), 56 (96.3), 55 (92.6).

cis-2-Carbomethoxy-(N-carbo[β-trimethylsilylethyl]oxy)-cyclopropylamine (13c)

A solution of isocyanate (12) (1.9 g, 0.0135 mol), trimethylsilylethanol (2 ml, 0.014 mol) and stannous-2-ethyl hexanoate (3 drops) in toluene (15 ml) was heated at 90 °C (1.5h.) with stirring. The cooled reaction mixture was washed with water, dried ($MgSO_4$) and evaporated in vacuo to a yellow oil. The residue was chromatographed on Florisil (80 g) eluting with increasing quantities of chloroform in light petroleum ether (b.p. 40-60 °C). The product (13c) was eluted as a colourless oil, b.p. 104-106 °C, 11 mm Hg, in 80% yield.

Analysis found (%) C 51.22 H 7.98 N 5.38,

$C_{11}H_{21}NO_4Si$ required (%) C 50.97 H 8.11 N 5.41.

I.r. (cm^{-1}) 3450, 1730.

^1H N.m.r. (δ, p.p.m.) 0.8-1.1 (2H, dd, J = 8Hz), 1.1-1.35 (2H, dt, J = 8Hz), 1.8-2.05 (1H, q, J = 8Hz), 3.1-3.6 (1H, quintet, J = 8Hz), 3.65 (3H, s), 4.0-4.3 (2H, dd, J = 8Hz), 5.5 (1H, br.s, exch. D_2O).

M/e mass units (%) 259 (M^+ 0.2), 200 (0.4), 186 (0.4), 158 (0.6), 114 (1.1), 101 (22.2), 99 (1.2), 73 (100), 40 (2.2).

Hydrolysis of cis-2-carbomethoxy-(N-carbo-t-butyloxy)-cyclopropylamine (13b)

Trifluoroacetic acid hydrolysis was performed according to the general method of Rafferty[132]. The carbamate (13b) (0.5 g) and trifluoroacetic acid (1 ml) in benzene (1 ml) were stirred (0.5h.) at room temperature. The solvent and excess trifluoroacetic acid were removed in vacuo and the residue treated with saturated sodium bicarbonate solution (3 mls). Extraction with chloroform (3 x 10 ml) and drying ($MgSO_4$) gave on evaporation a brown oil, i.r. (cm^{-1}) 1750 and 1790, ^1H n.m.r. (δ, p.p.m.) 2.6-2.8 (4H, m), 3.7 (3H, s), 9.85 (1H, s).

Methyl 4-carbomethoxyamino-4-methoxy-butanoate (16)

The carbamate (13a) (0.5 g) in methanol (3 ml) was applied to an OH^- loaded Amberlite column (Amberlite IRA - 400 resin washed with 10% aqueous sodium hydroxide, then water, then methanol) and eluted with methanol. Evaporation of the solvent gave the product (16) in quantitative yield, b.p. 112 °C, 0.02 mm Hg.

Analysis found (%) C 46.72 H 7.21 N 7.13,

$C_8H_{15}O_5N$ required (%) C 46.83 H 7.32 N 6.83.

I.r. (cm^{-1}) 3480, 1750.

^1H N.m.r. (δ, p.p.m.) 1.7-2.1 (2H, m), 2.3-2.55 (2H, m), 3.3 (3H, s), 3.7 (6H, s), 4.6-5.0 (1H, m), 5.2-5.5 (1H, br.s, exch. D_2O).

M/e mass units (%) 174 (63.8, $M^+ - CH_3CO$), 142 (50), 131 (19.4 $M^+ - NHCO_2Me$), 118 (100% $MeO.CH.NHCO_2Me$), 115 (16.6), 114 (91.6), 82 (22.2), 75 (13.8), 70 (41.6), 59 (27.7).

Methyl β-formylpropionate (15a)

Anhydrous zinc chloride (7.9 g, 0.0579 mol) was added to a solution of carbamate (13c) in dry nitromethane (40 ml) under nitrogen and stirred (0.25h.) at room temperature. The reaction mixture was filtered, and the filtrate evaporated in vacuo. The residue was partitioned between ethyl acetate (75 ml) and water (35 ml), the ethyl acetate layer washed with water (2 x 30 ml), dried ($MgSO_4$) and evaporated down to give the product (15a) in quantitative yield, b.p. 60 °C, 11 mm Hg (lit.,[133] b.p. 69-71 °C, 15 mm Hg).

Flash vacuum pyrolysis of cis-2-carbomethoxy-(N-carbo-t--butyloxy)cyclopropylamine (13b)

Compound (13b) (0.2 g) was heated to 50 °C and pyrolyzed at 500 °C and 0.02 mm Hg. The pyrolyzate was trapped on a cold finger at -70 °C and removed by washing with ice cold dichloromethane (100 ml). Evaporation of the solvent gave a colourless oil which was mainly one compound by thin layer chromatography in a 50% mixture of ethyl acetate and petroleum ether (b.p. 40-60 °C).

I.r. (cm^{-1}) 3400, 3000 and 1750.

^1H N.m.r. (δ, p.p.m.) 1.3 (1H, br.s), 1.7-1.95 (2H, br.t), 2.3-2.6 (3H, br.t), 3.7 (3H, s).

M/e mass units. A.P. 115 (M^+).

The oil decomposed on bulb distillation, chromatography and on standing more than 3 days, and therefore no satisfactory analysis was obtained.

Reaction between cis-2-carbomethoxycyclopropylisocyanate (12) and triphenyl tin hydride

Triphenyl tin hydride (10 g, 0.028 mol), weighed in a dry bag, was added to the isocyanate (12) (2 g, 0.014 mol) under nitrogen. The reactants after stirring at 80 °C (3h.) gave, on cooling, a pale yellow solid which was extracted with hot chloroform. Evaporation of the combined chloroform extracts gave hexaphenylditin (1 g) m.p. 180-220 °C. Prolonged extraction (2h.) of the yellow residue with water, gave, after evaporation, a yellow oil which was applied to a chromatotron using ethyl acetate as eluant. The first band from the plate was cis-2-carbomethoxy-(N-carbomethoxy)cyclopropylamine (13a), (0.2 g), m.p. 54-56 °C. The rest of the material eluted remained unidentified.

cis-2-Carbomethoxy-(N-acetyl)-cyclopropylamine (21)

Method a. Methyl magnesium iodide (0.04 mol) was prepared from dry magnesium (0.97 g, 0.04 mol) and methyl iodide (2.5 ml, 0.04 mol) in dry diethyl ether (50 ml). A solution of the isocyanate (12) (5g, 0.036 mol) in diethyl ether (25 ml) was added dropwise to the Grignard reagent, with ice/water cooling, then stirred for a further 0.5h. at room temperature. The reaction mixture was poured onto ice (50 g) and 15% ammonium chloride in ammonium hydroxide solution (2 g in 14 ml). The solution was firstly extracted with ether (250 ml) and the ether extract discarded, then with dichloromethane (3 x 100 ml). The combined dichloromethane extracts were dried ($MgSO_4$) and evaporated in vacuo to give an oil which solidified on trituration with diethyl ether. Column chromatography on Florisil (150 g) using increasing quantities of chloroform in petroleum ether (b.p. 40-60 °C) as eluant gave the

product (21) in 25% yield, m.p. 88 °C (from petroleum ether [b.p. 40-60 °C]/diethyl ether).

Analysis found (%) C 53.4 H 6.85 N 8.89,

$C_7H_{11}NO_3$ required (%) C 53.5 H 7.01 N 8.92.

I.r. (cm^{-1}) 3450, 3020, 1740, 1700.

^1H N.m.r. CD_3COCD_3 (δ, p.p.m.) 0.65-1.05 (2H, m), 1.4 (3H,s), 1.5-1.7 (1H, m), 2.8-3.2 (1H, m), 3.2 (3H, s), 6.5 (1H, br.s, exch. D_2O).

M/e mass units (%) 157 (M^+ 5.1), 115 (12.8), 114 (12.8), 100 (18 M^+ - $NCOCH_3$), 98 (61.5 M^+ - CO_2Me), 84 (25.6), 83 (38.5), 82 (12.8), 59 (5.1), 57 (100.o), 55 (23), 54 (5.1), 43 (77.0).

Method b. The isocyanate (12) (1 g, 0.0071 mol) and glacial acetic acid (0.4 ml, 0.0071 mol) were stirred together (24h.) at room temperature. The reaction mixture was chromatographed on Florisil (50 g) using increasing quantities of ethyl acetate in petroleum ether (b.p. 40-60 °C) as eluant. The product (21) was obtained in 24% yield.

Attempted preparation cis-2-carboxamido-(N-acetyl)--cyclopropylamine (22)

A solution of compound (21) (0.5 g) in dry methanol (10 ml) was cooled to 0 °C. Dry ammonia was bubbled into the solution until it was saturated. The reaction mixture was maintained at 0 °C for 24h., the solvent removed in vacuo and the residue applied to a chromatotron using 50% ethyl acetate in light petroleum ether (b.p. 40-60 °C) as eluant. The material from the plate did not exhibit cyclopropyl protons in the ^1H n.m.r. spectrum and remains unidentified.

Attempted alkylation of cis-2-carbomethoxy-(N-acetyl)--cyclopropylamine (21)

A solution of compound (21) (0.5 g, 3.2×10^{-3} mol) in toluene (25 ml) was heated with dimethylformamide dimethylacetal (0.45 ml, 3.3×10^{-3} mol) at 100 °C (5h.). Removal of solvent left starting materials.

cis-2-Carbomethoxy-(N,N-diacetyl)-cyclopropylamine (23)

Compound (21) (1 g) and acetic anhydride were refluxed (6h.), evaporated to dryness, and the residue applied to a chromatotron using chloroform as eluant. The product (23) was eluted as an orange oil in 93% yield. ^{1}H N.m.r. (δ, p.p.m.) 1.3-1.8 (2H, m), 2.1-2.45 (1H, m), 2.4 (6H, s), 2.9-3.2 (1H, m), 3.6 (3H, s). Attempts to bulb distill compound (23) failed, therefore no further purification was attempted.

Attempted ester hydrolysis of cis-2-carbomethoxy-(N,N-diacetyl)--cyclopropylamine (23)

A solution of compound (23) (0.5 g) in dichloromethane (25 ml) was stirred vigorously with 2M sodium hydroxide solution (25 ml) for 2h. The aqueous layer was separated, acidified, extracted with ethyl acetate (3 x 50 ml), dried ($MgSO_4$) and evaporated in vacuo to give a dark brown oil. The ^{1}H n.m.r. spectrum of this oil indicated ester hydrolysis, but no cyclopropyl protons were present.

Attempted preparation of cis-2-(N-benzyl)-carboxamido-(N,N--diacetyl)-cyclopropylamine

A solution of compound (23) (0.5 g, 2.5×10^{-3} mol) in dry toluene (25 ml) was refluxed (3h.) with benzylamine (0.3 ml, 2.8×10^{-3} mol). Evaporation of the solvent left an oil which was applied to the chromatotron using chloroform as eluant. The first

product from the plate was N-benzyl acetamide m.p. 58-60 °C (lit.,[137] m.p. 61 °C), the second component was cis-2-carbomethoxy--(N-acetyl)-cyclopropylamine (21). The total recovery accounted for 81% of the starting materials.

Attempted reaction of cis-2-carbomethoxy-(N-acetyl)-cyclopropylamine (21) with triethyloxonium tetrafluoroborate

To a solution of the amide (21) (1 g, 6.4 x 10^{-3} mol) in dry dichloromethane (20 ml) was added triethyloxoniumtetrafluoroborate (0.64 ml of a 1M solution in dichloromethane) under a dry nitrogen atmosphere. The reaction mixture was stirred overnight at room temperature under dry nitrogen. The volume was reduced by evaporation and diethyl ether added to precipitate out any salt formed but a quantitative recovery of unchanged starting material was obtained.

Reaction between cis-2-carbomethoxy-(N-acetyl-cyclopropylamine (21) and phosphorus pentachloride

To a suspension of the amide (21) (1 g,6.4 x 10^{-3} mol) in dry carbon tetrachloride (25 ml) was added phosphorus pentachloride (1.33 g, 6.4 x 10^{-3} mol). After 2 min a brown solid separated out which dissolved on heating. The reaction mixture was heated at 80 °C for 3h. Evaporation of the solvent gave a thick black oil whose ^{1}H n.m.r. spectrum gave no indication of cyclopropyl protons.

N-Benzyl-N'-(2-methoxycarbonylcyclopropyl)urea (25)

To a solution of the isocyanate (12) (1 g, 0.0071 mol) in diethyl ether (15 ml) was added, dropwise, a solution of benzylamine (0.77 ml, 0.0071 mol) in diethyl ether (10 ml). The reaction mixture was stirred for a further 15 min and filtered to give the product (25) in 81% yield, m.p. 140-143 °C (from abs. ethanol).

Analysis found (%) C 62.82 H 6.3 N 11.46,

$C_{13}H_{16}N_2O_3$ required (%) C 62.9 H 6.45 N 11.29.

I.r. (cm^{-1}) 3430, 1735, 1690.

^1H N.m.r. $(CD_3)_2SO$ (δ, p.p.m.) 0.85-1.2 (2H, m), 1.5-1.7 (1H, m), 2.8-3.2 (1H, m), 3.4 (3H, s), 4.0-4.1 (2H, d), 6.0 (1H, br.s, exch. D_2O), 6.4 (1H, br.s, exch. D_2O), 7.1 (5H, s).

M/e mass units (%) 248 (M^+ 6), 116 (6), 115 (30), 106 (6), 104 (8), 100 (24), 51 (14), 41 (12), 39 (16).

Attempted thermal cyclisation of N-Benzyl-N'-(2-methoxycarbonylcyclopropyl)urea (25)

The urea (25) was refluxed (6h.) in d_8 toluene with no change in the ^1H n.m.r. spectrum of the starting material.

Treatment of N-Benzyl-N'-(2-methoxycarbonylcyclopropyl)urea (25) with base

The urea (25) (0.5 g) was added to 5% potassium hydroxide solution (5 ml) at 75 °C. The solution was neutralized with glacial acetic acid and cooled in ice to give crystals of N-benzyl urea m.p. 144-6 °C (lit.,[133] 147 °C). Extraction of the aqueous layer with dichloromethane gave more N-benzyl urea. Evaporation of the aqueous layer gave an oily solid. The ^1H n.m.r. spectrum of the solid indicated the presence of ring opened material (15b, R=H).

Attempted acetylation of N-Benzyl-N'-(2-methoxycarbonylcyclopropyl)urea (25)

The urea (25) (0.5 g) was refluxed (6h.) with acetic anhydride (20 ml). The solvent was removed in vacuo and the residue applied to a Florisil column (30 g) eluting with increasing amounts of chloroform in petroleum ether (b.p. 40-60 °C). First from the column was a

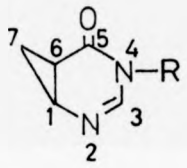
mixture of monoacylated products (28 mg) identified by the ^{1}H n.m.r. spectrum. Further separation was not attempted. Unreacted starting material was recovered when the column was stripped with methanol.

CHAPTER FOUR

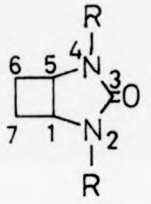
1,3-Diazepine precursors from imidazolones

4.1 Introduction

Previous attempts to prepare 2,4-diazabicyclo[4:1:0]heptan--5-ones (1) for ring expansion to a seven membered ring suggested as an alternative bicyclic diazepine precursor the 2,4-diazabicyclo-[3:2:0]heptan-3-one system(2).



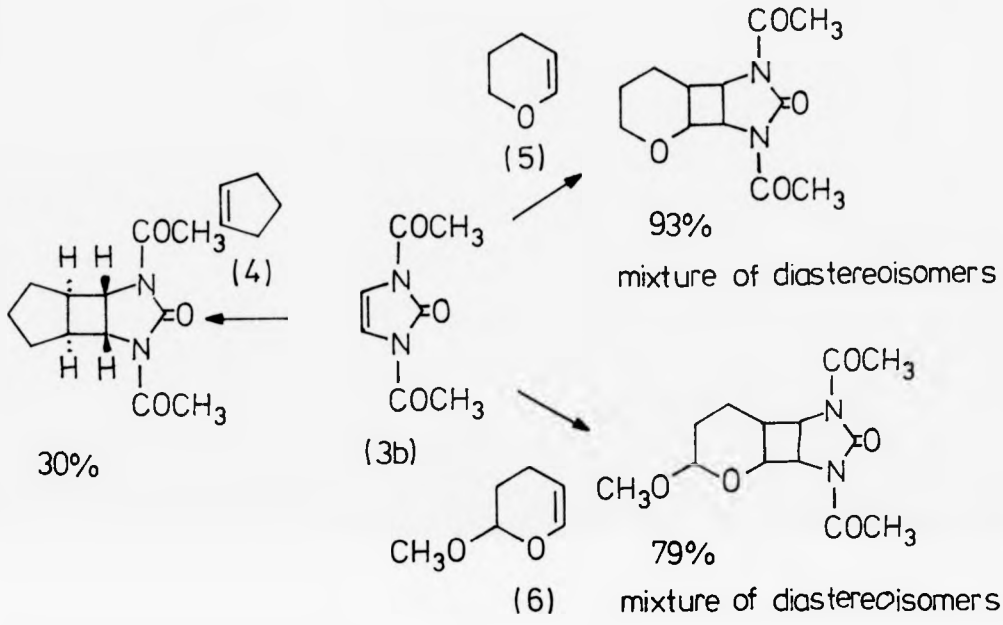
(1)



(2)

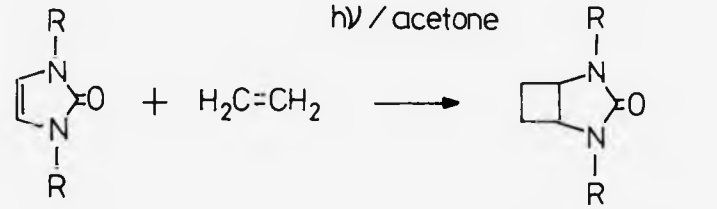
A simple means of forming this type of system is by the cycloaddition of an alkene to an imidazolone double bond.

Two reports of such systems have recently appeared in the literature. Whitney[140] performed several photochemical [2 + 2] cycloaddition reactions of olefins to 1,3-diacetyl-2-imidazolone (3b) using acetone as solvent and photosensitizer.



The adduct from the reaction with cyclopentene (4) was isolated by distillation, and the anti stereochemistry was assigned on the basis of a small coupling (< 1Hz) between the bridgehead protons. The use of enol ethers (5) and (6) in the photolysis gave good yields of cycloadducts which were mixtures of diastereoisomers that were not readily separable by chromatography.

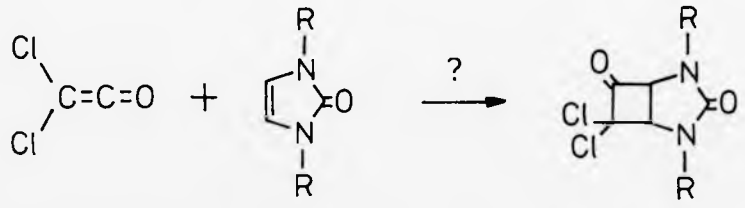
Hartmann et al.[150] have also synthesized 2,4-diazabicyclo-[3:2:0]heptan-3-ones (2) from the photochemical [2 + 2] cycloaddition of ethylene to the 2-imidazolones (3a) and (3b).



(3) a, R=H
b, R=$COCH_3$

(2) a, R=H
b, R=$COCH_3$

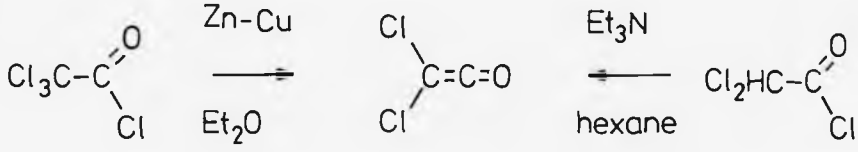
An alternative approach to the 2,4-diazabicyclo[3:2:0]-heptan-3-one system involved the addition of dichloroketene (8) to an imidazolone double bond in a [2 + 2] manner to form a cyclobutanone derivative (7).



(8) (3) (7)

Dichloroketene (8) has been used for some years in the synthesis of molecules containing a cyclobutanone fragment. Although electrophilic in nature, it shows a greater tendency to react in cycloaddition reactions rather than electrophilic addition-elimination reactions. Dichloroketene is easily polymerized and is therefore generated in situ in the presence of the other reactant. The two general methods of generating dichloroketene are the dehalogenation of trichloro-acetyl chloride by activated zinc in diethyl ether and the

dehydrohalogenation of dichloroacetyl chloride by triethylamine in hexane, as shown below.



(8)

There have been various reports[143-146] in the literature of improvements in the methodology of dichloroketene formation from trichloroacetyl chloride. Hassner and Krepski[143,144] have synthesized dichloroketene in the presence of an equimolar quantity of phosphorus oxychloride. The improved yields obtained by this method are attributed to the complexation of zinc chloride by phosphorus oxychloride which decreases the tendency of dichloroketene to polymerize. Bak and Brady[145] have found that a slow addition of trichloroacetyl chloride to the mixture of alkene and activated zinc improves the yield of cycloaddition, even to unreactive alkenes, by lowering the concentration of dichloroketene present at any one time and thus reducing polymerization of the ketene. Jeffs[146] has developed a method involving more vigorous conditions in which trichloroacetyl chloride is added to the reaction mixture fast enough to cause boiling of the solvent.

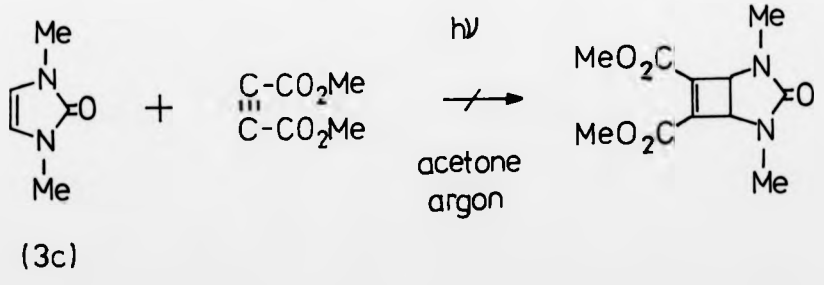
The other route by which dichloroketene may be prepared, the dehydrohalogenation of dichloroacetyl chloride, has been reported by Ghosez et al.[147].

Dichloroketene reacts with unactivated and electron rich alkenes to give αα-dichlorocyclobutanone cycloadducts. However there is no reaction with electron deficient alkenes. The reaction is both stereospecific, the original configuration being retained, and regiospecific, the most nucleophilic carbon atom of the alkene becoming attached to the α carbon atom of the ketene.

In this chapter are reported syntheses of some disubstituted imidazolones and the various attempts to convert them into 2,4-diazabicyclo[3:2:0]heptan-3-ones.

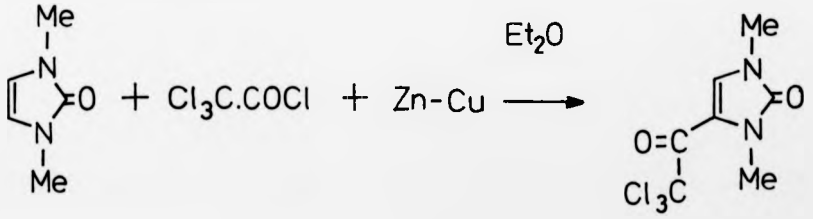
4.2 Synthesis and reactions of 1,3-dimethyl-2-imidazolone (3c)

The synthesis of 2-imidazolone (3a) from aminoacetaldehyde diethyl acetal has been reported by Duschinsky and Dolan[138]. Dialkylation of this compound (3a) using sodium hydroxide and dimethyl sulphate gave 1,3-dimethyl-2-imidazolone (3c) in 90% yield. In an attempt to achieve a photochemical [2 + 2] cycloaddition, the dimethylated material (3c) was irradiated with a 450 W lamp in the presence of dimethyl acetylenedicarboxylate using acetone as both solvent and photosensitizer. After 14h. most of the starting material was shown to have reacted by t.l.c., but when chromatographed on silica gel no identifiable products were isolated.



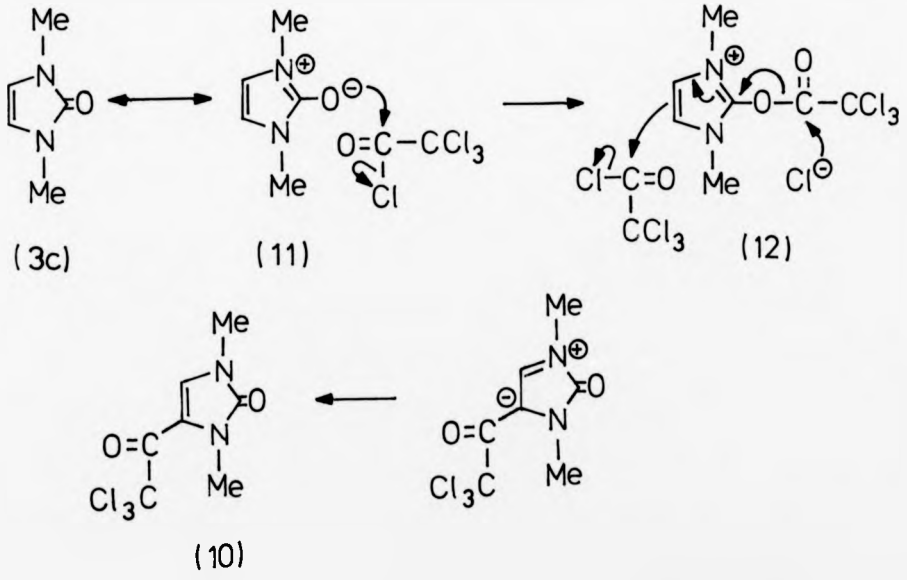
(3c)

Alternatively dichloroketene has been used[143-147] in [2 + 2] cycloaddition reactions. This reaction was first performed according to the general procedure of Jeffs[146]. After fast addition of trichloroacetyl chloride to an ethereal solution of 1,3-dimethyl-2--imidazolone (3c) and activated zinc (9), the reaction mixture was stirred overnight. Chromatography on alumina, eluting with a 50% solution of ethyl acetate in petroleum ether (b.p. 40-60 °C) gave a yellow crystalline solid (in 9% yield) having two carbonyl absorptions in the i.r. spectrum and a ^{1}H n.m.r. spectrum consisting of a sharp singlet at δ7.7 integrating for one proton and two sharp singlets at 3.45 and 3.55 p.p.m. each integrating for three protons, and indicating that the N-methyl groups were now non equivalent. The mass spectrum gave a molecular ion at 245, and the fragmentation pattern clearly indicated the presence of three chlorine atoms. Easy loss from the molecular ion of 117 and 145 mass units indicated the presence of a trichloroacetyl group. Elemental analysis confirmed the empirical formula as $C_7H_7Cl_3N_2O_2$ suggesting the structure (10).



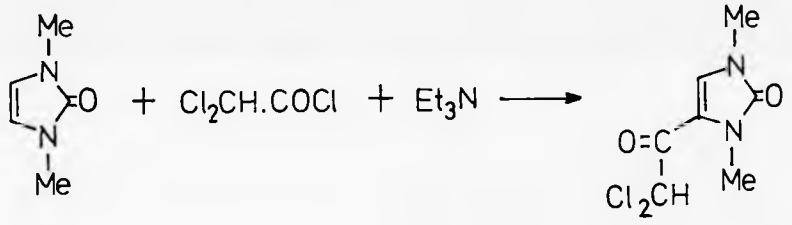
(3c) (9) (10)

Further elution gave no other products. The mechanism is unlikely to be that of Friedel Crafts acylation as this usually requires an aluminium chloride catalyst for the initial formation of an acylium ion. It is more reasonable to suppose that the ketone arose by electrophilic attack of trichloroacetyl chloride on the imidazolone. Obviously formation of this acetyl derivative competes successfully with the generation of dichloroketene. One possible mechanism involves shifting the charge on the starting imidazolone (3c) forming a dipolar species (11), acylation of which



produces a second intermediate (12). Reaction of compound (12) with a second molecule of trichloroacetyl chloride followed by rearrangement gives the product (10). On repeating the reaction using the method of Hassner and Krepski[143,144] the yield of 4-trichloroacetyl--1,3-dimethyl-2-imidazolone (10) was increased from 9 to 30%.

Treatment of 1,3-dimethyl-2-imidazolone (3c) with dichloroacetyl chloride in the presence of triethylamine according to the procedure of Ghosez et al.[147], gave on work up, a viscous brown oil which partly crystallized. Column chromatography on Florisil allowed the isolation of the dichloroacetyl derivative (13) m.p. 126 °C, in 28% yield, with spectral details similar to those of compound (10). The additional proton at δ6.3 p.p.m. in the n.m.r. spectrum was assigned to the $CHCl_2$ group.



(3c) (13)

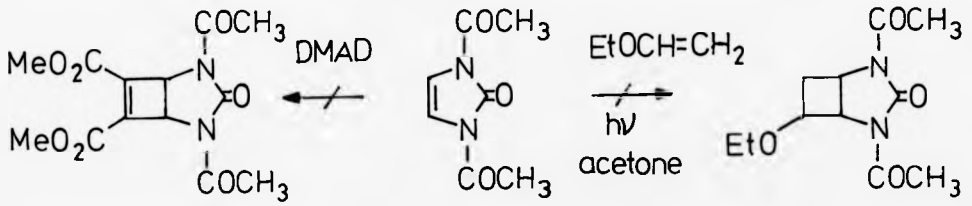
4.3 Synthesis and reactions of 1,3-diacetyl-2-imidazolone (3b)

The diacetyl derivative of 2-imidazolone (3a) was prepared[140] in 77% yield, by prolonged boiling in acetic anhydride.

Irradiation of 1,3-diacetyl-2-imidazolone (3b) in the presence of dimethyl acetylenedicarboxylate by the same procedure used in section 4.2 gave no identifiable products after attempted purification on a Chromatotron using chloroform and petroleum ether (b.p. 40-60 °C) as eluant.

To ensure that the conditions of photolysis used were correct, the photochemical reaction between compound (3b) and dihydropyran, reported by Whitney[140], was performed and the results obtained were comparable. The reaction was repeated using an acyclic enol

ether. Irradiation of ethyl vinyl ether, and compound (3b) by the general method, gave a viscous yellow oil shown by t.l.c. and the ^{1}H n.m.r. spectrum to contain no trace of the reactants. Column chromatography on Florisil using increasing amounts of chloroform in petroleum ether as eluant gave three different fractions. Repeated chromatography and distillation of these mixtures did not improve their purity but the mass spectra of these mixtures were notable for fragments at 168 corresponding to compound (3b), 84 [compound (3a)], 72 ($C_2H_5OCH.CH_2$), 45 (C_2H_5O) and 43 ($COCH_3$). The molecular ion at 240 mass units suggested the presence of compound (14) in the mixtures, but the ^{1}H n.m.r. spectra showed only four out of the five cyclobutane ring protons. Elemental analyses were not consistent with the formula of compound (14).



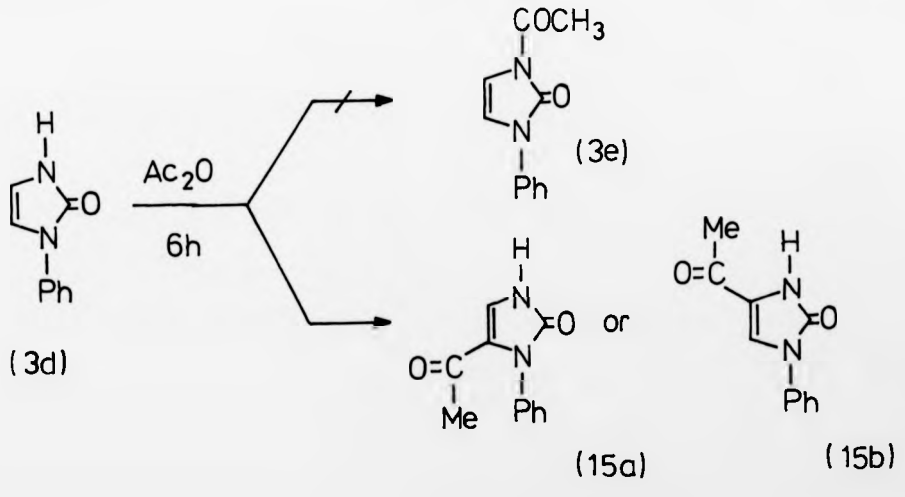
(3b) (14)

As anticipated, compound (3b) was unreactive to dichloroketene generated either from trichloroacetylchloride by Jeffs[146] method, or from dichloroacetylchloride by the method of Ghosez[147]. The two acetyl groups have a deactivating effect on the imidazole double bond making it electron deficient and hence inactive to dichloroketene.

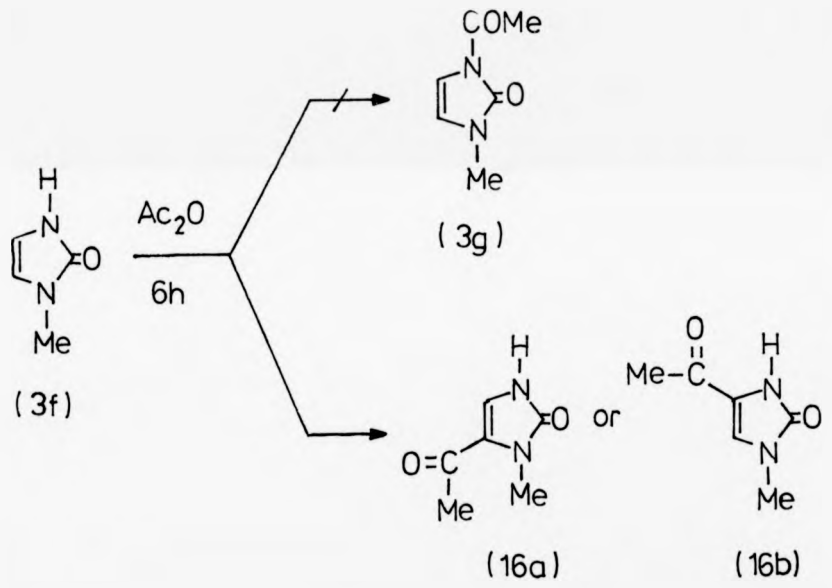
4.4 Attempted syntheses of other 1,3-disubstituted-2-imidazolones

Disubstituted imidazolones bearing different groups on each nitrogen were sought, in the hope that compounds of this type would have intermediate reactivity between the diacetyl (3b) and dimethyl imidazolones (3c).

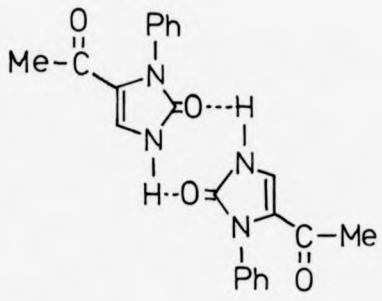
The procedure of Chen, Dauphinée and Forrest[148] was followed in the preparation of 1-phenyl-2-imidazolone (3d) from aminoacetaldehyde diethyl acetal. The product (3d) after boiling in acetic anhydride gave not the expected product (3e) but a crystalline solid m.p. 196-197 °C in 61% yield. The i.r. spectrum contained in addition to an NH absorption at 3470, two carbonyl absorptions at 1735 and 1675 cm^{-1}. Elemental analysis was consistent with the formula $C_{11}H_{10}N_2O_2$ indicating that acetylation had occurred, but the spectral data suggested that the acetyl group was attached to the double bond and not to the nitrogen atom. The presence of a large fragment corresponding to the loss of hydrogen cyanide is the only evidence in favour of structure (15a).



A similar result was obtained when 1-methyl-2-imidazolone (3f), synthesized by a literature[149] procedure, was boiled in acetic anhydride. The product obtained in 57% yield was 5-acetyl-1-methyl-2-imidazolone (16a). Again, the only evidence for structure (16a) is the loss of hydrogen cyanide in the mass spectrum.



When a $CDCl_3$ solution of compound (15a) was treated with the shift reagent 'Eufod', the proton n.m.r. spectrum exhibited a downfield shift of the ortho protons of the phenyl group, and not the amide NH group. This can be explained by assuming the existence of hydrogen bonding between molecules, shown below, which prevents 'Eufod' co-ordination to the amide nitrogen, hence co-ordination occurred to the other nitrogen bearing the phenyl group.



EXPERIMENTAL

2-Imidazolone (3a)

Prepared according to the method of Duschinsky and Dolan[138] m.p. 248-250 °C (lit.,[138] m.p. 250-251 °C).

1,3-Dimethyl-2-imidazolone (3c)

Prepared by the addition of dimethylsulphate (9.6 ml, 0.1 mol) to a stirred solution of sodium hydroxide (4.0 g, 0.1 mol) and 2-imidazolone (3.0 g, 0.036 mol) in water (5 ml). The reaction mixture was heated to 100 °C, cooled, extracted with chloroform, the combined chloroform extracts dried ($MgSO_4$) and evaporated to an oil, which was purified by chromatography to give the product (3c), m.p. ca. 52 °C (hygroscopic) (lit.,[139] m.p. not recorded, product hygroscopic) in 90% yield.

1,3-Diacetyl-2-imidazolone (3b)

Prepared according to the method of Whitney[140] m.p. 101 °C (lit.,[140-142] m.p. 106 °C).

General photolysis procedure

Photolyses were performed by the general method of Whitney[140], at room temperature under a dry argon atmosphere with a 450 W lamp filtered with pyrex. Acetone (250 ml) was used as solvent and sensitizer with an excess of olefin (5-10 ml per g of starting material) present. Photolyses were followed by t.l.c. and work up consisted of removal of acetone in vacuo and chromatography of the crude oil.

Attempted preparation of 7-ethoxy-2,4-diacetyl-2,4-diazabicyclo[3:2:0]heptan-3-one (14)

Compound (3b) (1.5 g) and ethyl vinyl ether (10 ml in acetone

(500 ml) were irradiated (24h.) as described in the general procedure. Removal of solvent and chromatography of the residue on Florisil (100 g) using increasing quantities of chloroform in petroleum ether (b.p. 40-60 °C) gave three main fractions. These fractions were purified further by chromatography followed by distillation. The first fraction distilled at 90-100 °C, 0.05 mm Hg, and the second at 119-124 °C, 0.02 mm Hg, but the third fraction formed a tar when distillation was attempted. Analyses were not consistent with the expected product (14) but the ^{1}H n.m.r. and mass spectral data are recorded below.

^{1}H N.m.r. (δ, p.p.m.) 1.02-1.16 (3H, t), 2.53 (3H, s), 2.57 (3H, s), 2.75-3.07 (1H, m), 3.31-3.53 (2H, q), 4.04-4.25 (1H, m), 4.35-4.54 (1H, m), 4.82-4.98 (1H, m).

M/e mass units (%) 240 (M^+ 18), 168 (21, 3b), 84 (23, 3a), 72 (16, $C_2H_5OCH.CH_2$), 45 (19, C_2H_5O), 43 (38, $COCH_3$).

Activated zinc (9)

Prepared according to the method of Hassner and Krepski[143].

4-Trichloroacetyl-1,3-dimethyl-2-imidazolone (10)

Method a[143,144] To a vigorously stirred suspension of 1,3-dimethyl-2-imidazolone (3c) (1 g, 8.93 x 10^{-3} mol) in dry diethyl ether (20 ml) and activated zinc (0.64 g, 0.0098 mol) under dry nitrogen, was added dropwise a solution of freshly distilled trichloroacetylchloride (1.04 ml, 0.0093 mol) and phosphorus oxychloride (0.87 ml, 0.0093 mol) (distilled from potassium carbonate) in diethyl ether (10 ml) over 1h. The reaction mixture was refluxed (2h.), cooled, and the ether solution decanted. The zinc mass was washed with ether (2 x 10 ml) and the volume of the combined ether

extracts reduced to 10 ml. The zinc salts were precipitated out with light petroleum ether (b.p. 40-60 °C), filtered and the filtrate washed with saturated sodium bicarbonate (20 ml) and water (20 ml). The organic solution was dried (Na_2SO_4) and evaporated in vacuo to a yellow solid. Recrystallization from cyclohexane gave the product (10) m.p. 110 °C in 30% yield.

Analysis found (%) C 32.63 H 2.54 N 10.93,

$C_7H_7Cl_3N_2O_2$ required (%) C 32.62 H 2.72 N 10.87.

I.r. (cm^{-1}) 1735, 1695. U.v., nm ($\log_{10}\varepsilon$) 334 (3.62).

^1H n.m.r. (δ, p.p.m.) 3.45 (3H, s), 3.55 (3H, s), 7.7 (1H, s).

M/e mass units (%) 262 (M^{+6}, 0.3), 260 (M^{+4}, 4), 258 (M^{+2}, 15), 256 (M^+, 15), 197 (3), 195 (15), 193 (21), 140 (12), 139 (100 , $M^+ - CCl_3$), 111 (18, $M^+ - COCCl_3$), 84 (2.5), 83 (18), 68 (5), 67 (6).

Method b[146] To a vigorously stirred suspension of 1,3-dimethyl-2-imidazolone (3c) (1.5 g, 0.013 mol) in dry diethyl ether (100 ml) and activated zinc (6.5 g) under dry nitrogen, was added a solution of trichloroacetylchloride (9 ml, 6 equiv.) in diethyl ether (60 ml) at such a rate as to cause initial boiling and then maintain a gentle reflux. The reaction mixture was stirred overnight at room temperature and then treated as in method a. Column chromatography on alumina (IV) using 50% ethyl acetate in petroleum ether (b.p. 40-60 °C) gave the product (10) m.p. 110 °C in 9% yield.

4-Dichloroacetyl-1,3-dimethyl-2-imidazolone (13)

To a refluxing solution of 1,3-dimethyl-2-imidazolone (3c) (1.4 g, 0.0125 mol) in dry hexane (120 ml) was added triethylamine

(0.9 ml, 6.3×10^{-3} mol) (distilled from potassium hydroxide). A solution of freshly distilled dichloroacetylchloride (0.6 ml, 6.25×10^{-3} mol) in hexane (20 ml) was added over 0.75h. and refluxing continued for 3h. The reaction mixture was washed successively with water (100 ml), 5% hydrochloric acid (100 ml), saturated sodium bicarbonate solution (100 ml), and water (50 ml). The hexane solution was dried (Na_2SO_4), evaporated, and chromatographed on Florisil giving the dichloroacetyl derivative (13) m.p. 126 °C (from benzene) in 28% yield.

Analysis found (%) C 37.40 H 3.42 N 12.68,

$C_7H_8Cl_2N_2O_2$ required (%) C 37.67 H 3.59 N 12.56.

I.r. (cm^{-1}) 1730, 1695. U.v., nm ($\log_{10}\varepsilon$), 318 (4.09).

^1H N.m.r. (δ, p.p.m.) 3.4 (3H, s), 3.6 (3H, s), 6.3 (1H, s), 7.6 (1H, s).

M/e mass units (%) 226 (M^{+4}, 3), 224 (M^{+2}, 19), 222 (M^+, 28), 159 (23), 139 (100, $M^+ - CHCl_2$), 111 (24, $M^+ - COCHCl_2$), 90 (12), 85 (7), 83 (26), 82 (10), 55 (9), 43 (20).

1-Phenyl-2-imidazolone (3d)

Prepared according to the method of Chen, Dauphinee and Forrest[148], m.p. 123 °C (lit.,[147] m.p. 123 °C).

5-Acetyl-1-phenyl-2-imidazolone (15a)

Compound (3d) (3 g, 0.019 mol), acetic anhydride (15 ml) and trifluoroacetic acid (0.4 ml) were boiled (6h.), cooled, and evaporated in vacuo. The residue was chromatographed on Florisil (120 g) using increasing amounts of ethyl acetate in petroleum ether (b.p. 40-60 °C) as eluant. The product (15a) was eluted in 61% yield, m.p. 196-197 °C (from ethyl acetate).

Analysis found (%) C 65.40 H 4.90 N 14.03,

$C_{11}H_{10}N_2O_2$ required (%) C 65.40 H 4.95 N 13.86.

I.r. (cm^{-1}) 3470, 1735, 1675.

U.v., nm ($\log_{10}\varepsilon$) 300 (4.04).

^1H N.m.r. (δ, p.p.m.) 2.38 (3H, s), 7.26-7.65 (6H, m, phenyl and H4), 9.00 (1H, br.s, exch. D_2O).

M/e mass units (%) 202 (M^+, 35.3), 159 (5.7, $M^+ - COCH_3$), 132 (12), 131 (13.2), 104 (14), 77 (25.6), 51 (13), 43 (15.5).

1-Methyl-2-imidazolone (3f)

Prepared according to the method of Leonard and Wiemar[149] m.p. 140 °C (lit.,[149] m.p. 139-140.5 °C).

5-Acetyl-1-methyl-2-imidazolone (16a)

Compound (3f) (1.5 g, 0.015 mol), acetic anhydride (10 ml) and trifluoroacetic acid (0.2 ml) were boiled (6h.), cooled, and evaporated in vacuo. Repeated recrystallization from petroleum ether (b.p. 40-60 °C) and chloroform gave the product (16a) m.p. 178-181 °C (decomp.) in 57% yield.

Analysis found (%) C 50.86 H 5.47 N 20.00,

$C_6H_8N_2O_2$ required (%) C 51.42 H 5.71 N 20.00.

I.r. (cm^{-1}) 3460, 1720, 1660.

U.v., nm ($\log_{10}\varepsilon$) 283 (3.87).

^1H N.m.r. (δ, p.p.m.) 2.15 (3H, s), 3.15 (3H, s), 7.07-7.09 (1H, d, J = 2Hz), 10.7-10.8 (1H, br.s, exch. D_2O).

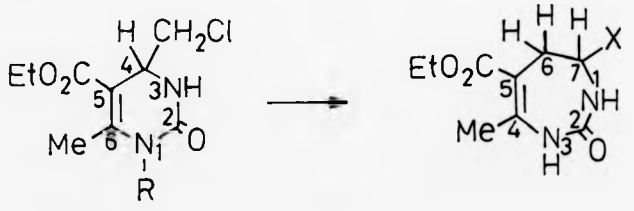
M/e mass units (%) 140 (M^+ 78), 125 (24.4 $M^+ - CH_3$), 97 (10, $M^+ - COCH_3$), 70 (18.3), 69 (23.7), 43 (53.8), 42 (100).

CHAPTER FIVE

Modifications of existing 1,3-diazepines

5.1 Introduction

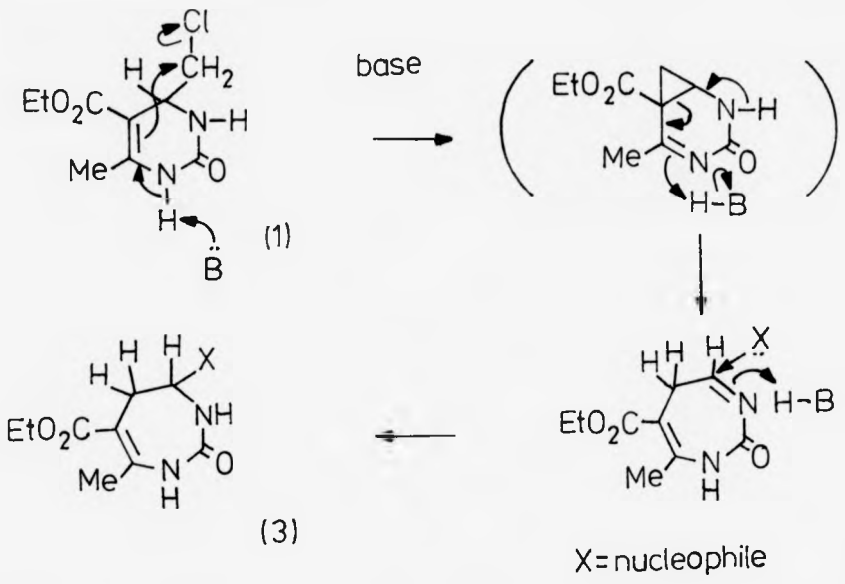
Previous research[21,22] has provided a convenient route to partly unsaturated 1,3-diazepines (3) by nucleophile induced ring expansion of 4-chloromethyl-2-oxo tetrahydropyrimidines (1). The reaction was first reported by Gregory et al.,[22] in 1972 and later studied in detail by Ashby and Griffiths[21]. Stable 1,3-diazepines (3a - d) were obtained in good yields on treatment of ethyl 4-chloromethyl-1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate (1) with potassium cyanide, sodium alkoxides, or guanidine followed by sodium borohydride.



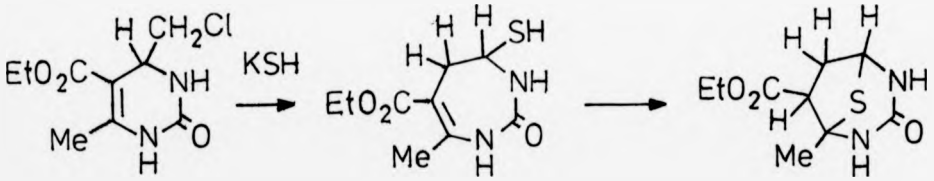
(1) R=H
(2) R=Me

(3) a X=CN
b X=OMe
c X=OEt
d X=H

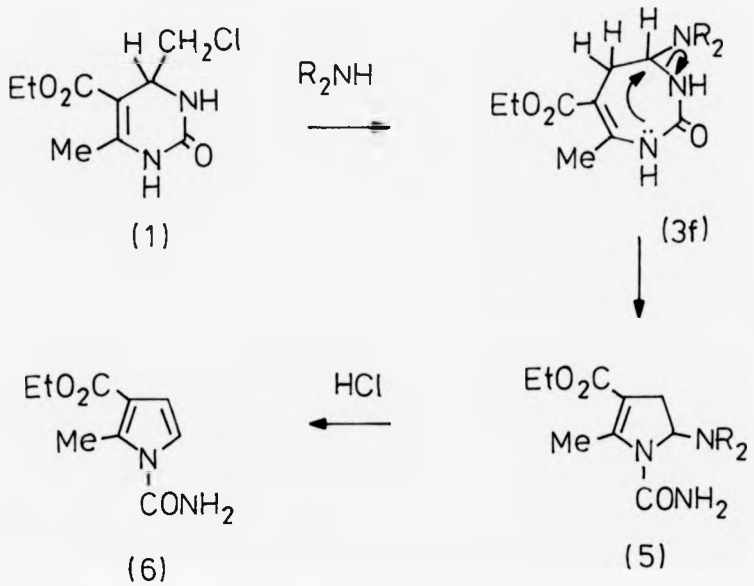
Ring expansion was thought to be initiated by the removal of the N-1 proton by a base of pKa > 10, and the importance of the N-1 proton in the ring expansion step was emphasized by the failure of compound (2) to react with a solution of potassium cyanide.



Brief treatment of compound (1) with potassium hydrogen sulphide in ethanol gave the sulphur bridged diazepine (4) presumably via formation of the mercapto compound (3e) followed by internal Michael addition to the β-ureido crotonate system.



Treatment of compound (1) with ethanolic solutions of secondary amines (pKa > 10) gave aminopyrrolines (5). These aminopyrrolines were thought to have resulted from ring contraction of the diazepine intermediate (3f). Elimination of amine from compound (5) was accomplished with warm ethanolic hydrogen chloride forming the N-carbamoyl pyrrole (6).



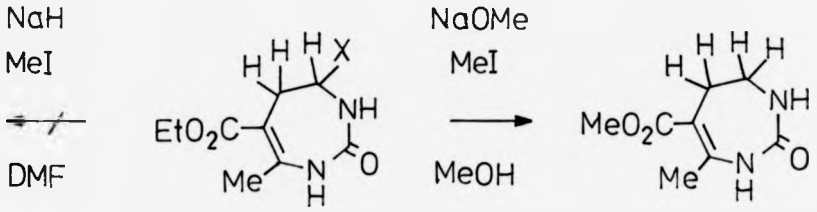
Any reaction which would permit the introduction of further unsaturation into these substituted 1,3-diazepines would be desirable. This chapter is an account of the various attempts made to modify both the diazepines (3) and the 4-chloromethyltetrahydropyrimidine (1).

5.2 Attempted alkylation of existing 1,3-diazepines

The 1,3-diazepines synthesized by Ashby and Griffiths[21] were stable, high melting solids, soluble only in the most polar solvents. Alkyl derivatives of these molecules were required in the first step towards introducing further unsaturation into the molecule, perhaps via successive bromination and dehydrobromination reactions.

Methylation of both the 7-cyano derivative (3a) and the tetrahydrodiazepine (3d) was attempted using standard procedures, but without success; treatment of the diazepines with sodium hydride and methyl iodide in DMF at 80 °C for 2-4h. resulted in a quantitative

recovery of starting material. A similar outcome was observed[151] following prolonged (6h) refluxing of diazepine (3d) in methanolic sodium methoxide in the presence of methyl iodide, except that in this case transesterification occurred producing the methyl ester (7).

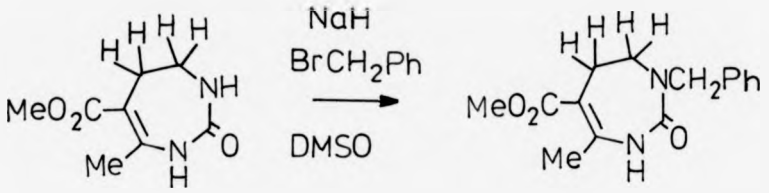


(3) a X=CN
d X=H

(7)

Treatment of the diazepine (7) with sodium hydride in DMSO followed by one equivalent of benzyl bromide gave, after 6h. stirring at 60-70 °C and aqueous work up, a mixture shown by the n.m.r. spectrum to consist of mainly starting diazepine (7) and traces of a benzylated product. Repeated chromatography using increasing amounts of chloroform in petroleum ether (b.p. 40-60 °C) as eluant gave a solid, m.p. 113 °C (from diethyl ether) in 1.7% yield. The proton n.m.r. spectrum consisted of a five proton singlet at δ7.3, a broad NH singlet at 6.27 exchangeable with D_2O and a two proton singlet at 4.51 p.p.m., in addition to the methylene multiplets and methyl singlets of the starting material (7). Irradiation of the NH produced no simplification of the C-7 protons in the n.m.r. spectrum, therefore benzylation was assumed to have occurred at N-1. Also D_2O exchange of the NH did not produce any simplification of the C-7 protons.

The i.r. spectrum was notable for its main absorptions at 3430, 1690 and 1650 cm^{-1}. Mass spectral data and elemental analysis were in agreement with a compound of molecular formula $C_{15}H_{18}N_2O_3$ suggesting the structure (8).



(7) (8)

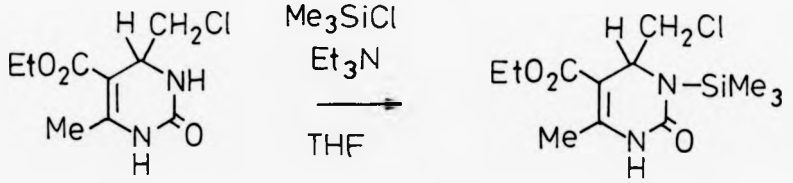
Attempts to increase the yield of the N-benzyl derivative (8) by using DMSO anion as the base and prolonging the reaction time were unsuccessful. Possibly the diazepine anion was not being formed and the benzyl bromide was reacting instead with DMSO anion, however no products were isolated from the chromatography to support this suggestion.

5.3 Attempted modification of the 1,3-diazepine precursor

An alternative to alkylation of the diazepine ring nitrogens was alkylation of the 4-chloromethyltetrahydropyrimidine precursor. Ashby and Griffiths[21] have reported the failure of compound (2) to react with potassium cyanide, explaining this in terms of a mechanism in which ring expansion is initiated by removal of the N-1 proton by base. However a group at N-3 would not, in theory prevent the ring expansion from occurring.

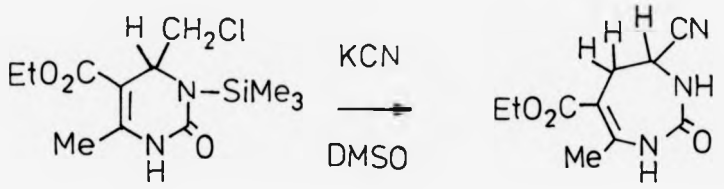
When ethyl 4-chloromethyl-1,2,3,4-tetrahydro-6-methyl-2--oxopyrimidine-5-carboxylate (1) was treated with trimethylsilylchloride

in the presence of triethylamine (to remove hydrogen chloride), a trimethylsilylated product m.p. 138 °C was obtained in quantitative yield analysing for $C_{12}H_{21}ClN_2O_3Si$. Attempts to recrystallize this product led to decomposition with loss of a trimethylsilyl group. The proton n.m.r. spectrum consisted of a nine proton singlet at δ0.4, an ethyl ester group at 1.2-1.4 (3H, t) and 4.0-4.35 (2H, q), a methylene group at 3.4-3.5 (2H, d) with a 6Hz coupling to one other proton and a one proton triplet at 4.4-4.6 p.p.m. with a 6Hz coupling to the methylene group. Only one NH group appeared in the spectrum at δ9.0 p.p.m. as a broadened singlet exchangeable with D_2O. Absence of coupling between the NH and the C-4 proton indicated that trimethylsilylation had occurred at N-3 producing compound (9).



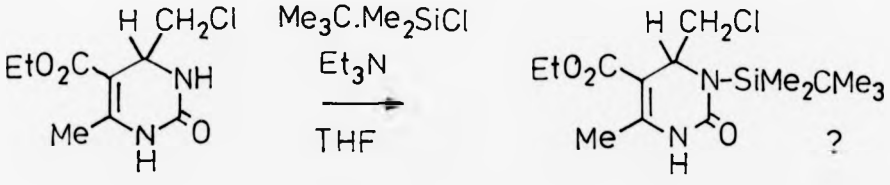
(1) (9)

The trimethylsilylated derivative (9) hydrolysed back to the starting 4-chloromethyltetrahydropyrimidine (1) in the presence of water, and was stored under dry argon. Unfortunately, although ring expansion of compound (9) was achieved using potassium cyanide in DMSO, the trimethylsilyl group was removed during the course of reaction and only ethyl 7-cyano-2,3,6,7-tetrahydro-4-methyl-2-oxo--1H-1,3-diazepine-5-carboxylate (3a) was isolated.



(9) (3a)

The t-butyldimethylsilyl group is reputed to have greater stability than the trimethylsilylgroup, but attempts to prepare 4-chloromethyl-3-(t-butyldimethylsilyl)-1,2,3,4-tetrahydro-6-methyl--2-oxopyrimidine-5-carboxylate (10) resulted in mixtures of starting material and product which hydrolyzed on recrystallization and when separation was attempted by Florisil chromatography.



(1) (10)

The final attempt to produce a precursor with a group at the N-3 site is outlined in the scheme below, and incorporates the benzyl group as a protecting group for the N-1 site.

(12)

Methylation at N-3 followed by de-protection would afford the product required for ring expansion.

The reaction of N-benzyl urea, (synthesized by a literature method[152]), with ethylacetoacetate and αβ-dichlorodiethylether in ethanol with a trace of hydrochloric acid was carried out by the general procedure of Ashby and Griffiths[21], and the 1-benzyl derivative (12) was obtained in 26% yield. The structure of compound (12) was confirmed by analysis, mass, i.r. and n.m.r. spectral data.

The 1-benzyl derivative unfortunately proved to be very resistant to alkylation at the other nitrogen. Standard alkylation procedures were used, in both methanol and DMF as solvents with lengthy reaction times, but starting material was always recovered.

Experimental

Ethyl 4-Chloromethyl-1,2,3,4-tetrahydro-6-methyl-2--oxopyrimidine-5-carboxylate (1)

Prepared according to the general procedure of Ashby and Griffiths[21] m.p. 173-174 °C (lit.,[21] m.p. 175-176 °C).

Ethyl 7-Cyano-2,3,6,7-tetrahydro-4-methyl-2-oxo-1H-1,3--diazepine-5-carboxylate (3a)

Prepared according to the method of Ashby and Griffiths[21] m.p. 250 °C (lit.,[21] m.p. 250-252 °C).

Ethyl 2,3,6,7-Tetrahydro-4-methyl-2-oxo-1H-1,3-diazepine--5-carboxylate (3d)

Prepared according to the method of Ashby and Griffiths[21] m.p. 189-191 °C (lit.,[21] m.p. 192-193 °C).

Methyl 2,3,6,7-Tetrahydro-4-methyl-2-oxo-1H-1,3-diazepine--5-carboxylate (7)

Prepared according to the procedure of Jones[151] m.p. 195-197 °C (lit.,[151] m.p. 196-197 °C).

Analysis found (%) C 52.17 H 6.55 N 15.27,

$C_8H_{12}N_2O_3$ required (%) C 52.17 H 6.52 N 15.22.

^1H N.m.r. $(CD_3)_2SO$ (δ, p.p.m.) 2.1 (3H, s), 2.4-2.6 (2H, m), 2.9-3.1 (2H, m), 3.5 (3H, s), 7.2 (1H, br.s, exch. D_2O), 7.9 (1H, br.s, exch. D_2O).

Methyl 2,3,6,7-Tetrahydro-1-benzyl-4-methyl-2-oxo-1,3-diazepine--5-carboxylate (8)

To a stirred solution of diazepine (7) (1 g, 5.4×10^{-3} mol) in DMSO (10 ml, distilled from calcium hydride) was added sodium hydride (0.26 g, 5.4×10^{-3} mol, 50% dispersion in paraffin) in two portions over 10 min under dry argon. When hydrogen evolution had

subsided the clear solution was stirred for a further 15 min. Benzyl bromide (0.65 ml, 0.93 g, 5.4×10^{-3} mol) was added dropwise and the reaction mixture heated at 60-70 °C for 6h. The solution was cooled, water (100 ml) added and the aqueous mixture extracted with chloroform (3 x 50 ml). The combined chloroform extracts were dried ($MgSO_4$) and evaporated down to a yellow oil. Preliminary chromatography using Florisil (60 g) and increasing amounts of chloroform in petroleum ether (b.p. 40-60 °C) separated the product (7) from the starting material (6) and DMSO. Further chromatography using a chromatotron and the same solvent mixtures as eluant gave the product (7) m.p. 113 °C (from diethyl ether) in 1.7% yield.

Analysis found (%) C 65.68 H 6.60 N 10.10,

$C_{15}H_{18}N_2O_3$ required (%) C 65.69 H 6.57 N 10.22.

I.r. (cm^{-1}) 3430, 1690, 1650. U.V., nm ($\log_{10}\varepsilon$) 274 (4.36).

^1H N.m.r. (δ, p.p.m.) 2.28 (3H, s), 2.61 (2H, m), 3.28-3.38 (2H, m), 3.67 (3H, s), 4.51 (2H, s), 6.27 (1H, br.s, exch. D_2O), 7.3 (5H, s).

M/e mass units (%) 274 (M^+ 65), 231 (13, M^+ - HCNO), 215 (11, M^+ - CO_2Me), 91 (100, CH_2Ph), 42 (24).

Ethyl 4-Chloromethyl-3-trimethylsilyl-1,2,3,4-tetrahydro--6-methyl-2-oxopyrimidine-5-carboxylate (9)

A solution of trimethylsilyl chloride (0.54 ml, 4.3×10^{-3} mol, freshly distilled) in sodium dried THF (10 ml) was added dropwise with stirring to a solution of the 4-chloromethyltetrahydropyrimidine (1) (1 g, 4.3×10^{-3} mol) in dry THF (40 ml) containing triethylamine (0.6 ml, 4.3×10^{-3} mol, distilled from potassium hydroxide). After 2h. the reaction mixture was filtered to remove triethylamine hydrochloride (0.6 g) and the filtrate evaporated to

give the product (9) m.p. 138 °C in quantitative yield. Recrystallization from diethyl ether gave the starting material (1) m.p. 173-174 °C.

Analysis (on crude product) gave (%) C 47.91 H 7.19 N 9.48,

$C_{12}H_{21}ClN_2O_3Si$ required (%) C 47.29 H 6.90 N 9.20.

^1H N.m.r. (δ, p.p.m.) 0.4 (9H, s), 1.2-1.4 (3H, t, J = 6Hz), 2.3 (3H, s), 3.4-3.5 (2H, d, J = 6Hz), 4.0-4.35 (2H, q, J = 6Hz), 4.4-4.6 (1H, t, J = 6Hz), 9.0 (1H, br.s, exch. D_2O).

M/e mass units (%) 182 (27, $M^+ - CH_2Cl$ and $SiMe_3$), 154 (14), 136 (18), 42 (10).

Attempted ring expansion of ethyl 4-chloromethyl-3--trimethylsilyl-1,2,3,4-tetrahydro-6-methyl-2-oxo--pyrimidine-5-carboxylate (9)

A solution of compound (9) (1.67 g, 5.5×10^{-3} mol) and potassium cyanide (1.8 g, 0.033 mol) in dry distilled DMSO (20 ml) was stirred (72h.) at room temperature. The reaction mixture was filtered and the filtrate extracted with dichloromethane (3 x 100 ml). Evaporation of the dichloromethane extracts gave only DMSO. Examination of the combined filtered solid and the solid residue from the dichloromethane extraction by proton n.m.r. spectroscopy revealed the absence of the trimethylsilyl protons. Recrystallization of the solid gave compound (3a) m.p. 250 °C (lit.,[21] m.p. 250-252 °C).

Ethyl 4-Chloromethyl-3-t-butyldimethylsilyl-1,2,3,4--tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate (10)

A solution of t-butyldimethylsilyl chloride (0.84 g, 5.59×10^{-3} mol) in dry THF (10 ml) was added to a stirred solution of the 4-chloromethyltetrahydropyrimidine (1) (1 g, 4.3×10^{-3} mol), in dry THF (40 ml) containing triethylamine

(0.8 ml, 5.59×10^{-3} mol). After 48h. a further equivalent of t-butyldimethylsilylchloride and triethylamine were added and stirring continued for a further 48h. Filtration and evaporation of the filtrate gave a mixture containing both product (10) and starting material by proton n.m.r. spectroscopy. Purification by chromatography or recrystallization from diethyl ether gave only starting material (1) m.p. 173-175 °C.

N-Benzyl-urea (11)

Prepared according to the method of Davis and Blanchard[152] m.p. 147 °C (lit.,[152] m.p. 147-148 °C).

Ethyl 1-Benzyl-4-chloromethyl-1,2,3,4-tetrahydro-6-methyl--2-oxopyrimidine-5-carboxylate (12)

Prepared from N-benzyl urea (11)[152] by the general procedure of Ashby and Griffiths[21]. Recrystallization from diethyl ether gave the product (12) m.p. 102-105 °C in 26% yield.

Analysis found (%) C 59.80 H 5.93 N 8.98,

$C_{16}H_{19}ClN_2O_3$ required (%) C 59.53 H 5.89 N 8.68.

I.r. (cm^{-1}), 3450, 1700, 1640. U.v., nm ($\log_{10}\varepsilon$) 290 (4.09).

^1H N.m.r. (δ, p.p.m.), 1.1-1.3 (3H, t, J = 6Hz), 2.3 (3H, s), 3.3-3.4 (2H, m), 3.9-4.25 (2H, q, J = 6Hz), 4.3-4.6 (1H, m), 4.9 (2H, d, J = 6Hz), 6.3 (1H, br.s, exch. D_2O), 7.1 (5H, s).

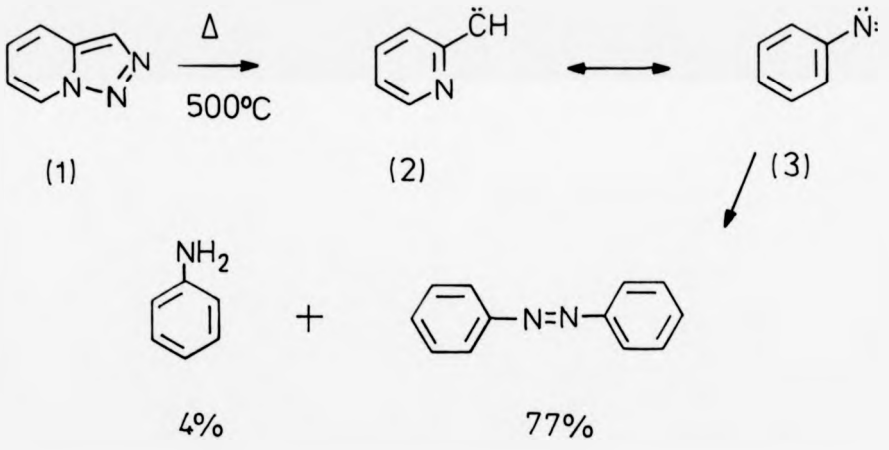
M/e mass units (%) 273 (34, $M^+ - CH_2Cl$), 91 (100), 65 (11).

CHAPTER SIX

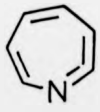
Synthesis and reactions of 2-dibromomethylpyridines

6.1 Introduction

Reports by Crow and Wentrup[153] in 1968 revealed that aniline and azobenzene were the major products from the flash vacuum pyrolysis of 1,2,3-triazolo[1,5-a]pyridine (1) at 500 °C. These products were characteristic of phenyl nitrene (3). Presumably, loss of molecular nitrogen from 1,2,3-triazolo[1,5-a]pyridine gave pyridyl carbene (2) which was thermally interconverted to phenyl nitrene (3).

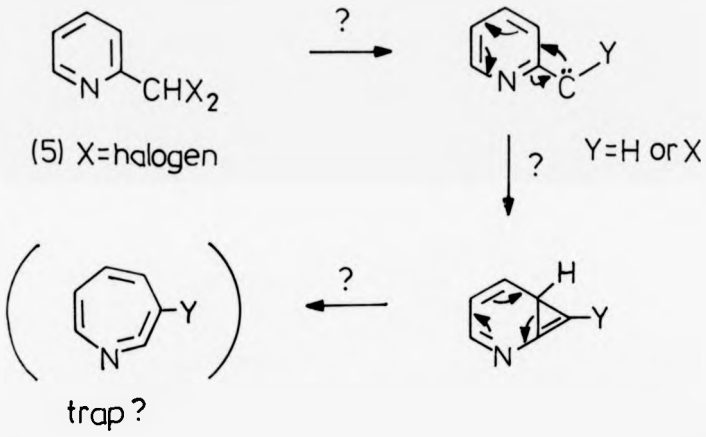


The key intermediate in the pyridyl carbene ↔ phenyl nitrene interconversion is thought[154] to be 1-aza-1,2,4,6-cycloheptatetraene (4).



(4)

It has been suggested[155] that pyridyl carbene or a halogenated carbene might be generated from dihalomethylpyridines (5) by bases or by flash vacuum pyrolysis. If pyridyl carbene could be induced to undergo intramolecular reaction, ring expansion would produce an azepine.



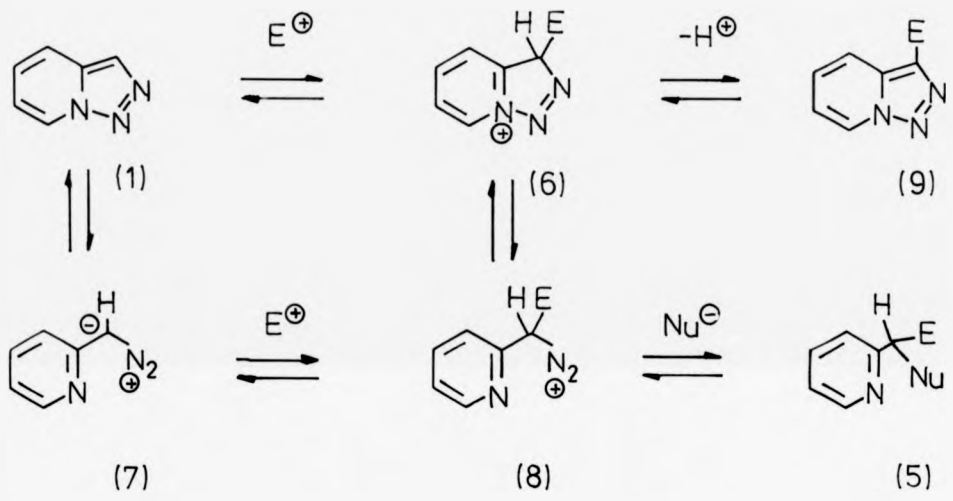
By analogy therefore pyrimidinyl carbene might afford a diazepine.

Dihalomethylpyridines, being more easily prepared than the pyrimidine analogues, were used as models.

The starting material from which dihalomethylpyridines were prepared is 1,2,3-triazolo[1,5-a]pyridine (1), first synthesized in 1957 by Bower and Ramage[156], from the hydrazone obtained by the action of hydrazine hydrate on pyridine-2-aldehyde, by oxidation using alkaline ferricyanide.

The reactions between 1,2,3-triazolo[1,5-a]pyridine (1) and electrophiles have since been investigated in detail[157-159], and a general scheme to explain the two types of reaction observed

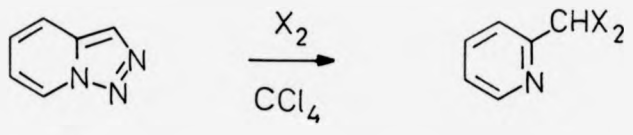
has been put forward[157]. Straightforward electrophilic substitution is attributed to the sequence (1) ⇌ (6) ⇌ (9).



Thus when E^+ is a hard electrophile and strongly electron withdrawing (such as NO_2^+ and HCO^+) the intermediate (8) is longer lived and deprotonation of the cyclic form (6) competes successfully with loss of nitrogen.

But when E^+ is a soft electrophile such as the halogens, it is only weakly stabilising to the diazonium intermediate (8) which is so short lived that nucleophilic attack with loss of nitrogen becomes the favoured process.

All three dihalomethylpyridines (5) have thus been prepared[157,159] by the action of the appropriate halogen on 1,2,3-triazolo[1,5-a]-pyridine (1), although the iodide was more difficult to isolate[159].



(1)

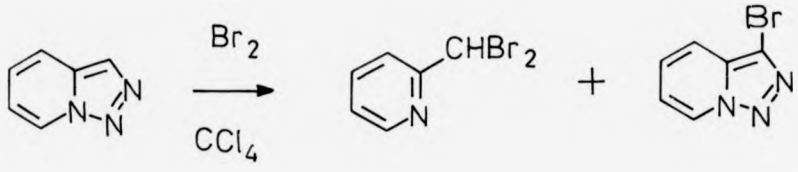
(5) a X=Cl
b X=Br
c X=I

Dibromomethylpyridine has also been prepared by the action of N-bromosuccinimide on 1,2,3-triazolo[1,5-a]pyridine[157] or α-picoline[160] where peroxide radicals were used as initiator. A mixture of both mono- and di-bromomethylpyridines were produced in the latter case.

6.2 Synthesis and reactions of 2-dibromomethylpyridines

The general method of Jones et al.[157] was used to prepare 2-dibromomethylpyridine (5b) by the addition of an equimolar quantity of bromine to a cooled carbon tetrachloride solution of 1,2,3--triazolo[1,5-a]pyridine (1). T.l.c. of the crude reaction mixture indicated the presence of a second minor product in addition to the expected 2-dibromomethylpyridine. Hence the product was applied to a silica gel column using 50% chloroform in petroleum ether (b.p. 40-60 °C) as eluant. The expected product (5b) was eluted in 50% yield and was identified by its ^{1}H n.m.r. spectrum, i.r. spectrum, elemental analysis and mass spectrum. The second component a crystalline solid having m.p. 91 °C and analysing for $C_6H_4N_3Br$ had a molecular ion of 202 and 200 mass units and fragments corresponding to the loss of nitrogen and of one bromine atom in the mass spectrum. The proton n.m.r. spectrum was very

similar to that of 1,2,3-triazolo[1,5-a]pyridine except for the absence of the C3 proton, and the compound was therefore identified as 3-bromo-triazolo[1,5-a]pyridine (9a).



(1) (5b) (9a)

Previous workers had assumed that compound (9a) was too unstable to exist, the bromine electrophile being only weakly stabilizing to the diazonium intermediate (8). However it was apparent from the low yield that the favoured pathway was ring opening with loss of nitrogen.

In order to observe the rearrangement products of pyridyl carbene or a halogenated carbene, 2-dibromomethylpyridine (5b) was subjected to flash vacuum pyrolysis. A range of furnace temperatures from 300-750 °C were used. Compound (5b) vaporized at room temperature, hence no external heating was required. The pressure was maintained at 2×10^{-2} mm Hg throughout the pyrolysis. At the lower temperatures 2-dibromomethylpyridine passed unchanged through the pyrolysis tube and was recovered from the cold finger which was maintained around -70 °C. As the furnace temperature was raised there was increased decomposition and deposition of carbonized material around the walls of the pyrolysis tube. At 750 °C the material collected from the cold finger was shown by t.l.c. to contain starting material and one other component.

Chromatography enabled the isolation of a white solid having m.p. 114-118 °C. The proton n.m.r. spectrum of this material exhibited a three proton multiplet between δ6.95 and 7.75, a one proton singlet at 7.6 and a one proton doublet at 8.5-8.6 p.p.m. The mass spectrum gave a molecular ion of 182 mass units and the fragmentation pattern indicated loss of a C_5H_4N fragment; one of the pyridyl groups. The data corresponded to that of a commercial sample of 1,2-bis-(2-pyridyl)ethylene (10) having m.p. 118-119 °C.

In principle, dimerization of (2-pyridyl)carbene would afford compound (10), but in practice the dimerization of carbenes is a statistically unlikely process since they are such short lived species and the concentration of carbene at any one time will always be low.

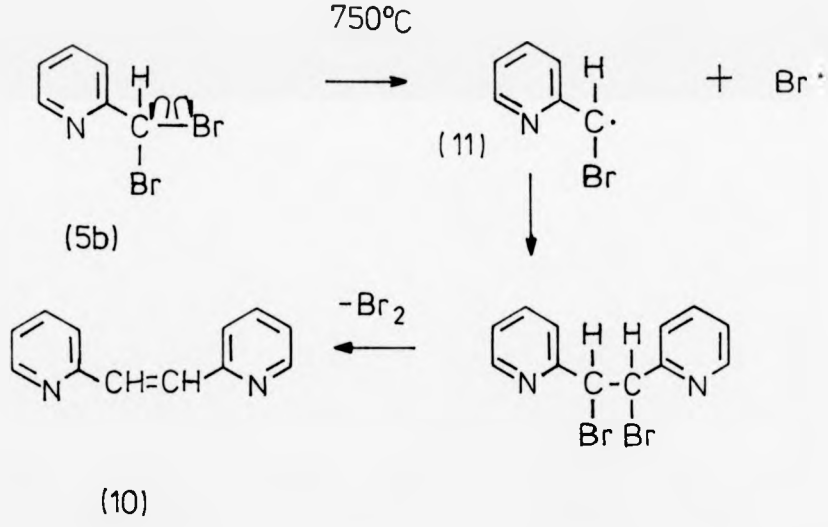
(10)

Also Crow and Wentrup[153] reported the usual products from pyridyl carbene to be azobenzene and aniline. Therefore it is unlikely that pyridyl carbene plays any part in the formation of 1,2-bis-(2-pyridyl)ethylene (10).

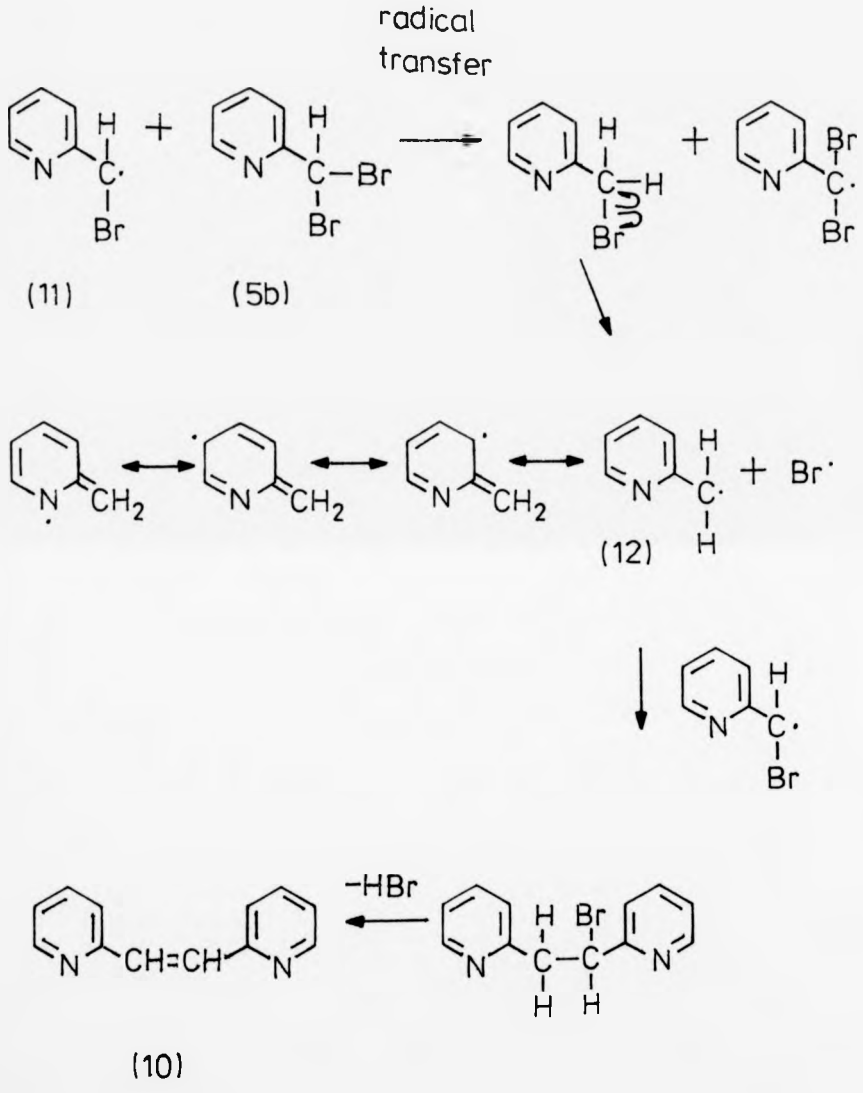
A more feasible mechanism to account for the formation of compound (10) can be postulated using radicals.

The homolytic fission of a C-Br covalent bond by thermolysis requires about 272 kJ mol^{-1} (65 Kcal)[164] of energy.

At temperatures above 500 °C thermal excitation of molecules becomes strong enough to disrupt even the relatively stable C-C bonds in alkanes. Therefore the pyrolysis temperature of 750 °C was more than sufficient to accomplish the gas phase dissociation of 2-dibromomethylpyridine (5b) into radical (11) and a bromine radical. Dimerization of radical (11) followed by elimination of bromine would produce the product (10).

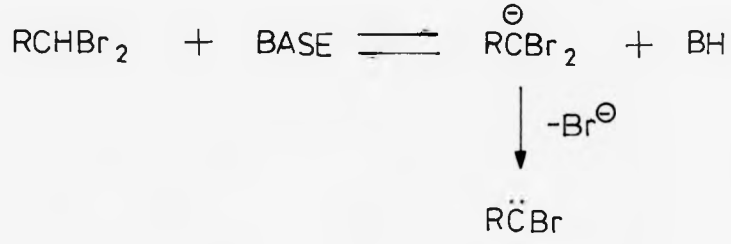


Alternatively hydrogen abstraction from a second molecule of starting material (5b) followed by homolytic fission of the C-Br bond would afford the benzyl-type radical (12) which is stabilized by conjugation.

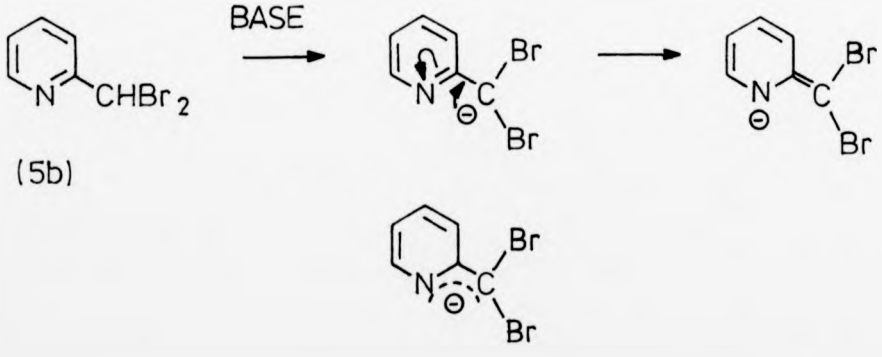


This radical being too reactive for prolonged existence would react as rapidly as possible with the molecules or radicals around it, the driving force being the energy liberated in bond formation. One possible reaction with radical (11) provides a termination step which after dehydrobromination affords the dimer (10).

The normal route to carbenes from dibromomethyl derivatives is by proton abstraction to give an anion followed by loss of a halogen atom.

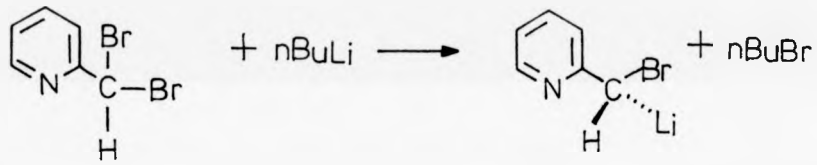


In the case of the pyridyl derivative (5b) the negative charge may be centred on the carbon atom attached to C-2, on the nitrogen, or delocalized:



Compound (5b) was treated with n-butyllithium as the base, in diethyl ether as solvent. A deep red colouration characteristic of anion formation in lithiation reactions was observed and the extent of anion formation was monitored by removal of a small sample for treatment with D_2O. After 0.5h. 50% deuteration of

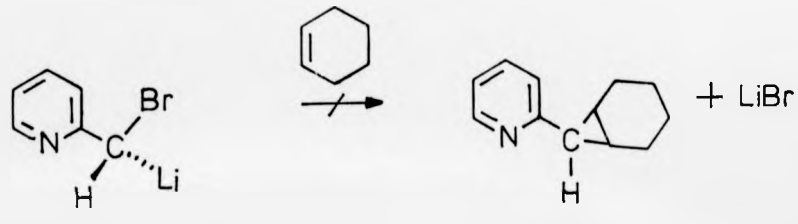
2-dibromomethylpyridine was observed. This was cross checked by adding a small piece of lithium to D_2O and shaking the resultant lithium deuteroxide with 2-dibromomethylpyridine. No deuteration was observed in this case. The organolithium compound (13) formed by α elimination of n-butyl bromide, can be regarded as a masked carbene, but it would react in a similar way to a free carbene towards nucleophiles giving the same type of products.



(5b) (13)

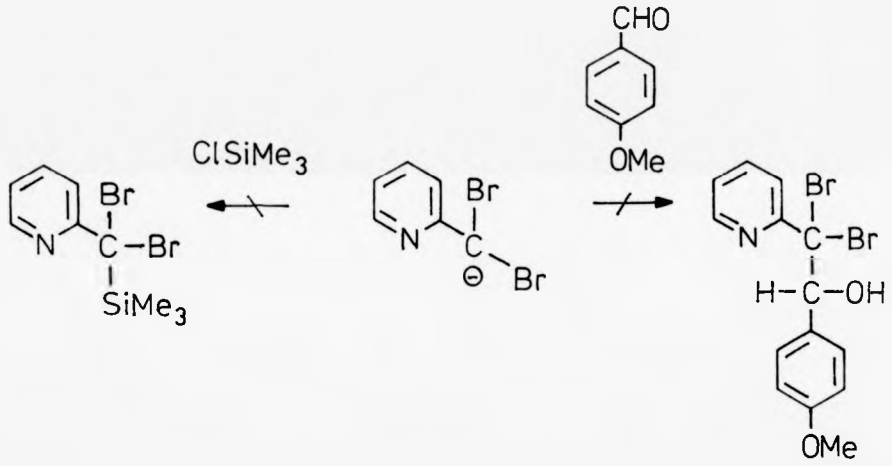
A variety of co-reagents were added to the reaction mixture, but although the reaction times and conditions were varied none of the reagents used led to the formation of products and work up resulted always in quantitative recovery of 2-dibromomethylpyridine.

The first co-reagent used was cyclohexene, a common trapping agent for carbene intermediates. The expected product from this reaction was the cyclopropane derivative (14).

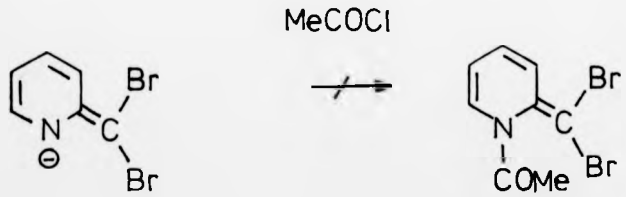


(13) (14)

No products were formed from this reaction, and the assumption made was that the intermediate was a stable anion, rather than a carbenoid species, the pyridyl group acting to stabilize the anion. However no products were obtained with trimethylsilylchloride, a standard co-reagent in lithiation reactions, or with anisaldehyde, a common electrophile normally reacting with anions to form secondary alcohols.



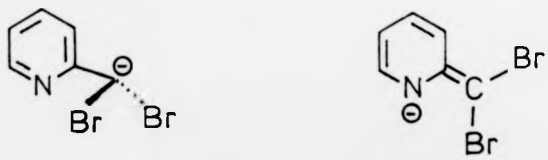
Alternatively if the anion were centred on nitrogen, reaction with acetyl chloride would be expected to produce the acylated derivative (15), but again only 2-dibromomethylpyridine was recovered after work up.



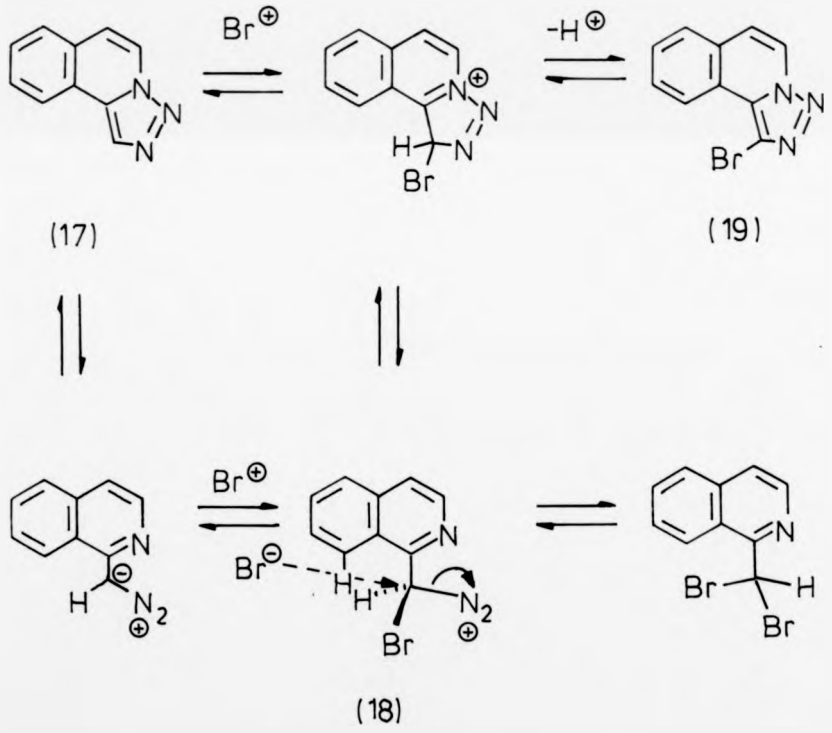
(15)

The anion was finally treated with the co-reagent dimethyl acetylene dicarboxylate (DMAD). If the anion were written as its delocalized form with a partial negative charge at both ends it could in theory undergo a 1,3-anionic cycloaddition to DMAD producing compound (16). No products were formed and unchanged starting material was recovered.

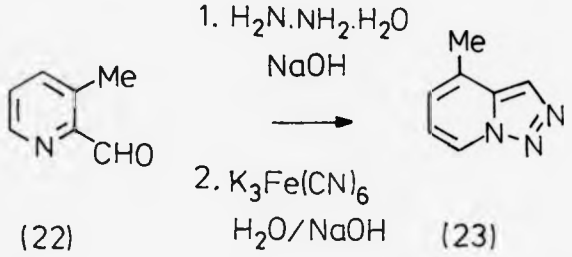
None of the co-reagents reacted as expected with the anion except for D_2O. The only possible explanation is that of steric hindrance, the large bromine atoms making it sterically unfavourable for any group other than the small deuterium atom to react with the anion. However the shape of the carbanion, shown below, is approximately tetrahedral and would appear to be favourably disposed towards attack. On the other hand the anion centred on nitrogen may well be susceptible to steric hindrance from the large bromine atoms.



As previously mentioned the bromination of 1,2,3-triazolo-[1,5-a]pyridine (1) gave only traces of 3-bromotriazolo[1,5-a]-pyridine (9a). However bromination of triazoloisoquinoline (17) gave solely the 3-bromo derivative (19). The explanation for this was thought to be steric hindrance to SN2 attack by nucleophilic bromide ion in the intermediate (18) shown in the sequence below.

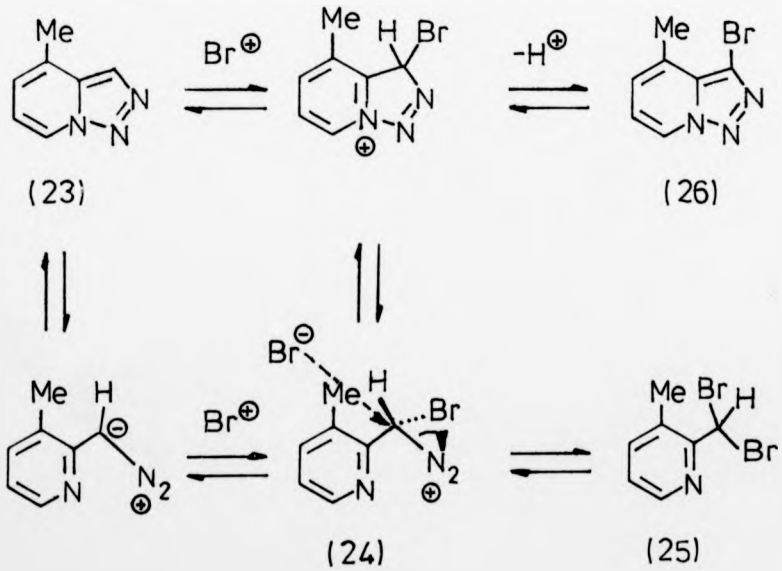


To test this theory 4-methyl-1,2,3-triazolo[1,5-a]pyridine (23) was synthesized by the general procedure of Bower and Ramage[156] from 3-methyl-pyridine-2-carboxaldehyde (22).



(22) (23)

Bromination of compound (23) in the usual manner[157] gave 2-dibromomethyl-3-methylpyridine (25) in 58% yield, with no trace of 3-bromo-4-methyl-triazolo[1,5-a]pyridine (26). Compounds (23) and (25) were identified on the basis of elemental analysis, ^1H n.m.r. and mass spectral data.



A similar degree of hindrance must be present in intermediate (24) as in intermediate (18) because the preferred line of attack in the SN2 substitution is obstructed by the 3-methyl group, therefore the 'steric hindrance' theory for the bromination of triazoloisoquinoline must be abandoned.

Experimental

1,2,3-Triazolo[1,5-a]pyridine (1)

Prepared according to the method of Bower and Ramage[156] b.p. 84-88 °C, 0.03 mm Hg (lit.,[156] m.p. 39-40 °C).

2-Dibromomethylpyridine (5b)

Prepared according to the methods of Jones et al.[157] using either bromine or N-bromosuccinimide and 1,2,3-triazolo[1,5-a]pyridine. The crude product was purified both by distillation and by chromatography using 50% chloroform in petroleum ether (b.p. 40-60 °C) as eluant. Pure 2-dibromomethylpyridine b.p. 78 °C, 0.005 mm Hg, was obtained in 50% yield as a colourless oil which gradually turned orange on standing.

Analysis found (%) C 28.57 H 2.04 N 5.31,

$C_6H_5NBr_2$ required (%) C 28.71 H 1.99 N 5.58.

I.r. (cm^{-1}) 3020, 670. U.v., nm ($\log_{10}\varepsilon$) 266 (3.46).

^1H N.m.r. (δ, p.p.m.) 6.6 (1H, s), 7.1 (1H, t, J = 4Hz), 7.7 (2H, m), 8.4 (1H, d, J = 4Hz).

M/e mass units (%) 253 (M^{+4}, 4.1), 251 (M^{+2}, 8.2), 249 (M^+, 4.4), 172 (98.8 M^{+2} - Br), 170 (100, M^+ - Br), 91 (49.6, $M^+ - Br_2$).

3-Bromotriazolo[1,5-a]pyridine (9a)

Isolated from the chromatography of crude 2-dibromomethylpyridine as a crystalline solid m.p. 91 °C (from petroleum ether b.p. 40-60 °C) in 3% yield.

Analysis found (%) C 36.57 H 1.89 N 21.37,

$C_6H_4N_3Br$ required (%) C 36.36 H 2.02 N 21.21.

I.r. (cm^{-1}) 3020, 1050. U.v., nm ($\log_{10}\varepsilon$) 286 (3.79), 320 (sh). ^1H N.m.r. (δ, p.p.m.) 6.8-7.3 (2H, m), 7.5-7.6 (1H, d, J = 6Hz), 8.5-8.6 (1H, d, J = 6Hz).

M/e mass units (%) 200 (M^{+1} 7.3), 198 (M^+, 81), 172 (21.8, $M^{+1} - N_2$), 179 (16.8, $M^+ - N_2$), 90 (100).

Flash vacuum pyrolysis of 2-dibromomethylpyridine

2-Dibromomethylpyridine (0.5 g, freshly distilled) was pyrolysed at 750 °C at 0.02 mm Hg over 2h., using a cold finger at -70 °C to trap the pyrolyzate. The crude pyrolyzate was dissolved in cold dichloromethane under a dry nitrogen atmosphere and evaporated in vacuo to give a green oil (250 mg). The crude mixture was applied to a Chromatotron using 50% chloroform in petroleum ether (b.p. 40-60 °C) as eluant. The first band eluted from the plate was starting material (200 mg). The second band, after evaporation, left an off white solid m.p. 114-118 °C (from diethyl ether), having a molecular ion of 182 mass units in the mass spectrum. A prominent fragment corresponded to the loss of a pyridyl group from the molecular ion.

^1H N.m.r. (δ, p.p.m.) 6.95-7.7 (3H, m), 7.6 (1H, s), 8.5-8.6 (1H, d).

The product was identified on the base of spectral data and m.p. as 1,2-bis-(2-pyridyl)ethylene (10) (commercial sample m.p. 118-119 °C).

Lithiation of 2-dibromomethylpyridine - general procedure

A solution of 2-dibromomethylpyridine (1.5 g, 6×10^{-3} mol) in sodium dried ether (25 ml) was added dropwise with stirring to a solution of n-butyl lithium (6×10^{-3} mol of a 1.5M solution in hexane) at -40 °C (liquid nitrogen/dichloromethane cooling bath)

under dry argon, all apparatus having been dried at 300 °C and flamed prior to use. A deep red colouration was immediately observed. After stirring 0.5h. at -40 °C a sample was withdrawn, shaken with D_2O (5 ml), the organic layer separated, dried ($MgSO_4$), and evaporated in vacuo. The ^1H n.m.r. spectrum indicated 50% deuteration. A further 0.5 equivalents of n-butyl lithium was added and the reaction mixture stirred for a further hour at -40 °C. The co-reagent (1 equivalent) was added, stirred (2h.) at -40 °C, then at room temperature overnight. Basification using saturated ammonium chloride in ammonium hydroxide solution, followed by chloroform extraction and evaporation of the dried ($MgSO_4$) chloroform extracts gave the crude oil requiring purification.

2-Hydroxymethyl-3-methylpyridine (20)

Prepared according to the procedure of Ginsberg and Wilson[161] b.p. 54 °C, 0.08 mm Hg (lit.,[161] b.p. 53-56 °C, 0.08 mm Hg).

Activated manganese dioxide (21)

Prepared according to the method of Attenburrow et al.[162].

3-Methyl-pyridine-2-carboxaldehyde (22)

Prepared according to the general procedure of Attenburrow et al.[162]. Stirring at room temperature was continued for seven days. The product had b.p. 30-32 °C, 0.05 mm Hg (lit.,[163] b.p. 52-54 °C, 0.2 mm Hg).

4-Methyl-triazolo[1,5-a]pyridine (23)

Prepared according to the general procedure of Bower and Ramage[156]. The crude reaction mixture was purified by chromatography using chloroform as eluant. The product m.p. 46-47 °C was eluted in 63% yield.

Analysis found (%) C 63.19 H 5.50 N 31.83,

$C_7H_7N_3$ required (%) C 63.16 H 5.26 N 31.58.

U.V. nm ($\log_{10}\varepsilon$) 282 (3.83).

^1H N.m.r. (δ, p.p.m.) 2.5 (3H, s), 6.6-6.8 (2H, m), 7.95 (1H, s), 8.5-8.6 (1H, d).

M/e mass units (%) 133 (M^+, 68), 105 (82, $M^+ - N_2$), 104 (100), 78 (52).

2-Dibromomethyl-3-methylpyridine (25)

Prepared according to the general procedure of Jones[157]. The crude reaction mixture was purified by chromatography using 50% chloroform in petroleum ether (b.p. 40-60 °C). The product m.p. 41-42 °C was isolated in 58% yield.

Analysis found (%) C 31.88 H 2.65 N 5.42,

$C_7H_7NBr_2$ required (%) C 31.70 H 2.64 N 5.28.

I.r. (cm^{-1}) 3020, 680. U.v. nm ($\log_{10}\varepsilon$) 274 (3.56).

^1H N.m.r. (δ, p.p.m.) 2.5 (3H, s), 6.8 (1H, s), 6.95-7.5 (2H, m), 8.3-8.4 (1H, d, J = 6Hz).

M/e mass units (%) 267 (M^{+4}, 1.4), 265 (M^{+2}, 3.0), 263 (M^+, 1.5), 186 (98, $M^{+2} - Br$), 184 (100, $M^+ - Br$), 105 (80, $M^+ - Br_2$), 79 (22.4).

References

1. L.H. Sternbach, Angew. Chem., Int. Ed. Eng., 10, 34 (1971).
2. F.D. Popp and A.C. Noble, Advan. Heterocycl. Chem., 8, 21 (1967).
3. G. Hornyak, K. Lempert and G. Simig, Kem Kozchem, 33, 81 (1970); Chem. Abstr., 72, 132576p (1970).
4. T. Tsuchiya, Yuki Gosei Kagaku Kyokai Shi, 41, 641 (1983); Chem. Abstr., 99, 212426n (1983).
5. G.A. Archer and L.H. Sternbach, Chem. Rev., 68, 747 (1968).
6. F. Troxler, H.P. Weber, H.R. Loosli and A. Jaunin, Helv. Chim. Acta, 57, 750 (1974).
7. J.A. Moore, W.J. Freeman, R.C. Gearhart and H.B. Yokelson, J. Org. Chem., 43, 787 (1978).
8. J.A. Moore, H.B. Yokelson, W.J. Freeman and J. Blount, Ibid, 44, 2683 (1979).
9. T. Tsuchiya, J. Kurita and H. Kojima, J. Chem. Soc. Chem. Commun., 444, (1980).
10. T. Tsuchiya, T. Kunieda and H. Kojima, Heterocycl., 16, 137 (1981).
11. T. Tsuchiya, J. Kurita and H. Kojima, Chem. Pharm. Bull. (Tokyo), 29, 3688 (1981).
12. Idem, Ibid, 29, 3696 (1981).
13. T. Tsuchiya, S. Okajima, M. Enkaku and J. Kurita, Ibid, 30, 3757 (1982).
14. T. Tsuchiya, M. Enkaku and S. Okajima, Ibid, 29, 3173 (1981).
15. A.V. Bogatskii, N.G. Luk'yanenko, T.A. Savenko, V.G. Vongai, E.I. Nazarov, T.I. Kirichenko and T.A. Afanaseva, Byull. Eksp. Biol. Med., 94, 52 (1982); Chem. Abstr., 98, 179p (1983).

16. T. Kunieda and B. Witkop, J. Amer. Chem. Soc., 93, 3478 (1978).

17. H.P.M. Thiellier, G.J. Koomen and U.K. Pandit, Tetrahedron, 33, 2603 (1977).

18. Idem, Ibid, 33, 2609 (1977).

19. Idem, Heterocycl., 3, 707 (1975).

20. Idem, Ibid, 5, 19 (1976).

21. J. Ashby and D. Griffiths, J. Chem. Soc. Perkin I, 657 (1975).

22. E. Bullock, R.A. Carter, B. Gregory and D.C. Shields, J. Chem. Soc. Chem. Commun., 97 (1972).

23. M. Abed-Rabboh, R.E. Banks and B. Beagley, J. Chem. Soc. Chem. Commun., 1117 (1983).

24. R.J. Breckenridge and C.J. Suckling, J. Chem. Res. (S), 166 (1982).

25. J. Hanafin and D. Ben-Ishai, J. Heterocycl. Chem., 13, 889 (1976).

26. G. Kollenz, E. Ziegler, H. Igel and C. Labes, Chem. Ber., 109, 2503 (1976); Chem. Abstr., 85, 143070p (1976).

27. J.M. Desmarchalier, N.A. Evans, R.F. Evans and R.B. Johns, Aust. J. Chem., 21, 257 (1968).

28. V.E. Marquez, P.S. Liu, J.A. Kelly and J.S. Driscoll, J. Org. Chem., 45, 485 (1980).

29. V.E. Marquez, P.S. Liu, J.S. Driscoll and J.J. McCormack, J. Med. Chem., 23, 713 (1980); Chem. Abstr., 93, 72184f (1980).

30. V.E. Marquez, P.S. Liu and J.S. Driscoll, J. Org. Chem., 45, 5525 (1980).

31. V.E. Marquez, J.S. Driscoll and J.A. Kelly, Ibid, 45, 5308 (1980).

32. V.E. Marquez, P.S. Liu and J.S. Driscoll, U.S. Patent Appl. 115,900 (1981); Chem. Abstr., 95, 115946s (1981).

33. Idem, U.S. Patent 4,275,057 (1981); Chem. Abstr., 95, 204369y (1981).

34. V.E. Marquez, P.S. Liu and J.K. Linevsky, J. Org. Chem., 47, 1712 (1982).

35. T.W. Drab and B.J. Lovell, Braz. Pedido P1 7904,960 (1980); Chem. Abstr., 93, 220789z (1980).

36. B.J. Lovell, Proc. Br. Crop Prot. Conf. - Pests Dis., 575 (1979); Chem. Abstr., 93, 216636e (1980).

37. A. Brandner, Synthesis, 973 (1982).

38. C.R. Rasmussen, Eur. Patent Appl. EP42,279 (1981); Chem. Abstr., 96, 18132e (1982).

39. Idem, U.S. Patent Appl. U.S.815,393 (1979); Chem. Abstr., 92, 111014b (1980).

40. Chau Der Li, S.L. Mella and A.C. Sartorelli, J. Med. Chem., 24, 1089 (1981); Chem. Abstr., 95, 90793z (1981).

41. A. Kosasayama and F. Ishikawa, Chem. Pharm. Bull. (Tokyo), 27, 1596 (1979).

42. G. Ferrand, Fr. Demande 2,414,510 (1979); Chem. Abstr., 92, 215470p (1980).

43. G. Bormann and R. Berthold, Ger. Offen. 2,948,074 (1980); Chem. Abstr., 94, 3924f (1981).

44. A.V. Bogatskii, K.S. Zakharov, N.G. Luk'yanenko and T.I. Kirichenko, Zh. Org. Chim., 18, 1101 (1982); Chem. Abstr., 97, 91299w (1981).

45. A.V. Bogatskii, E. Nazarov, N.G. Luk'yanenko, I.P. Konup, T.I. Kirichenko, T.A. Afanaseva and E.O. Puchov, Khim. Farm. Zh., 17, 308 (1981); Chem. Abstr., 98, 215574z (1983).

46. A.V. Bogatskii, N.G. Luk'yanenko and T.I. Kirichenko, Synthesis, 464 (1982).

47. M. Yokoyama, K. Hosi and T. Imamoto, Synthesis, 908 (1981).

48. Chung-yan Lin, U.S. Patent US4 391,751 (1983); Chem. Abstr., 99, 105883n (1983).

49. M. Augustin, M. Richter and S. Salas, J. Prakt Chem., 322, 55 (1980); Chem. Abstr., 93, 26307a (1980).

50. G.T. Vigrant and V.V. Vigrant, Khim. Tekhnol. Topl. Massel., 12, 37 (1980); Chem. Abstr., 94, 139755j (1981).

51. V.V. Lakiza, T.K. Zolotareva, V.I. Raevskaya, Y.L. Pekarskii, L.B. Vashevnik and S.M. Pekarskaya, U.S.S.R. Patent 737,428 (1980); Chem. Abstr., 94, 32343w (1981).

52. C. Klein, G. Schulz and W. Steglich, Liebigs Ann. Chem., 1623 (1983); Chem. Abstr., 99, 21289p (1983).

53. T. Tsuchiya, M. Enkaku, J.Kurita and H. Sawanishi, J. Chem. Soc. Chem. Commun., 534 (1979).

54. Idem, Fukusokan Kagaku Toronkai Koen Yoshishu 12th, 301 (1979); Chem. Abstr., 93, 46621b (1980).

55. T. Tsuchiya, M. Enkaku and S. Okajima, Chem. Pharm. Bull. (Tokyo), 28, 2602 (1980).

56. T. Tsuchiya, S. Okajima, M. Enkaku and J. Kurita J. Chem. Soc. Chem. Commun., 211 (1981).

57. J. Kurita, M. Enkaku and T. Tsuchiya, Heterocycles, 20, 2173 (1983).

58. U. Stauss, H.P. Harter, M. Neuenschwander and O. Schindler, Helv. Chim. Acta., 55, 771 (1972).

59. F.M.F. Chen and T.P. Forrest, Can. J. Chem., 51, 881 (1973).

60. P.W. Manley, C.W. Rees and R.C. Storr, J. Chem. Soc. Chem. Commun., 1007 (1983).

61. G. De Stevens, H.R. Rodriguez and B. Zitko, J. Inorg. Chem., 33, 670 (1968).

62. G. De Stevens and H.R. Rodriguez, U.S. Patent 3,681,340 (1972); Chem. Abstr., 77, 140178d (1972).

63. J.T. Suh and R.A. Schnettler, U.S. Patent 3,780,024 (1973); Chem. Abstr., 80, 83079h (1974).

64. Idem, U.S. Patent 3,780,023 (1973); Chem. Abstr., 80, 83080b (1974).

65. Idem, U.S. Patent 3,849,400 (1974); Chem. Abstr., 82, 73041s (1975).

66. Idem, U.S. Patent 3,867,388 (1975); Chem. Abstr., 83, 10183q (1975).

67. Idem, U.S. Patent 3,905,980 (1975); Chem. Abstr., 83, 206342k (1975).

68. Idem, U.S. Patent 3,838,122 (1974); Chem. Abstr., 82, 4327c (1975).

69. T. Kunieda and B. Witkop, J. Amer. Chem. Soc., 93, 3487 (1971).

70. B.A. Burdick, P.A. Benkovic and S.J. Benkovic, J. Amer. Chem. Soc., 99, 5716 (1979).

71. M. Partridge and A. Smith, J. Chem. Soc. Perkin I, 453 (1973).

72. Y. Ito, K. Kobayashi and T. Saegusa, Tetrahedron Lett., 12, 1039 (1979).

73. L.L. Martin, M. Worm and C.A. Crichlow, Eur. Patent Appl. 9800 (1980); Chem. Abstr., 94, 15780u (1981).

74. J.B. Taylor and W.R. Tully, J. Chem. Soc. Perkin I, 1331 (1976).

75. E.F. Elslager, J. Heterocycl. Chem., 6, 491 (1969).

76. W. Taub and A. Loeffler, Ger. Offen. 1,947,062 (1970); Chem. Abstr., 72, 111521b (1970).

77. U. Golik, J. Heterocycl. Chem., 903 (1975).

78. U. Golik and W. Taub, Ibid, 1155 (1976).

79. U. Golik, Tetrahedron Lett., 1327 (1975).

80. U. Golik and W. Taub, Ger. Offen. 2,411 522 (1974); Chem. Abstr., 82, 31360q (1975).

81. CIBA Ltd., Brit. Patent 1,183,135 (1970); Chem. Abstr., 72, 121598w (1970).

82. E.F. Elslager, J. Heterocycl. Chem., 5, 609 (1968).

83. H.W. Heine and C. Tintel, Tetrahedron Lett., 23 (1978).

84. H.W. Heine, D.W. Ludovici, J.A. Pardoen, R.C. Weber, E. Bonsall and K.R. Osterhout, J. Org. Chem., 44, 3843 (1979).

85. T. Tsuchiya, M. Enkaku and S. Okajima, J. Chem. Soc. Chem. Commun., 454 (1980).

86. J. Kurita, M. Enkaku, T. Tsuchiya, Chem. Pharm. Bull. (Tokyo), 31, 3684 (1983).

87. T. Kurihara, K. Nasu, J. Bayakuno and T. Toni, Chem. Pharm. Bull. (Tokyo), 30, 1289 (1982).

88. T. Kunhara, E. Kawasaki and K. Nasu, Heterocycl., 20, 1913 (1983).

89. P.K. Woo and H.W. Dion, J. Heterocycl. Chem., 641 (1974).

90. J. Soloducho, A. Mrozikiewicz and T. Bobkiewicz-Kozlowska, Pol. J. Pharmacol. Pharm., 35, 131 (1983); Chem. Abstr., 100, 34513t (1984).

91. T. Jen, P. Bender, H.V. Hoeven, B. Dienel and B. Loev, J. Med. Chem., 16, 407 (1973); Chem. Abstr., 79, 49091q (1973).

92. F. Ishikawa and Y. Watanabe, Chem. Pharm. Bull. (Tokyo), 28, 1307 (1980).

93. A.R. Katritzky and F. Yates, J. Chem. Soc. Perkin I, 309 (1976).

94. M. Eckstein and A. Drabczynska, Synthesis, 581 (1979).

95. G. Ferrand, M. Bayssat, J.C. Depin and A. Betbeder-Matibet, Fr. Demande FR 2,521,563 (1983); Chem. Abstr., 100, 103402v (1984).

96. D.J. Brown, J. Soc. Chem. (Ind)., 69, 353 (1950).

97. J. Clarke, R.K. Grantham and J. Lydiate, J. Chem. Soc. (C), 1122, (1968).

98. E.H. Northey, U.S. Patent 2,417,318 (1947); Chem. Abstr., 41, 3824c (1947).

99. J.P. Jonak, G.C. Hopkins, H.J. Minnemeyer and H. Tieckelmann, J. Org. Chem., 35, 2512 (1970).

100. D.J. Brown, E. Hoeger and S.F. Mason, J. Chem. Soc., 211 (1955).

101. L. Bauer, G.E. Wright, B.A. Mikrut and C.L. Bell, J. Heterocycl. Chem., 2, 447 (1965).

102. O.S. Tee and S. Banerjee, J. Org. Chem., 44, 3256 (1979).

103. H.J. den Hertog, H.C. Van Der Plas, M.U. Pieterse and J.W. Streef, Rec. Trav. Chim. Pays-Bas, 84, 1569 (1965).

104. S. Gabriel, Ber., 37, 3638 (1904).

105. F.H.S. Curd and D.N. Richardson, J. Chem. Soc., 1853 (1955).

106. H.W. Barrett, I. Goodman and K. Dittmer, J. Amer. Chem. Soc., 70, 1753 (1948).

107. M. Gacek and K. Undheim, Acta. Chem. Scand., 36, 2 (1982).

108. H. Fritz, P. Hug, S.O. Lawesson, E. Logeman, B.S. Pedersen, H. Sauter, S. Scheibye and T. Winkler, Bull. Soc. Chim. Belges., 87, 525 (1978).

109. H.C. Koppel, R.H. Springer, R.K. Robins and C.C. Cheng, J. Org. Chem., 26, 792 (1961).

110. A. Albert and G.B. Barlin, J. Chem. Soc., 3129 (1962).

111. D.J. Brown, J. Appl. Chem. (London), 9, 203 (1959).

112. R. Kuhn and H. Trischmann, Liebigs Ann. Chem., 611, 117 (1958); Chem.Abstr., 52, 4523r (1958).

113. E.J. Corey and M. Chaykovsky, J. Amer. Chem. Soc., 87, 1353 (1965).

114. C.R. Johnson, M. Haake and C.W. Shroek, J. Amer. Chem. Soc., 92, 6594 (1970).

115. H.J. Emeléus and H.G. Heal, J. Chem. Soc., 1126 (1946).

116. P.C. Hayes, Ph.D. Thesis p.113, Keele University, Staffordshire (1980).

117. S. David and H. Hirshfeld, Bull. Soc. Chim. Fr., 527 (1966).

118. O.S. Tee and M. Paventi, J. Org. Chem., 46, 4172 (1981).

119. H. Yamanaka, S. Kondo, T. Sakamoto, S. Niitsuma and S. Noji, Chem. Pharm. Bull. (Tokyo), 29, 2837 (1981).

120. T.J. Curphey, Organic Syntheses, 51, 142 (1971).

121. J.S. Gillespie, Jr., S.P. Acharya and D.A. Shamblee, J. Org. Chem., 40, 1838 (1975).

122. A. Haider, G. Cornuz and H. Wyler, Helv. Chim. Acta., 58, 1287 (1975).

123. W. Lwowski and T.J. Maricich, J. Amer. Chem. Soc., 87, 3630 (1965).

124. M.O. Forster and H.E. Fierz, J. Chem. Soc., 93, 72 (1908).

125. B. Abarca and C. Soriano, 1984, personal communication.

126. S.G. Warren, "Designing Organic Syntheses: The Synthon Approach", J. Wiley, 1978.

127. J.G. Cannon and J.E. Garst, J. Org. Chem., 40, 182 (1975).

128. D.J. LeCount, 1983, personal communication.

129. C.C. Schroff, W.S. Stuart, S.J. Ulm and J.W. Wheeler, J. Org. Chem., 36, 3356 (1971).

130. T.K. Au, A.E. Baydar and G.V. Boyd, J. Chem. Soc. Perkin I, 2884 (1981).

131. T. Francis and M.P. Thorne, Can. J. Chem., 54, 24 (1976).

132. P. Rafferty, Ph.D. Thesis, p221, Keele University, Staffordshire (1978).

133. I. Heilbron "Dictionary of Organic Compounds", p1464, Eyre and Spottiswoode.

134. D.H. Lorenz and E.I. Becker, J. Org. Chem., 28, 1707 (1963).

135. P.A.S. Smith, Organic Reactions III p337, Wiley (1947).

136. L. Weintraub, S.R. Oles and N. Kalish, J. Org. Chem., 33, 1679 (1968).

137. "Handbook of Chemistry and Physics" 61st Ed., C-66. 1980-1981.

138. R. Duschinsky and L.A. Dolan, J. Amer. Chem. Soc., 68, 2350 (1946).

139. G.E. Hilbert, J. Amer. Chem. Soc., 54, 3413 (1932).

140. R.A. Whitney, Tetrahedron Lett., 22, 2063 (1981).

141. H.J.H. Fenton and W.A.R. Wilks, J. Chem. Soc., 95, 1329 (1909).

142. W. Hartmann and H.G. Heine, Synthesis, 579 (1979).

143. A. Hassner and L. Krepski, J. Org. Chem., 44, 1376 (1979).

144. Idem, Ibid, 43, 2879 (1978).

145. D. A. Bak and W.T. Brady, J. Org. Chem., 44, 107 (1979).

146. P. Jeffs, personal communication, P.M. Radley, Ph.D. Thesis, p98, Keele University, Staffordshire (1981).

147. L. Ghosez, R. Montaigne, A. Roussel, V. Vanderleide and P. Mollet, Tetrahedron, 27, 615 (1971).

148. T.P. Forrest, G.A. Dauphinee and F.M.F. Chen, Can. J. Chem., 52, 2725 (1974).

149. N.J. Leonard and D.F. Wiemar, J. Amer. Chem. Soc., 98, 8218 (1976).

150. K.H. Scholz, J. Hinz, H-G. Heine and W. Hartmann, Liebigs Ann. Chem., 248 (1981).

151. G. Jones, 1984, personal communication.

152. T.L. Davis and K.C. Blanchard, J. Amer. Chem. Soc., 45, 1816 (1923).

153. W.D. Crow and C. Wentrup, Tetrahedron Lett., 6149 (1968).

154. O.L. Chapman and J.P. Le Roux, J. Amer. Chem. Soc., 100, 6245 (1978).

155. G. Jones, A. Rogers and G.A. Jones, unpublished results (1972).

156. J.D. Bower and G.R. Ramage, J. Chem. Soc., 4506 (1957).

157. G. Jones, D.R. Sliskovic, B. Foster, J. Rogers, A.K. Smith, M.Y. Wong and A.C. Yarnham, J. Chem. Soc. Perkin I, 78 (1981).

158. L.S. Davies and G. Jones, J. Chem. Soc. (C), 688 (1970).

159. D.R. Sliskovic, Ph.D. Thesis p21, Keele University, Staffordshire, (1982).

160. M. Hasegawa, Chem. Pharm. Bull. (Tokyo), 1, 293 (1953).

161. S. Ginsberg and I.B. Wilson, J. Amer. Chem. Soc., 79, 481 (1957).

162. J. Attenburrow, A.F.B. Cameron, J.H. Chapman, R.M. Evans, B.A. Hems, A.B.A. Jansen and T. Walker, J. Chem. Soc., 1094 (1952).

163. W. Mathes and W. Sauermilch, Chem. Ber., 90, 758 (1957).

164. N.S. Isaacs, Reactive Intermediates in Organic Chemistry, p297, Wiley (1974).