REARRANGEMENTS OF

QUINOLIZINIUM-1-DIAZONIUM SALTS

AND RELATED REACTIONS

by

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SUMMARY

The methods of synthesis and known properties of aminoquinolizinium compounds are reviewed.

A number of 1-aminoquinolizinium salts when treated with aqueous nitrous acid undergo rearrangement. Investigation by degradation and synthesis showed the initial products are cis-3-(v-triazolo[1,5-a]pyridyl)acraldehydes. These are rapidly isomerised to the trans-isomers. The mechanism of the rearrangement is discussed and the synthesis and properties of other v-triazolo[1,5-a]pyridines are reviewed.

The thermal isomerisation and decomposition of 3-(v-triazolo[1,5-a]pyridyl)acraldehydes to 5-(2-pyridyl)-pyrazoles is reported and a mechanism for the rearrangement is suggested.

In the last section the photochemistry of α,β-unsaturated carbonyl compounds is briefly reviewed. The photochemical conversion of some heterocyclic acraldehydes to derivatives of propionic acid is described. Some limitations of the reaction are reported and a mechanism proposed, support for which is provided by studies on suitably deuterium labelled compounds.

ACKNOWLEDGMENTS

I am indebted to Dr. G. Jones for his guidance and encouragement during this work.

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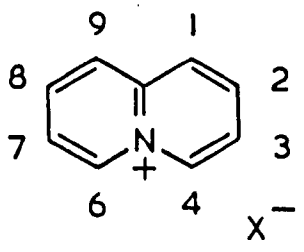
NOMENCLATURE

The terms dehydropyridocolinium ion and dehydroquinolizinium ion have been used to designate the bicyclic naphthalenic ring system with a quaternary bridgehead nitrogen atom (1) but the name quinolizinium ion has come into common use and will be used throughout this thesis. The system (2) in which the nitrogen atom is non-quaternary is one (4-H) of several isomers known as quinolizines. The partially reduced system (3) will be referred to as a 1,2,3,4-tetrahydroquinolizinium salt.



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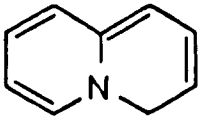

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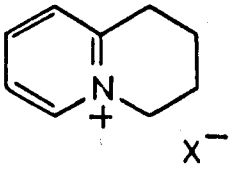

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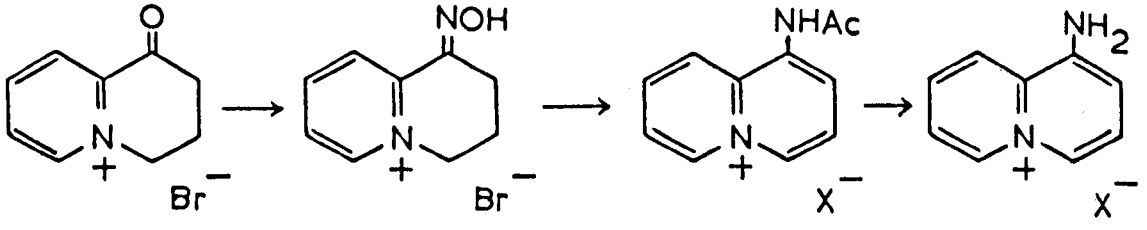
SURVEY OF PREVIOUS WORK

Synthesis of Aminoquinolizinium Salts

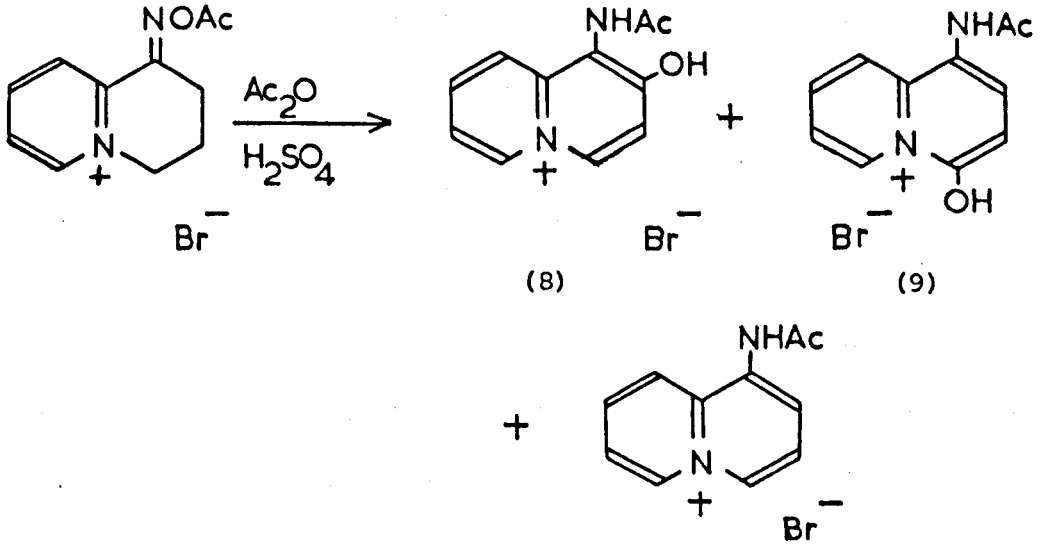
There are two major reported synthetic routes to aminoquinolizinium salts. The first reported synthesis was by Collicutt and Jones[1] from 1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (4). Treatment of the ketone bromide (4) with hydroxylamine



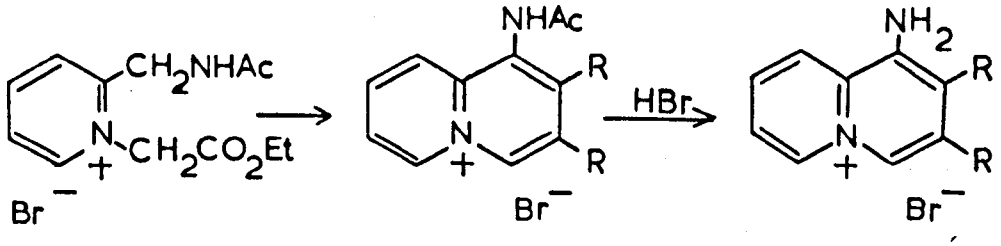
(4) (5) (6) (7)

gave the oxime (5). Hot acetic anhydride gave the expected O-acetyl derivative which in acetic anhydride solution underwent Wolff aromatisation when treated with dry hydrogen chloride to give 1-acetamidoquinolizinium chloride (6, X = Cl). A better overall yield was obtained if the oxime bromide (5) was boiled with acetic anhydride containing a trace of sulphuric acid; isolation of the O-acetyl oxime being unnecessary. Hydrolysis of the amide (6) with hot concentrated hydrobromic acid gave 1-aminoquinolizinium bromide (7, X = Br).

In the original synthesis the only compound isolated in Wolff aromatisation was the acetamido compound (6). However, when this was later repeated[2] a mixture of 1-acetamido-2-hydroxy- (8) and 1-acetamido-4-hydroxyquinolizinium bromide (9) was obtained in addition to the acetamido compound (6).



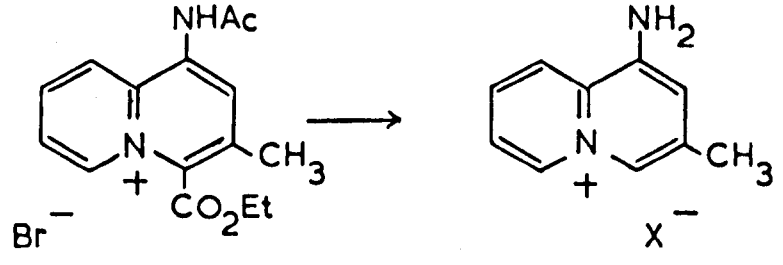
Hough and Jones[3] used an alternative route to prepare a number of aminoquinolizinium salts following a method originally reported by Westphal, Jann and Heffer.[4] Quaternisation of 2-acetamidomethylpyridine with ethyl bromoacetate in sulpholane gave the quaternary salt (10).



(10) (11) R = CH_3 (12) R = Et (13) R = CH_3 (14) R = Et

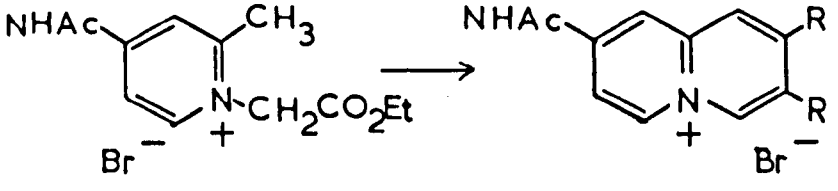
Cyclisation by boiling an ethanolic solution of the quaternary salt (10), di-n-butylamine and biacetyl or bipropionyl gave 1-acetamido-2,3-dimethyl- (11) and 1-acetamido-2,3-diethyl-quinolizinium bromide (12) respectively. Acid hydrolysis of the quinolizinium salt (11) gave 1-amino-2,3-dimethylquinolizinium bromide (13). Similarly was prepared the 1-amino-2,3-diethyl-quinolizinium bromide (14). Attempts to prepare quinolizinium salts unsubstituted in the 2 and 3 positions using glyoxal in place of the usual α-diketone were unsuccessful.

Reaction of the quaternary salt (10) and pyruvic aldehyde gave in good yield 1-acetamido-4-carbethoxy-3-methyl-quinolizinium bromide (15) which underwent acid hydrolysis to give



(15) (16)

1-amino-3-methylquinolizinium bromide (16,X = Br). The quaternary salt (17) from the N-acetyl derivative of 4-amino-2-picoline with biacetyl and di-n-butylamine gave 2-acetamido-7,8-dimethyl-quinolizinium bromide (18). Using benzil and di-n-butylamine a

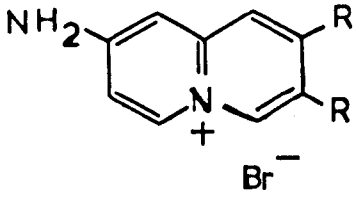


(17)

(18) R = CH_3

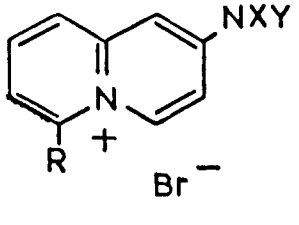
(19) R = Ph

mixture was obtained from which 2-acetamido-7,8-diphenylquinolizinium bromide (19) was separated. Acid hydrolysis with boiling hydrobromic acid gave the corresponding amines (20) and (21).



(20) R = CH_3

(21) R = Ph



(22) R = H or CH_3

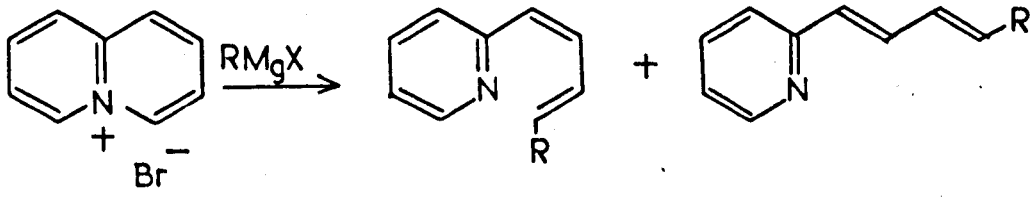
The synthesis of quinolizinium salts using pyruvic aldehyde as the α-dicarbonyl reagent was limited to the preparation of the acetamido-ester (15). When cyclisations were attempted on 2-methyl-1-carbethoxymethylpyridinium bromide and 4-acetamido-2-methyl-1-carbethoxymethylpyridinium bromide, no pure products were obtained.

A further preparation of substituted 2-aminoquinolizinium salts has been reported by Alaimo[5] in which a 2-bromoquinolizinium bromide is boiled in ethanol with a substituted amine to give a mono or disubstituted aminoquinolizinium salt of the type (22) depending on the degree of substitution of the starting amine.

Properties of Quinolizinium Salts

The ultraviolet absorption spectrum of the quinolizinium system is very similar in character to that of quinoline and isoquinoline and confirms its highly aromatic nature. The fact that it forms a crystalline picrate and perchlorate and exists in a cationic form with chloride, bromide or iodide as the anion is indicative of its ionic character. As an aromatic system carrying a delocalised positive charge the quinolizinium ion would be expected to be π-electron deficient and very susceptible to nucleophilic attack. Calculations of π-electron densities in the quinolizinium

ion by Acheson and Goodall[6] indicate that they are least in the 2 and 4 positions and this implies that nucleophilic substitution should occur in these positions. Confirmation is provided by the work of Miyadera[7]. Nucleophilic attack by Grignard reagents on quinolizinium bromide (23) occurs at the 4-position but with subsequent ring opening giving as the main product 1-cis-3-trans-pyridyl butadiene (24). The 1-trans-3-trans-isomer (25) is produced

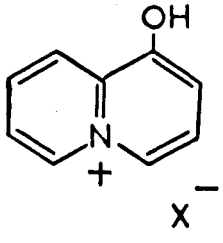


(23) (24) (25)

in small yield. The intermediate in this reaction is thought to be the 4-H quinolizine which rearranges to the more stable pyridyl-butadienes. Similar reactions on 1-, 2-, 3-, and 4-methyl quinolizinium bromides occurred with ring opening, in most cases the nucleophile attacking the unsubstituted ring. Reactions between substituted and unsubstituted quinolizinium salts and lithium aluminium hydride[8] or aliphatic amines[9] gave similar results. Electrophilic attack should take place much less readily than in pyridine or quinoline due to the

quaternary nature of the quinolizinium cation. However the introduction of a single powerful electron donating group activates the quinolizinium system sufficiently to allow electrophilic substitution to occur.

Evidence has been accumulated by Fozard and Jones[10,11,12,13] who have shown that hydroxyquinolizinium salts readily undergo electrophilic substitution. The bromination of 1-, 2-, and 3-hydroxyquinolizinium bromides (26, 27 and 28, X = Br) in hydrobromic acid



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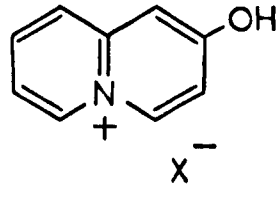

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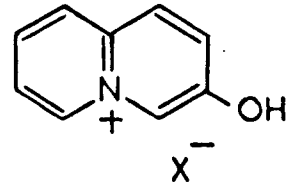
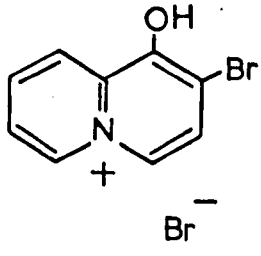


(28)

gave, respectively, 2-bromo-1-hydroxy,1-bromo-2-hydroxy and 4-bromo-3-hydroxyquinolizinium bromides (29, 30 and 31).



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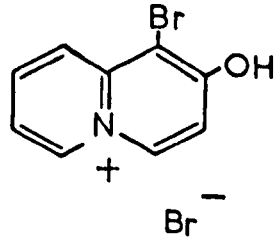

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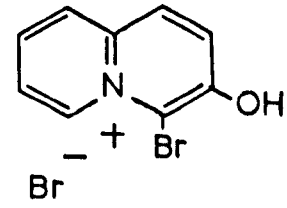
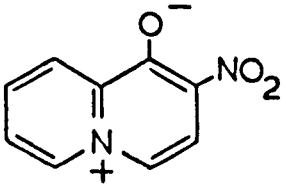


(31)

In the latter two cases no isomeric hydroxy compounds were obtained indicating a "naphthalene" or "isoquinoline" pattern of disubstitution.

The nitration of these hydroxy compounds has also been studied.[11,12] Boiling dilute nitric acid converted 1-hydroxyquinolizinium nitrate (26, X = NO_3) into the zwitterion (32). Longer heating of the salt (26, X = NO_3) in boiling dilute nitric acid gave 1-hydroxy-2,4-dinitroquinolizinium betaine (33).



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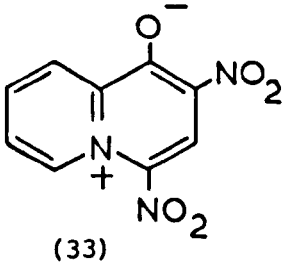

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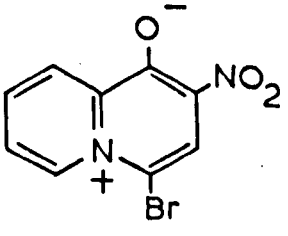


(34)

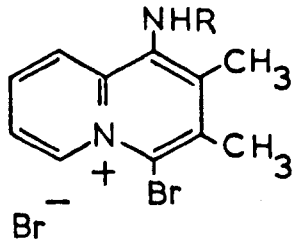
Treatment of 1-hydroxyquinolizinium bromide (26, X = Br) with the same reagent gave the zwitterion (34) of the 4-bromo-1-hydroxy-2-nitroquinolizinium salt. Initial nitration being followed by substitution by the bromide ions present in the solution. Under the same conditions 2- and 3-hydroxyquinolizinium bromides have been shown to brominate in positions 1 and 4 respectively, but without simultaneous nitration.

The work of Fozard and Jones,[10,11,12] and Boekelheide and

his co-workers[14,15] established that hydroxyquinolizinium compounds show some analogy with the corresponding hydroxy-pyridines. The 1- and 3-hydroxyquinolizinium salts are typically phenolic in behaviour producing coloured solutions with aqueous ferric chloride. However 2- and 4-hydroxyquinolizinium salts behave more as quinolizones and are readily converted into 2- and 4-quinolizone respectively with loss of a proton. The ultraviolet spectra and the fact that they form crystalline salts with picric and hydrochloric acids indicate that there are resonance hybrids to which the corresponding hydroxy zwitterions are major contributors.

The synthesis of 1-aminoquinolizinium salts has been described earlier. Collicutt and Jones[1] have reported that the 1-amino salt (7, X = Br) formed an unstable hydrobromide and a mono picrate which could be converted into a mono perchlorate indicating the low basicity of the 1-amino group. Confirmation of this was provided by the ultraviolet absorption of the amine (7) over a range of pH values, with no change in the spectrum from pH 10 to pH 1.

The amines (13, 14, 16, 20 and 21) were all shown[16] to react readily with bromine at room temperature. The 1-amino-2,3-dimethylquinolizinium salt (13) gave a 4-bromo derivative (35) as did the diethyl compound (14). Bromination of the N-acetylamine (11) was more difficult but was achieved by using a higher temperature and a mixture of bromine and sodium acetate to give the brominated amide (36).

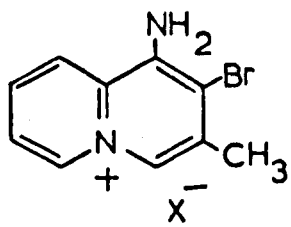


(35) R = H

(36) R = Ac

This represents the lowest degree of activation of a quinolizinium salt (reported to date) at which bromination has been achieved.

Bromination of 1-amino-3-methylquinolizinium bromide[15] (16) gave a mixture of 1-amino-2-bromo- (37,X = Br) and 1-amino-2,4-dibromo-3-methylquinolizinium bromide (38,X = Br). Bromination of



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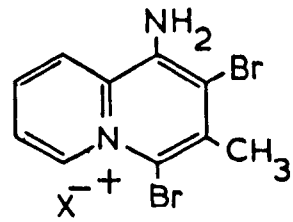

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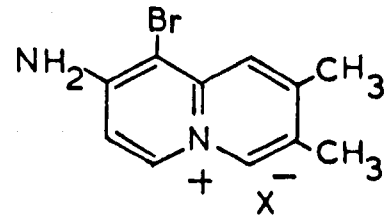
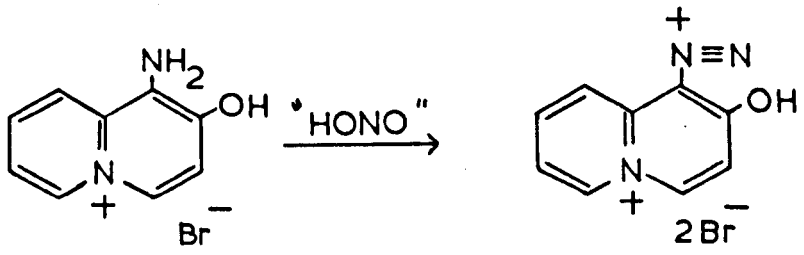


(39)

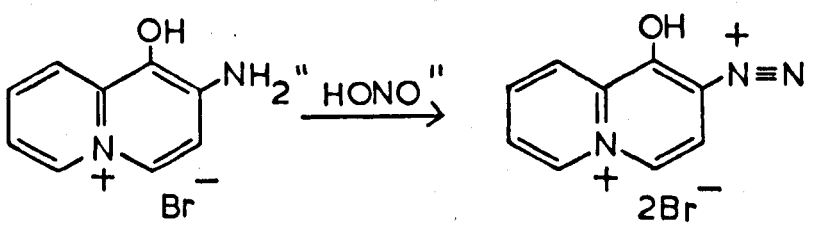
2-amino-7,8-dimethylquinolizinium bromide (20) gave 2-amino-1-bromo-7,8-dimethylquinolizinium bromide (39,X = Br). The other main reaction which has been performed on aminoquinolizinium salts is

treatment with nitrous acid. The action of aqueous nitrous acid on the 1-amino-2-hydroxyquinolizinium salt (40), obtained by acid hydrolysis of the acetamidoquinolizinium salt (8), gave a diazonium



(40) (41)

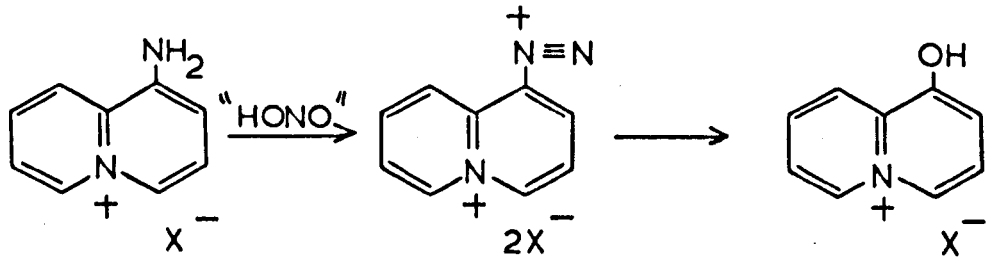
salt of unusual stability[2] (41) no decomposition being observed when the compound was heated to temperatures of 130° and above. On heating in dimethylformamide until nitrogen was evolved the diazonium group underwent nucleophilic replacement to give the 1-bromo-2-hydroxyquinolizinium bromide (30). Similarly Fozard and Jones[12] reported the diazotisation of 2-amino-1-hydroxyquinolizinium bromide (42) obtained by reduction of the zwitterion of 1-hydroxy-2-nitroquinolizinium bromide (32) to give another stable diazonium salt (43). Heating in



(42) (43)

dimethylformamide until nitrogen was evolved gave 2-bromo-1-hydroxyquinolizinium bromide (29).

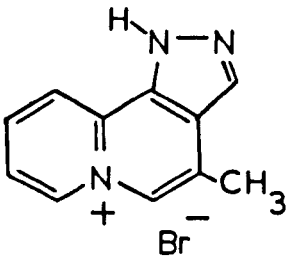
Diazotisation[1] of 1-aminoquinolizinium chloride (7, X = Cl) was achieved in acetic-sulphuric acid mixture with nitrosylsulphuric acid to give a diazonium compound (44) (the solution gave a deep red



(7) (44) (26)

colour with alkaline β-naphthol) but no 1-hydroxyquinolizinium salt could be isolated. Diazotisation of the 1-aminoquinolizinium chloride hydrochloride (7, X = Cl, as hydrochloride) in ethanol using pentyl nitrite gave the diazonium compound (44) which on diluting and heating gave 1-hydroxyquinolizinium picrate (26, X = picrate).

Nitrosation[15] of aminoquinolizinium salts containing active methyl groups (γ to the positive nitrogen) leads to tricyclic structures. Treatment of 1-amino-2,3-dimethylquinolizinium bromide (13) with sodium nitrite in aqueous acid gave a pyrazoloquinolizinium salt (45) resulting from intramolecular cyclisation. A similar pyrazoloquinolizinium salt was obtained from the bromoamine (35).



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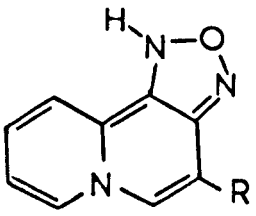


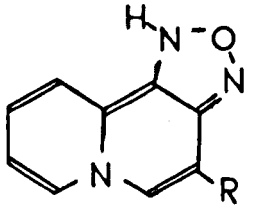
(46) R = H

(47) R = CH_3

Diazotisation[1] of the amine chloride (7, X = Cl) in very dilute acid solution with cold aqueous sodium nitrite gave a precipitate of a neutral species, $C_9H_7N_3O$ formulated as a furazan (46). Hough and Jones[15] reported a similar diazotisation of 1-amino-3-methylquinolizinium chloride to give an insoluble compound formulated as the 4-methyl 1H-1,2,5-oxadiazolo[3,4-a]quinolizine (47). They noted the initially precipitated material was yellow and had a different melting point from the final product (47); recrystallisation of this isomer from solvents containing a trace of acid gave rapid and irreversible conversion to the tricyclic compound (47).

DISCUSSION

The introduction made reference[1,16] to the reaction products resulting from nitrosation of 1-aminoquinolizinium salts. These were neutral nonionic compounds tentatively formulated as furazans (46, 47) and it was noted[16] that the primary product of the reaction of the aminoquinolizinium salt (16, X = Cl) was rapidly converted by traces of acid or base into a more stable isomer.

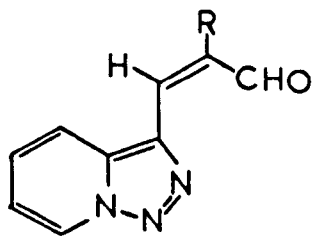


(46) R = H

(47) R = CH_3

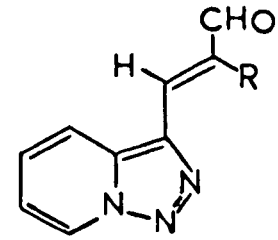
To investigate the structures of these products a detailed study of the reaction was undertaken. Most of the exploratory work on the product of nitrosation has been done on the products from 1-amino-3-methylquinolizinium salts[3] which were most readily available. Repetition of the nitrosation of 1-amino-quinolizinium chloride (7, X = Cl)[1] in very dilute acid solution showed the initially isolated material was again converted to the more stable isomer originally isolated by Collicutt and Jones[1]

under strongly acid conditions. The evidence given below shows these compounds to be the cis- (48, 49) and trans- (50, 51) isomers of 3-(3-v-triazolo[1,5-a]pyridyl)acraldehydes. It is



(48) R = H

(49) R = CH_3



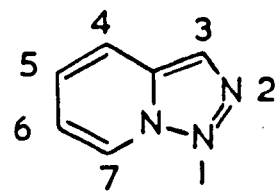
(50) R = H

(51) R = CH_3

therefore convenient to review the synthesis and properties of v-triazolo[1,5-a]pyridines.

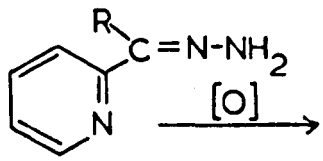
Review of v-Triazolo[1,5-a]pyridines

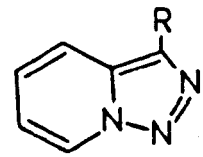
The term v-triazolo[1,5-a]pyridine has become the accepted terminology for the ring system (52) and is used in this thesis although the terms 2,3,4-pyridotriazole, 1,2,7a-triazaindene and 1,2,3-triazolo[3,4-a]pyridine have been used.

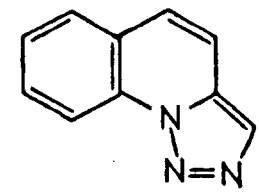


(52)

The preparation of v-triazolo[1,5-a]pyridine (52) has been reported by the oxidation of the hydrazone of pyridine-2-aldehyde (53) with silver oxide[17] or alkaline potassium ferricyanide.[18] The hydrazone of methyl-2-pyridylketone was similarly oxidised to the 3-methyl derivative (55).[18] Oxidation[17] of the hydrazones of quinoline-2-aldehyde and 2-benzoylpyridine with silver







(53) R = H

(54) R = CH_3

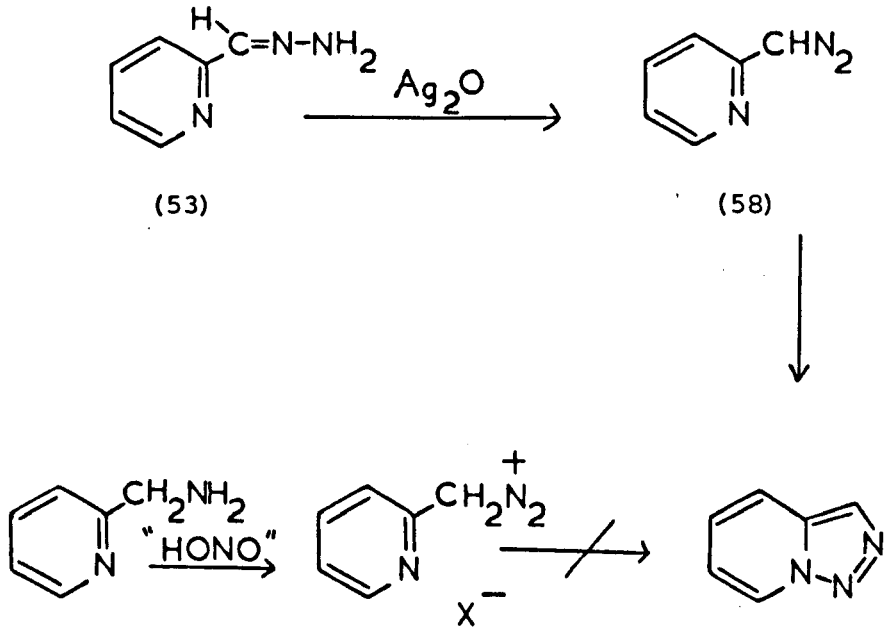
(52) R = H

(55) R = CH_3

(57) R = Ph

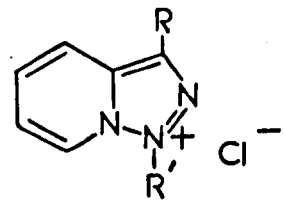
(56)

oxide was achieved at higher temperatures to give v-triazolo[1,5-a]-quinoline (56) and 3-phenyl-v-triazolo[1,5-a]pyridine (57). Boyer, Borgers, and Wolford[17] suggest the intermediate in the reaction is the 2-diazomethylpyridine (58). However diazotisation of 2-aminomethylpyridine (59) gave no v-triazolopyridine (52), the intermediate diazonium cation losing molecular nitrogen more rapidly than loss of a proton.



(53) (58) (59) (52)

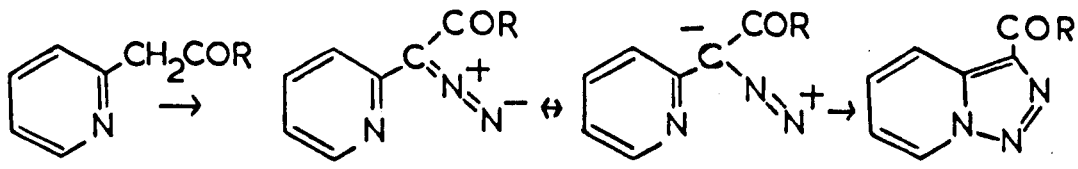
Kuhn and Münzing have reported that oxidation of the hydrazones of 2-acylpyridines with lead tetraacetate,[19] or N-bromosuccinimide,[20] followed by treatment with hydrogen chloride led to 3-substituted-v-triazolo[1,5-a]pyridinium salts (60).



(60)

There are several reports of the decomposition of the p-toluenesulphonylhydrazones of acylpyridines in basic media to give 3-substituted-v-triazolo[1,5-a]pyridines.[21,22,23]

Regitz[24,25,26] has shown that direct diazo transfer from p-toluenesulphonylazide onto β-iminoketones, for example alkyl- and aryl-(2-pyridyl)methyl ketones (61) in the presence of base, led to v-triazolo derivatives. Again the diazo stage (62) could not be

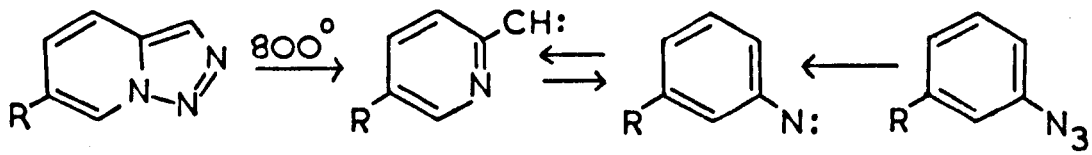


(61) (62) (63)

isolated but high yields of 3-acyl-v-triazolo[1,5-a]pyridines and quinolines were obtained.

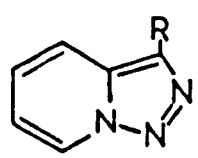
Most of the reactions reported of v-triazolo[1,5-a]pyridines involve loss of molecular nitrogen. Crow and Wentrup[27] report the pyrolysis of v-triazolo[1,5-a]pyridine at 500° to yield aniline (4%) and azobenzene (77%), products which are characteristic of phenyl nitrene. Similarly the 6-methyl derivative gave m-toluidine and

3,3'-dimethylazobenzene. The thermal extrusion of nitrogen at 800° gave 2-pyridyl carbene which was thermally interconverted to phenylnitrene. This was confirmed by the fact that the mass spectra of phenyl azide and v-triazolo[1,5-a]pyridine were identical suggesting a common set of structures for $C_6H_5N^*$.



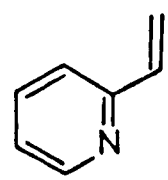
(64) (65) (66) (67)

Pyrolysis of 3-methyl-v-triazolo[1,5-a]pyridine (55) at 800° also resulted in loss of nitrogen and gave 2-vinylpyridine (67) while the corresponding phenyl derivative (57) isomerised thermally at 500° to give carbazole (68).

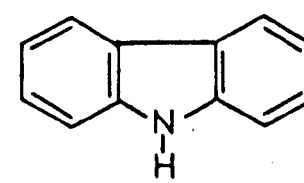


(55) R = CH_3

(57) R = Ph

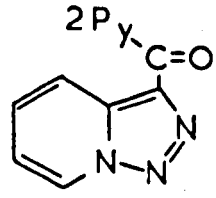


(67)

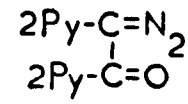


(68)

The irradiation of v-triazolopyridine (52) in methanol or acetic acid has been reported[21,28] to yield 2-picoline and its derivatives in low yield. Similar results were reported in strong acidic solvents.[17,21] In carboxylic acids v-triazolopyridines react to form esters of corresponding 2-pyridylcarbinols.[29] Triazolopyridines with electron withdrawing groups in the 3-position, for example 3-(2-picolinoyl)-v-triazolo[1,5-a]pyridine (69), were found to be resistant to the attack of carboxylic acids.[23] Bromine, iodine or boiling aniline transformed compound (69) to (70) which further reacted with elimination of nitrogen to give dihaloketones or di(2-pyridyl)acetanilide.

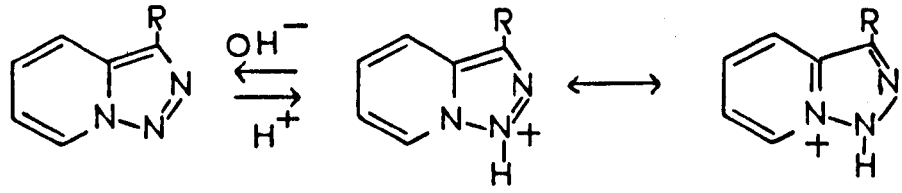


(69)



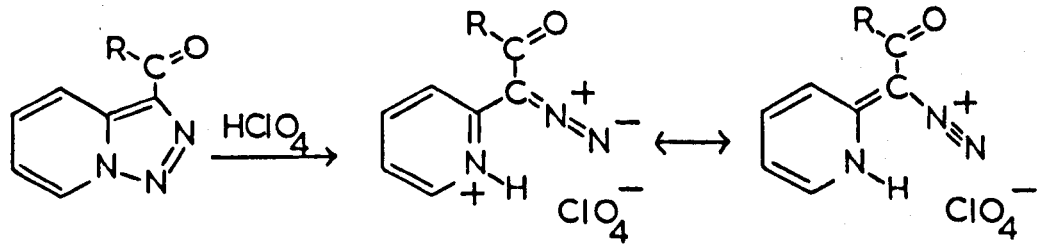
(70)

The unsubstituted v-triazolopyridine (52) reacted with bromine to give dibromo-2-picoline.[30] With aqueous silver nitrate it gave a silver salt complex[17] and gave a methiodide in 1:1 ratio with methyl iodide.[18] Protonation[29] with dilute acid gave a stable conjugate acid, the stability reflecting the contribution of the pyridinium cation (72).



(71) (72)

Regitz[26] has reported that treatment of 3-acyl-v-triazolo-[1,5-a]pyridines (63) with perchloric acid in dioxane resulted in ring cleavage and led to yellow-orange perchlorates of the diazo stage (73) which could not be isolated during the diazo transfer onto the ketone (61). The salts were cyclised by loss of perchloric acid even in ethanol with regeneration of the triazoles (63).



(63) (73)

Reimlinger and co-workers[22] have reported the oxidative degradation of 3-phenyl-v-triazolo[1,5-a]pyridine (57) to

60 MHz N.m.r. spectrum of cis-3-(3-v-triazolo[1,5-a]pyridyl)acraldehyde (48) in $CDCl_3$

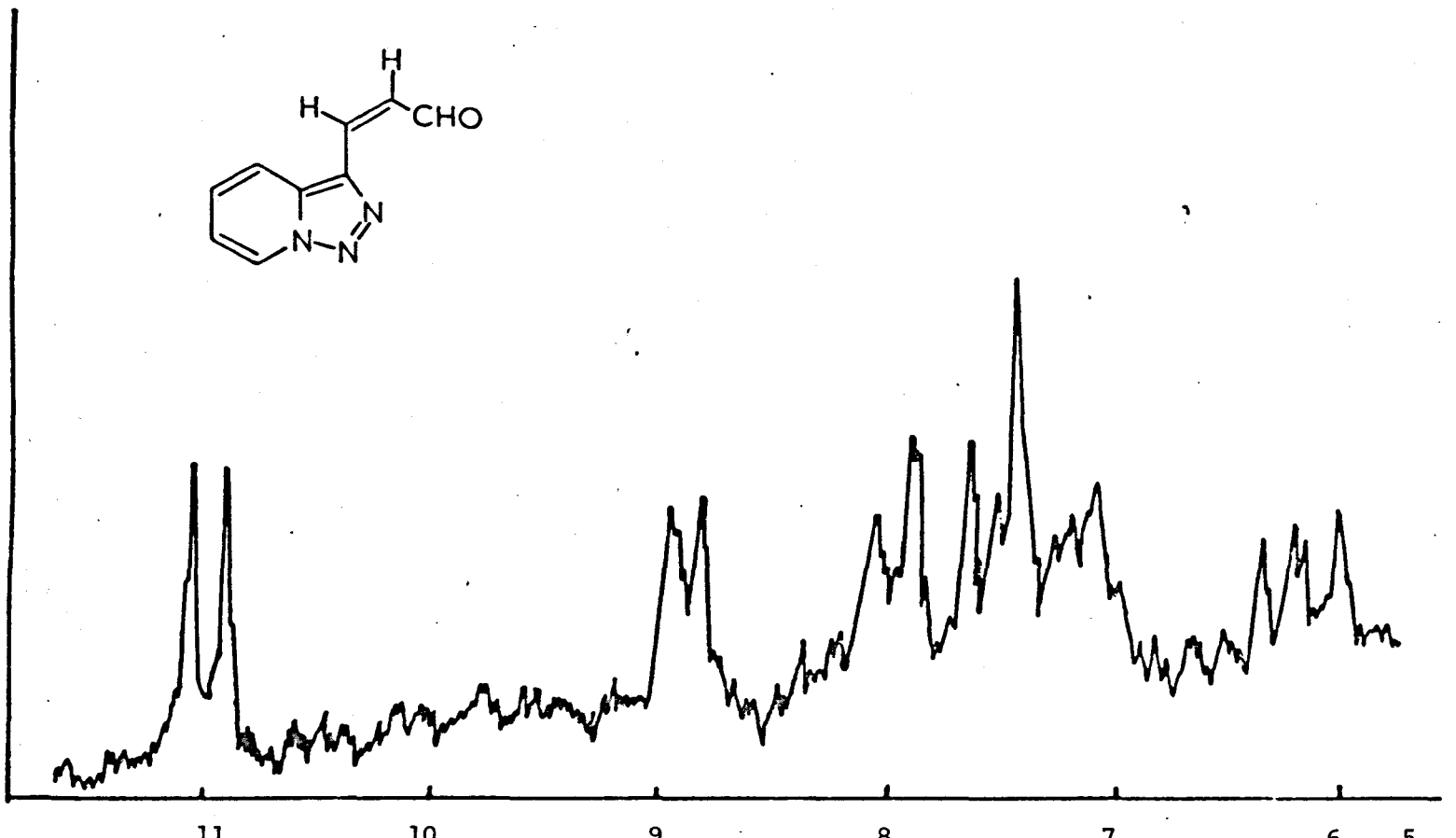


Figure 1

100 MHz N.m.r. spectrum of trans-3-(3-v-triazolo[1,5-a]pyridyl)-acraldehyde (49) in DMSO

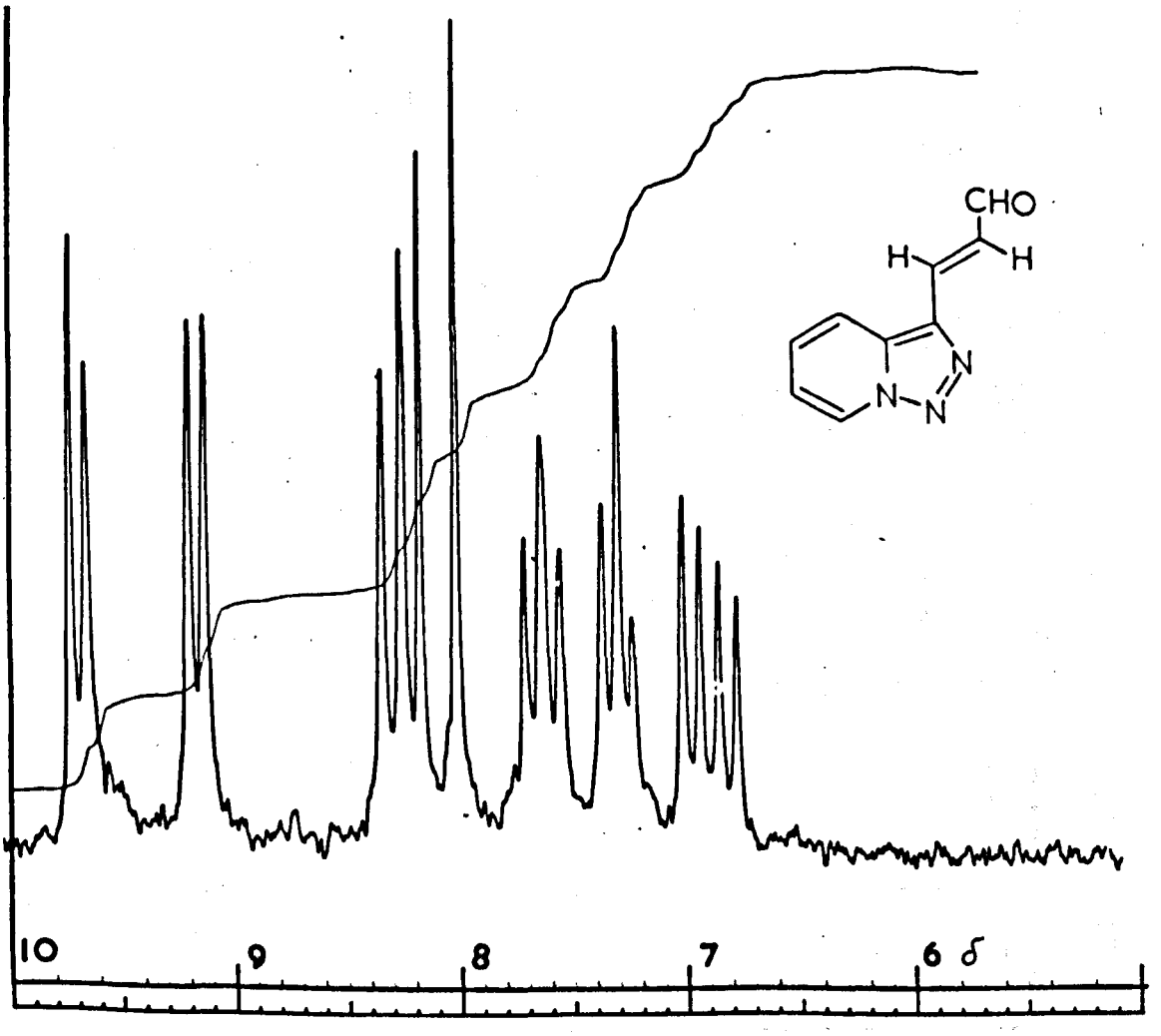


Figure 2

100 MHz N.m.r. spectrum of a mixture of cis- (48) and trans-3-(3-v-triazolo[1,5-a]pyridyl)-acraldehyde (49) in $CDCl_3$

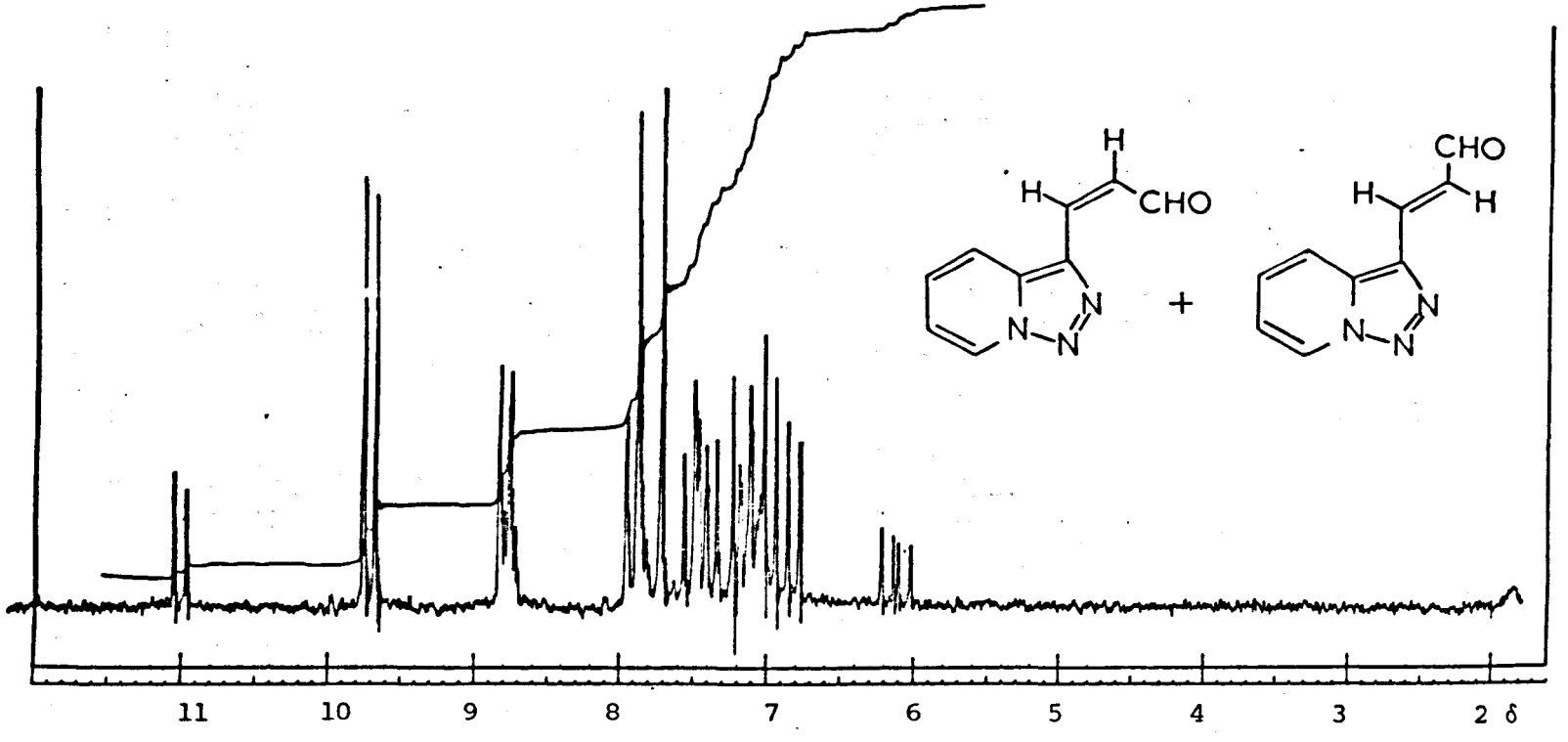


Figure 3

100 MHz N.m.r. spectrum of cis- (48) and trans-3-(3-v-triazolo-[1,5-a]pyridyl)acraldehyde (49) in $CDCl_3$

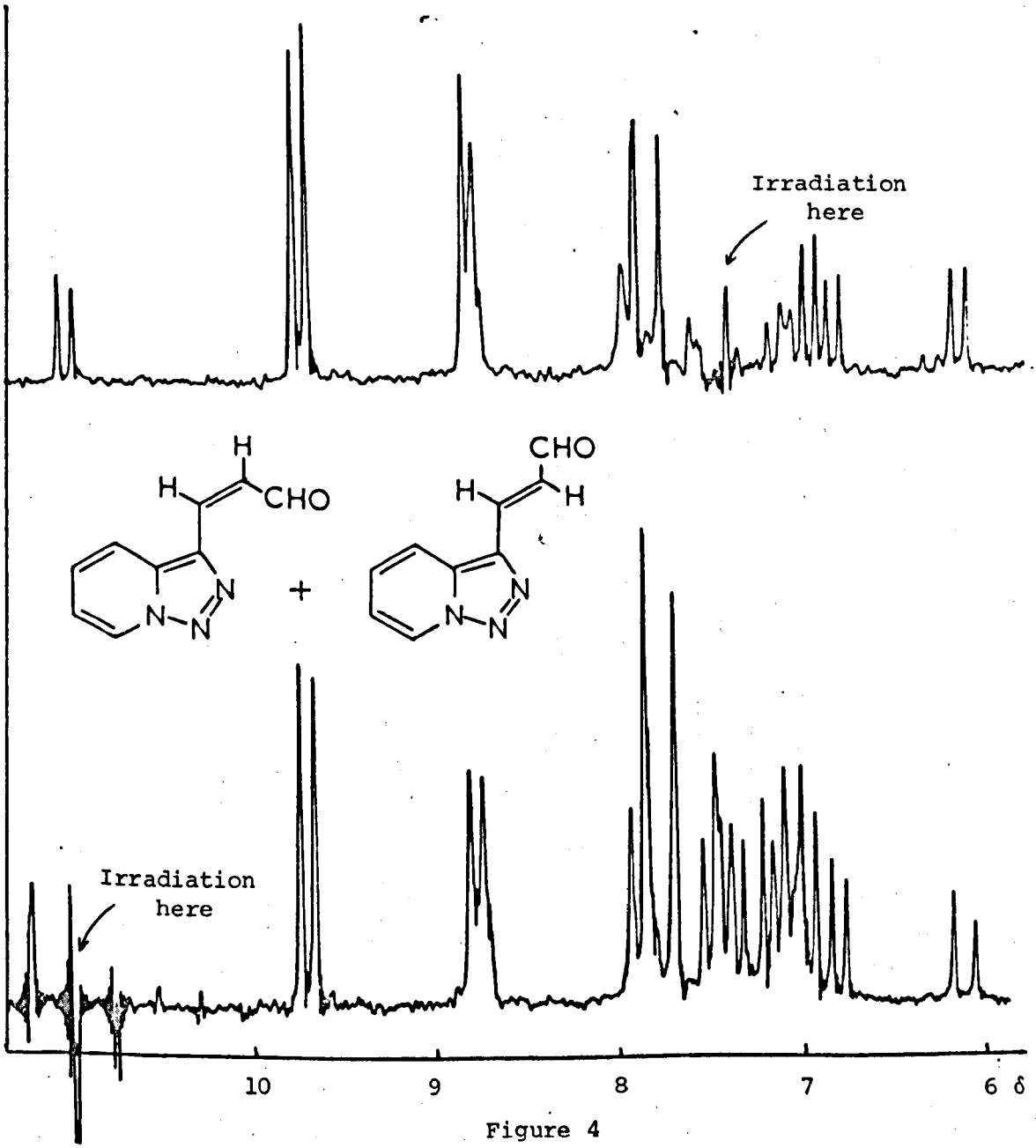


Figure 4

100 MHz N.m.r. spectrum of cis- (48) and trans-3-(3-v-triazolo[1,5-a]-pyridyl)acraldehyde (49) in $CDCl_3$

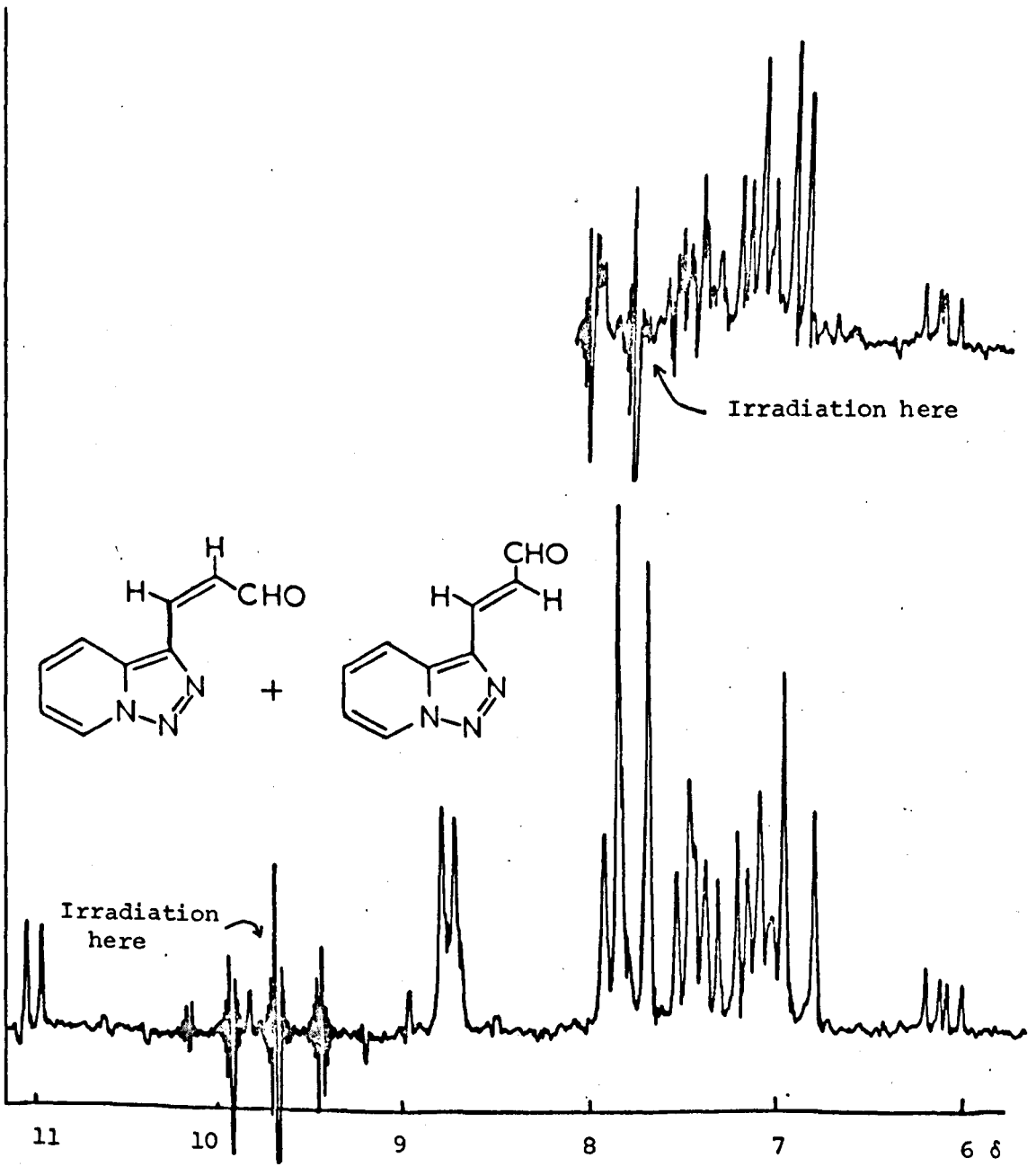
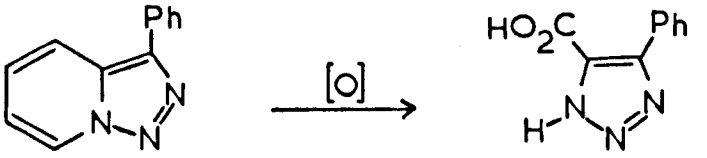


Figure 5

4-phenyl-1,2,3-triazole-5-carboxylic acid (74).

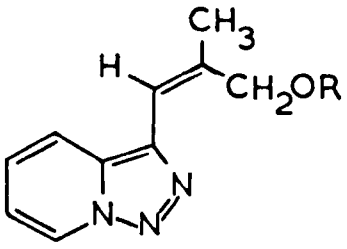


(57) (74)

The ultraviolet spectrum of v-triazolo[1,5-a]pyridine (52) has been reported[18] and this has been interpreted[31,32] in terms of the molecular orbitals and electronic structure of the ring system.

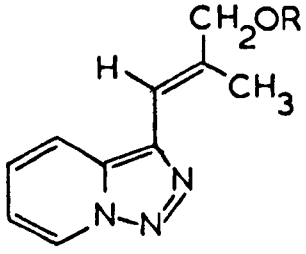
The nuclear magnetic resonance (n.m.r.) spectra (fig. 1-3) of compounds (48) and (49) show downfield one proton signals at δ10.98 and δ10.9 parts per million (p.p.m.); in the corresponding trans-isomers (50) and (51) these were at δ9.7 and δ9.6 p.p.m. respectively. They were doublets in compounds (48) and (50), and singlets in (49) and (51) indicating the grouping C.(R).CHO. Spin-decoupling experiments on the parent compounds (48) and (50) (fig. 4,5) revealed the sequence $\overset{\beta}{CH}=\overset{\alpha}{CH}-CHO$ and the coupling constants $J_{\alpha\beta}$ were 12 Hz and 16 Hz respectively indicating a cis and trans relationship in a β-substituted acraldehyde. Further discussion of the spectral details is given later. The presence of the aldehyde function was

confirmed by reduction with sodium borohydride to the isomeric primary alcohols (75) and (76).



(75) R = H

(77) R = $COCH_3$



(76) R = H

(78) R = $COCH_3$

Treatment with acetic anhydride gave the corresponding acetates (77) and (78). The alcohols showed much more similarity in their n.m.r. spectra than did the aldehydes; the major difference being in the width of the -OH signal, which was much larger in the cis- (75) than the trans- alcohol (76). This indication of intramolecular hydrogen bonding being confirmed by dilution studies on the infra red (i.r.) absorption at 3370 cm^{-1}. A plot of extinction coefficient against molar concentration (fig. 6) gave a non-zero intercept when extrapolated to zero concentration which indicated the hydrogen bonding was intra- rather than intermolecular.[33]

Oxidation of the aldehydes (49) or (51), or alcohols (75) or (76) with periodate-permanganate[34] gave in all cases a crystalline product of empirical formula $C_7H_5N_3O$ initially formulated as

Plot of Extinction Coefficient of Absorption at 3370 cm.$^{-1}$: Molar Concentration of cis-2-Methyl-3-(3-v-triazolo[1,5-a]-pyridyl)allyl Alcohol (75)

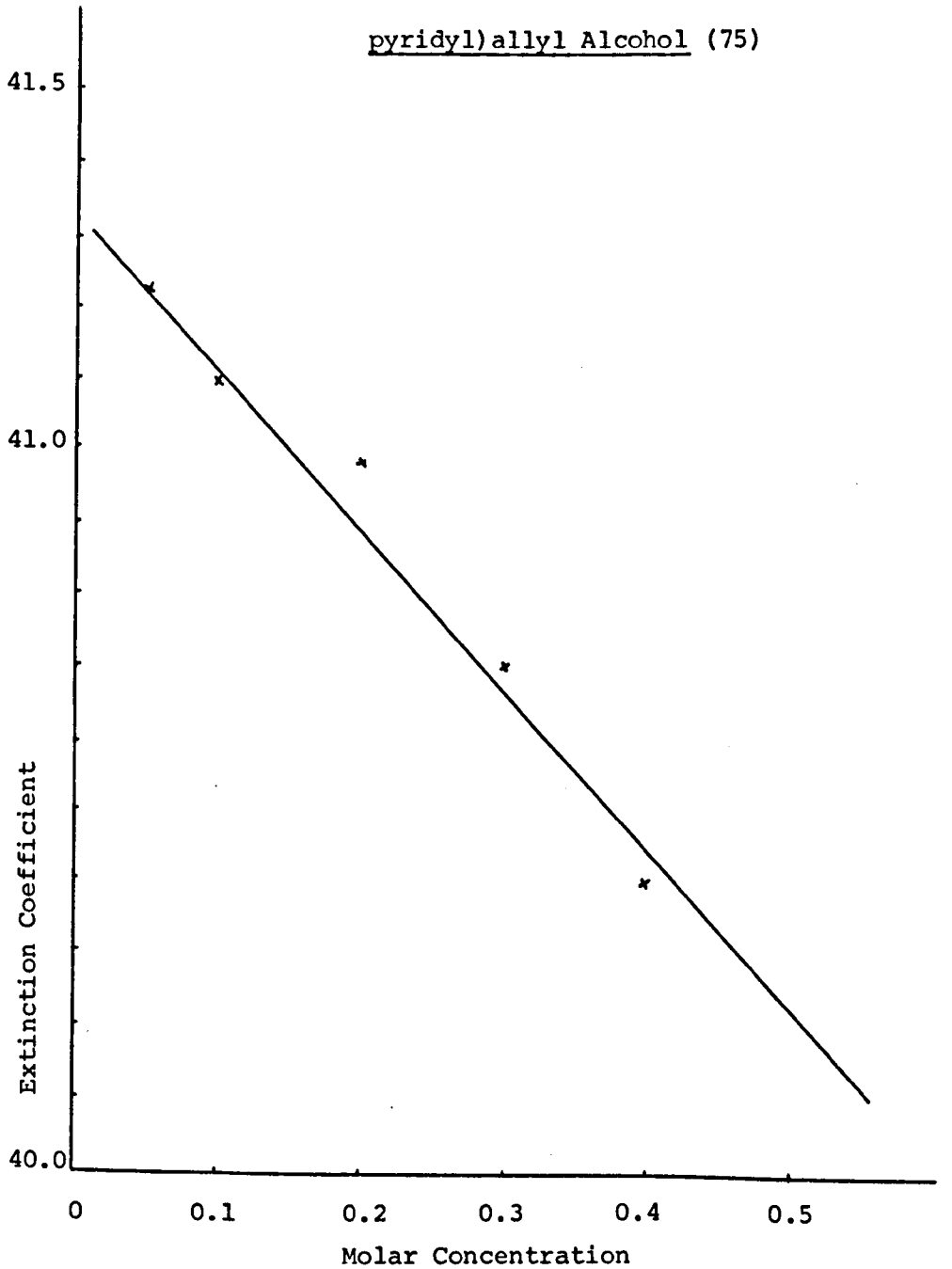
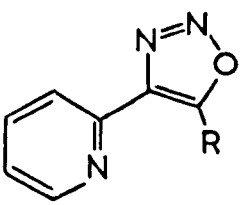


Figure 6

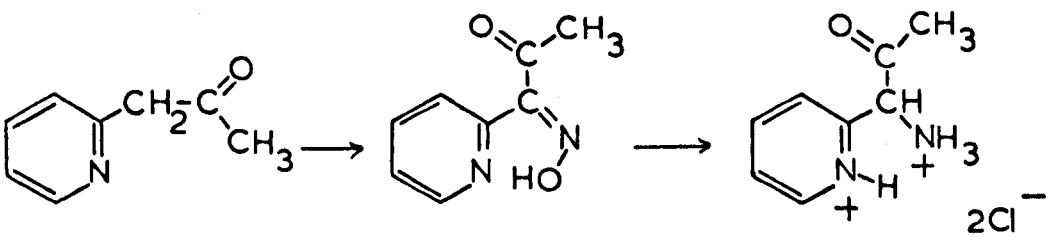
4-(2-pyridyl)-1,2,3-oxadiazole (79). An identical product was obtained in better yield by the action of powdered potassium permanganate in acetone on the cis-aldehyde (49).



(79) R = H

(80) R = CH_3

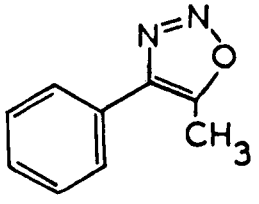
Attempts were then made to synthesise the 5-methyl derivative (80) of this oxadiazole by diazotisation of 1-amino-1-(2-pyridyl)propan-2-one dihydrochloride (83).



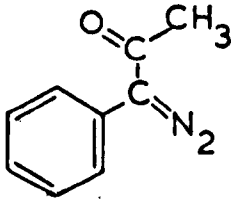
(81) (82) (83)

It was possible to obtain the iso-nitrosopyridylpropanone (82) in good yield by treatment of a solution of 1-(2-pyridyl)-propan-2-one[35] (81) in ethanol (saturated with hydrogen chloride)

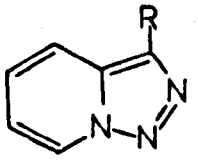
with pentyl nitrite followed by catalytic hydrogenation which gave 1-amino-1-(2-pyridyl)propan-2-one dihydrochloride (83). However this compound proved very unstable and it was not possible to purify the crude product without decomposition. Hence attempts were made to obtain 5-methyl-4-phenyl-1,2,3-oxadiazole (84) from the known 1-amino-1-phenyl-propan-2-one[36] by a similar route. However under a variety of conditions with nitrous acid the amino-ketone either failed to react or gave a complex mixture of products. The isocyclic 1-diazo-1-phenyl-propan-2-one (85) was prepared by the method of Hendrickson and Wolf[37] from phenylpropanone and p-toluenesulphonyl azide[38] in the presence of sodium hydride and shown to have an i.r. diazo absorption at 2080 cm^{-1}.



(84)



(85)



(86) R = H

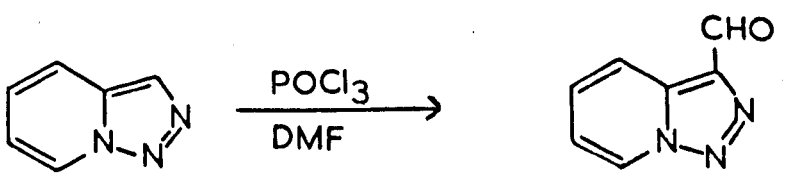
(87) R = CHO

An attempt to obtain 1-diazo-1-(2-pyridyl)propan-2-one from 1-(2-pyridyl)propan-2-one[35] using the same reagents resulted in isolation

of v-triazolo[1,5-a]pyridine (86), the structure of which was confirmed by comparison of its spectral details and melting point with an authentic sample synthesised by oxidation of the hydrazone of pyridine-2-aldehyde (53) by the method of Bower and Ramage.[18]

Although Wolff[39] formulated the structure of α-diazoketones as cyclic 1,2,3-oxadiazoles, Hodgson and Dodgson[40] have presented evidence that shows α-diazoketones to exist as open-chain compounds unlike 1,2,3-thiadiazoles (diazosulphides) which exist as cyclic structures. This together with the i.r. diazo absorption of phenyldiazopropanone led to rejection of the proposed 1,2,3-oxadiazole structure (79).

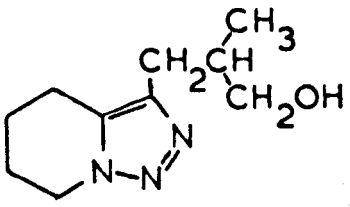
The formulation of the oxidation product of aldehydes (49) and (51), or alcohols (75) and (76) as 3-formyl-v-triazolo[1,5-a]-pyridine (87) was confirmed by treatment of the parent v-triazolo-[1,5-a]pyridine (86)[18] in ethylene dichloride, with a mixture of dimethylformamide and phosphorus oxychloride to give in poor yield the aldehyde (87). The specimens had identical melting point and spectra.



(86) (87)

An attempt to synthesise the acraldehyde (50) by an aldol condensation between 3-formyl-triazolopyridine (87) and acetaldehyde in the presence of sodium hydroxide proved unsuccessful, as did the attempted synthesis of acraldehyde (51) with propionaldehyde and potassium hydroxide; 3-formyltriazolo-pyridine (87) was recovered in each case.

Catalytic hydrogenation of the alcohol (76) over palladium-charcoal in ethanol resulted in absorption of three molar equivalents of hydrogen and the isolation of a primary alcohol (88).

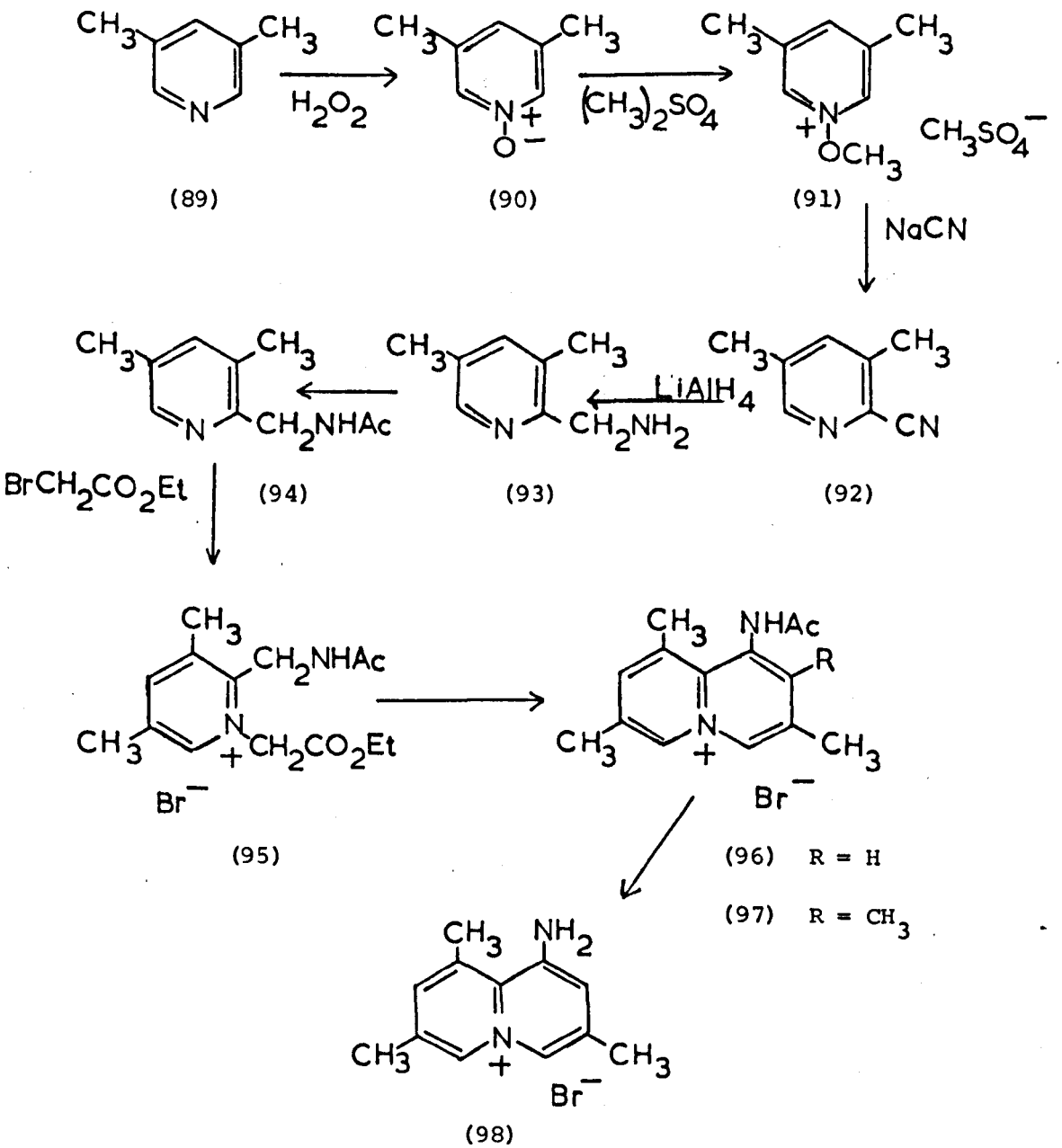


(88)

The ultraviolet (u.v.) absorption of the product (λ_{max} 225 nm.) showed the presence of a simple v-triazole, which are known to be resistant to catalytic hydrogenation.[41]

To examine the generality of the rearrangement, a study of the reaction between other substituted 1-aminoquinolizinium salts and aqueous nitrous acid was made. Hough and Jones[16] have shown that methyl groups in positions 2 and 8 of the quinolizinium ring were reactive in the nitrosation reaction and so the first attempted

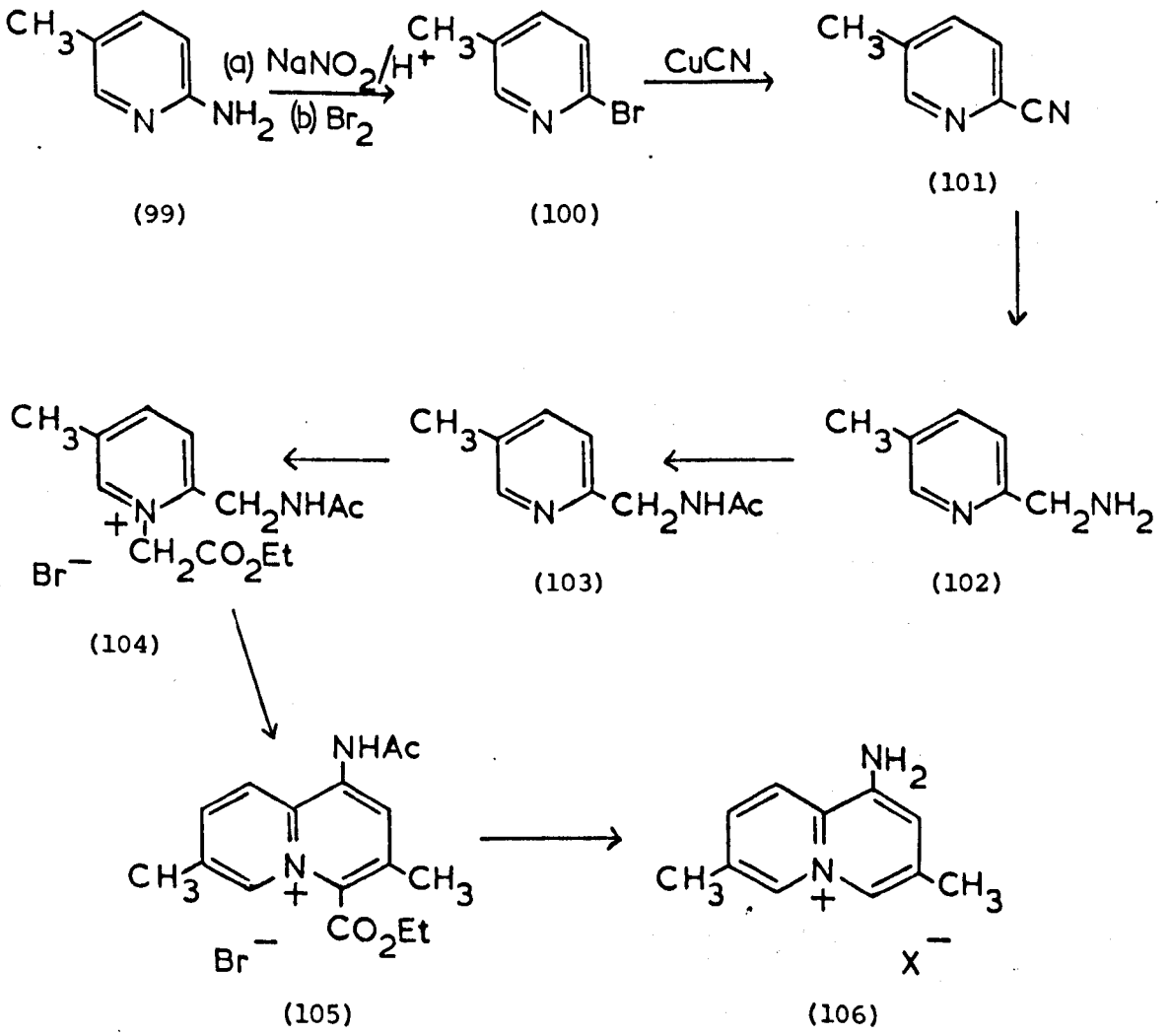
synthesis was of 1-amino-3,7,9-trimethylquinolizinium bromide (98) by the route outlined below.



Treatment of 3,5-dimethylpyridine (89) with hydrogen peroxide in acetic acid at 70°-80° gave 3,5-dimethylpyridine-1-oxide[42] (90) which with dimethyl sulphate gave 3,5-dimethyl-1-methoxypyridinium methosulphate (91). This, when treated with sodium cyanide in water by the method of Feely and Beavers[43] gave 2-cyano-3,5-dimethylpyridine[44] (92). Reduction was achieved with lithium aluminium hydride to the aminomethyl compound (93), followed by acylation with acetic anhydride to give 2-acetamidomethyl-3,5-dimethylpyridine (94). This was quaternised with ethyl bromo-acetate in sulpholane at 35° over a period of 3 days to give 2-acetamidomethyl-1-carbethoxymethyl-3,5-dimethylpyridinium bromide (95). However when this salt was boiled with pyruvic aldehyde and di-n-butylamine in ethanol the only isolable product was di-n-butyl-amine hydrobromide, with no quinolizinium salt being formed. To confirm the formation of the quaternary salt (95) it was boiled with diacetyl and di-n-butylamine in ethanol to give 1-acetamido-2,3,7,9-tetramethylquinolizinium bromide (97) in poor yield. The isolation of di-n-butylamine hydrobromide in the former case was attributed to an intramolecular cyclisation leading to an indolizine rather than intermolecularly to give a quinolizinium salt. Work done by Hough[45] has shown that the reactivity of the 2-methyl or methylene group in the pyridinium salt together with the α-diketone used in the condensation are the determining factors in the type of cyclisation

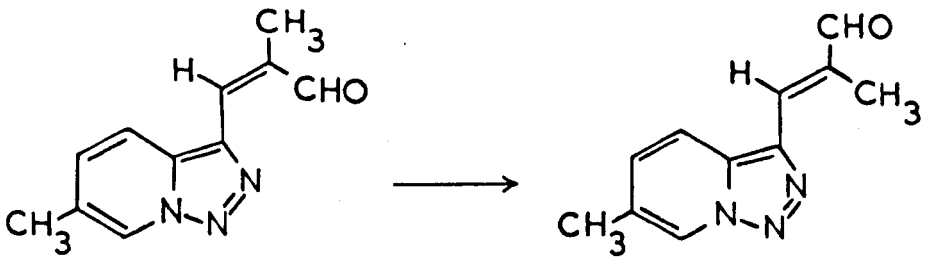
that occurs. Hough showed the effect of an electron withdrawing group ($-CO_2Et$, $-CONH_2$) in position 3 of the salt enhanced the activity of the 2-methyl group sufficiently for intramolecular cyclisation to occur.

Due to the failure of the previous synthesis to produce a suitable aminoquinolizinium salt 1-amino-3,7-dimethylquinolizinium bromide (106) was prepared by the following route.



Decomposition of the diazonium salt, formed by diazotisation of 2-amino-5-methylpyridine (99) in the presence of bromine gave 2-bromo-5-methylpyridine (100).[46] The cyano compound (101)[47] was prepared by the dry distillation of the product from an intimate mixture of cuprous cyanide and 2-bromo-5-methylpyridine (100). The cyanopyridine (101) was reduced, acylated and quaternised as before to yield 2-acetamidomethyl-1-carbethoxymethyl-5-methylpyridinium bromide (104). Boiling a solution of this salt with pyruvic aldehyde and di-n-butylamine in ethanol gave 1-acetamido-4-carbethoxy-3,7-dimethylquinolizinium bromide (105). Acid hydrolysis gave 1-amino-3,7-dimethylquinolizinium bromide (106, X = Br). This was converted to the chloride (106, X = Cl) by passage down a chloride loaded ion-exchange resin column.

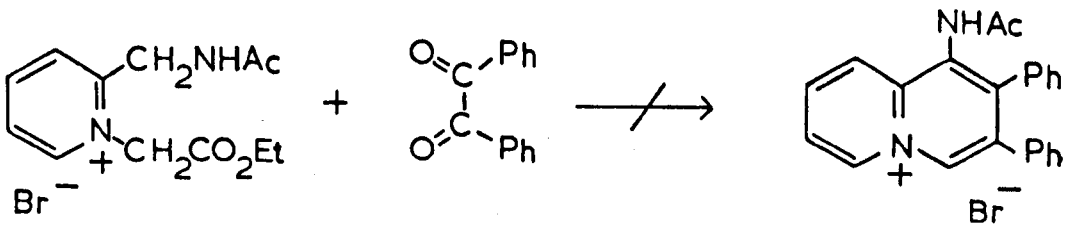
Nitrosation of this aminoquinolizinium chloride (106, X = Cl) at room temperature with an excess of saturated aqueous sodium nitrite gave an insoluble material whose n.m.r. spectrum again showed the downfield one proton singlet at δ10.8 p.p.m. indicating rearrangement to cis-2-methyl-3-(6-methyl-3-v-triazolo[1,5-a]pyridyl)-acraldehyde (107) had occurred. This was isomerised with piperidine



(107) (108)

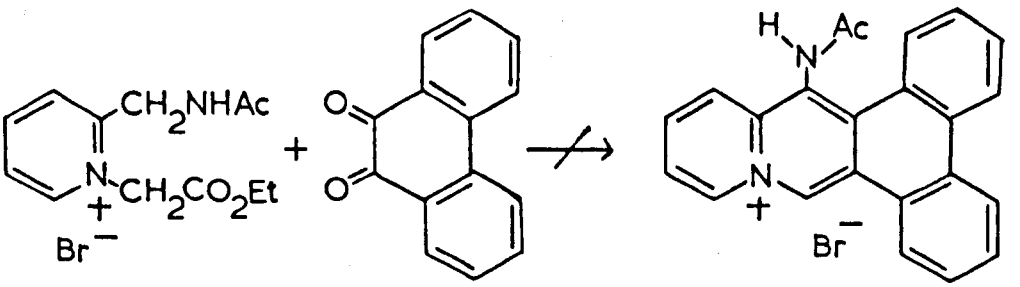
in ethanol to the trans-acraldehyde (108). An aldehyde singlet at δ9.56 p.p.m. in the n.m.r. spectrum confirmed the trans assignment.

Due to the facile isomerisation of the acraldehydes so far prepared it was thought that the introduction of bulky or cyclic substituents at positions 2 and 3 of the acraldehyde might make the isomerisation more difficult. Attempts to make 1-acetamido-2,3-diphenylquinolizinium bromide (109) by boiling a mixture of 2-acetamidomethyl-1-carbethoxymethylpyridinium bromide (10)[3] with benzil and di-n-butylamine (or ammonia) in ethanol were unsuccessful; the only isolated material being di-n-butylamine hydrobromide or ammonium bromide.



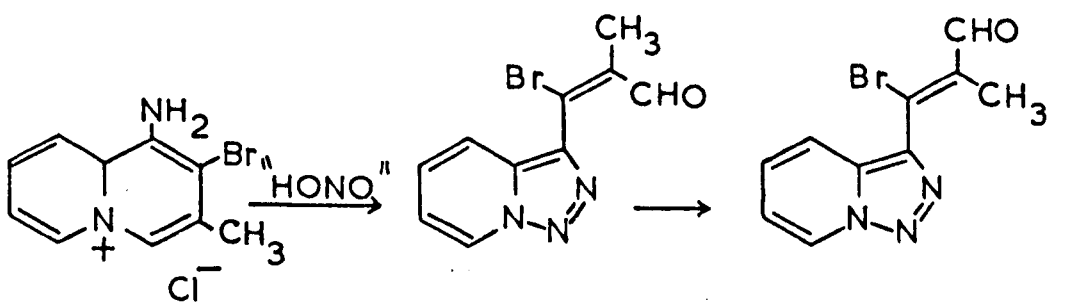
(10) (109)

An attempt to prepare 15-acetamidophenanthro[9,10-b]-quinolizinium bromide (110) by boiling a mixture of the quaternary salt (10) with 9,10-phenanthraquinone and sodium bicarbonate in acetone-ethanol was also unsuccessful.



(10) (110)

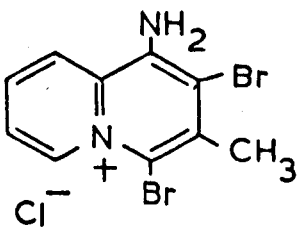
Treatment of 1-amino-2-bromo-3-methylquinolizinium chloride (37, X = Cl)[16] with excess saturated aqueous sodium nitrite at 0° in dilute hydrochloric acid gave a mixture of the cis- (111) and trans-aldehydes (112) indicated by the absorptions at δ9.67 p.p.m. and δ9.9 p.p.m. in the n.m.r. spectrum. In nearly neutral medium almost pure cis-aldehyde was obtained.



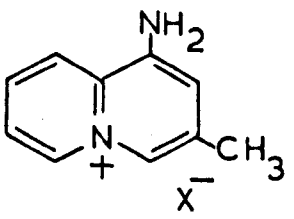
(37, X = Cl) (111) (112)

The isomerisation of the cis-aldehyde proved more difficult in this case, requiring hot glacial acetic acid to form the trans-aldehyde (112). This was attributed to the non-planarity of the side-chain and triazolopyridine ring further discussed below. That the triazole ring of the bromoacraldehyde (111) was stable to treatment with hot carboxylic acid confirms the work of Boyer and Goebel[32] which showed that v-triazolo[1,5-a]-pyridines containing electron withdrawing groups in the 3-position were resistant to acidic attack.

The 1-amino-2,4-dibromo-3-methylquinolizinium salt (38, X = Cl),[16] which was expected to give either the triazolo-pyridylacrylic acid or the corresponding acid bromide, when treated with saturated aqueous sodium nitrite in dilute hydrochloric acid at room temperature, failed to give a precipitate. Extraction of the aqueous solution with chloroform gave a tar from which no pure material could be isolated.

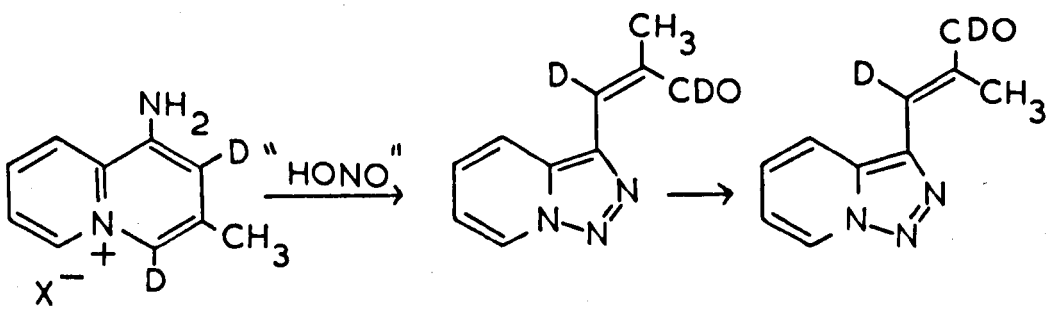


(38)



(16)

Electrophilic substitution of hydrogen by deuterium in 1-amino-3-methylquinolizinium chloride (16, X = Cl) occurred on heating in concentrated deuterosulphuric acid at 150° for 24 hours and led to replacement of the 2H and an 80% replacement of the 4H. Further heating resulted in exchange of the methyl H by D. Nitrous acid treatment of the predominantly 1-amino-2,4-dideutero-3-methylquinolizinium salt (113) gave a cis-aldehyde (114) which was isomerised to a trans-aldehyde (115) by piperidine in ethanol.

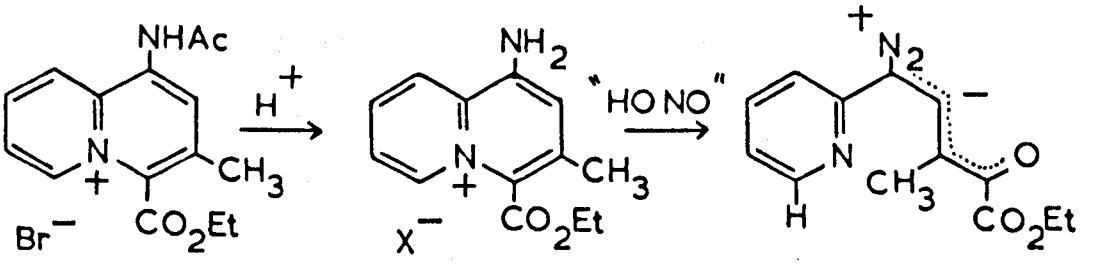


(113) (114) (115)

In both isomers the deuterium substituents appeared to be completely retained by n.m.r. and mass spectral measurements indicating that at no stage during the rearrangement reaction were these atoms exchangeable with the aqueous solvent.

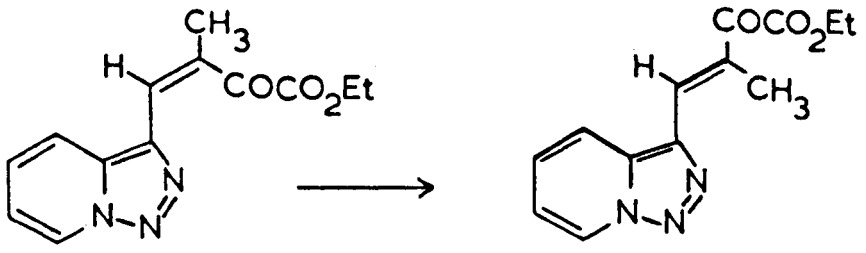
A further example which provided an insight to the mechanism of the rearrangement was the reaction of 1-amino-4-carbethoxy-3-methylquinolizinium chloride (116, X = Cl) prepared by the mild acid

hydrolysis of 1-acetamido-4-carbethoxy-3-methylquinolizinium bromide (15).[3] Soxhlet extraction of the hydrolysis residue with chloroform gave the aminocarbethoxy salt which was converted to the chloride by passage down a chloride loaded ion-exchange resin column. Treatment with nitrous acid at room temperature gave a precipitate which showed a sharp absorption maximum at 2270 cm^{-1} which corresponds to that expected for the intermediate diazo derivative (117). The integral of peaks at δ2.05 and δ2.2



(15) (116) (117)

p.p.m. and δ8.63 and δ8.75 p.p.m. in the n.m.r. spectrum showed the crude product contained 24% of the uncyclised diazo compound (117). Crystallisation from methanol gave the pure cis-ketoester (118) which was isomerised by treatment with piperidine in chloroform to the trans-ketoester (119).



(118) (119)

The intermediate diazo-aldehyde in the rearrangement was never observed in any of the examples described. The stability of the monocyclic intermediate (117), a vinylogous diazo ketone, therefore agrees well with the known greater stability of diazo ketones over diazo aldehydes.

The isomerisation of the cis-aldehydes to the corresponding trans-compounds has already been mentioned, a variety of reagents having been used; piperidine in ethanol, acetic acid or piperidine in chloroform. The isomerisation of cis-2-methyl-3-(3-v-triazolo[1,5-a]-pyridyl)allyl alcohol (76) proved more difficult. Treatment with sodium hydroxide (10%) at 100° for one hour gave after neutralisation and extraction, a mixture of the starting cis-alcohol (75) (66%) and the trans-isomer (76) (33%) shown by the integral of the absorptions due to $-\underline{CH_2}OH$ in the n.m.r. spectrum at δ4.5 (cis) and δ4.38 p.p.m. (trans).

60 MHz N.m.r. spectrum of 3-methyl-1-(2-pyridyl)but-3-en-1-yne (120) in $CDCl_3$

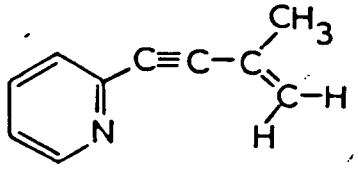
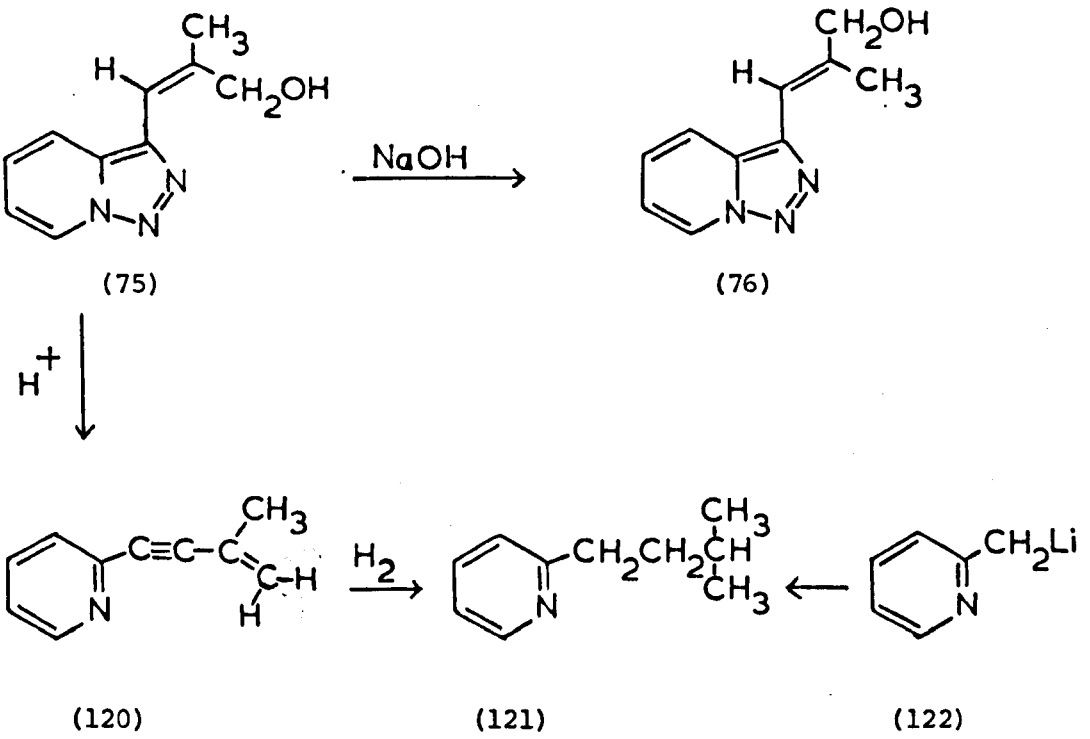


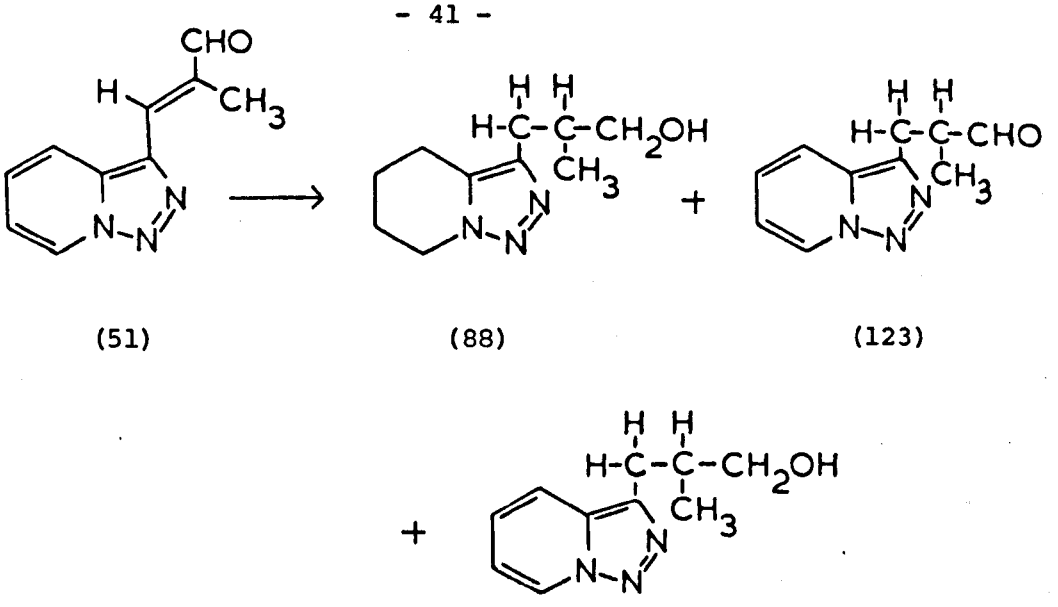
Figure 7



An attempt to induce isomerisation of the alcohol (75) to (76) using dilute hydrochloric acid at 100° proved unsuccessful. Cleavage of the triazole ring occurred with loss of nitrogen, as for the parent v-triazolo[1,5-a]pyridine[27,30] (52), followed by deoxygenation to yield 3-methyl-1-(2-pyridyl)but-3-en-1-yne (120) identified by the n.m.r. spectrum (fig. 7) which had a methyl doublet at δ2.0 p.p.m. (J = 1 Hz), trans-vinyl proton multiplet at δ5.35 p.p.m. cis-vinyl proton singlet at δ5.4 p.p.m. Aromatic proton absorptions in the region δ7-7.7 p.p.m. integrated in the ratio of 3 protons with the α-pyridine proton as a doublet at δ8.5 p.p.m. The presence of the acetylene group was confirmed by an

absorption at 2220 cm^{-1}. This oil was unstable above room temperature but catalytic hydrogenation over palladium-charcoal resulted in uptake of three molar equivalents of hydrogen to give 3-methyl-1-(2-pyridyl)butane (121) which was identical in all spectral details with a sample synthesised[48] from 2-picolyl-lithium (122) and isobutyl bromide. A mixed melting point of the picrates prepared from each sample showed no depression. Bromination and hydrogenation of the trans-(triazolo[1,5-a]pyridyl)acraldehyde (51) were reactions further illustrating the properties of the system. Attempted bromination by boiling a solution of trans-acraldehyde (51) in chloroform with bromine for 12 hours gave on evaporation an intractable tar from which no pure material could be obtained. Decomposition was attributed to the presence of acid because when the reaction was repeated in the presence of diethyl-amine starting material was recovered unchanged.

Catalytic hydrogenation of the trans-aldehyde (51) using palladium-charcoal in ethanol resulted in a complex mixture of products. The n.m.r. spectrum showed the presence of the fully hydrogenated material (88) together with material showing absorptions due to some 3-substituted-v-triazolo[1,5-a]pyridine.



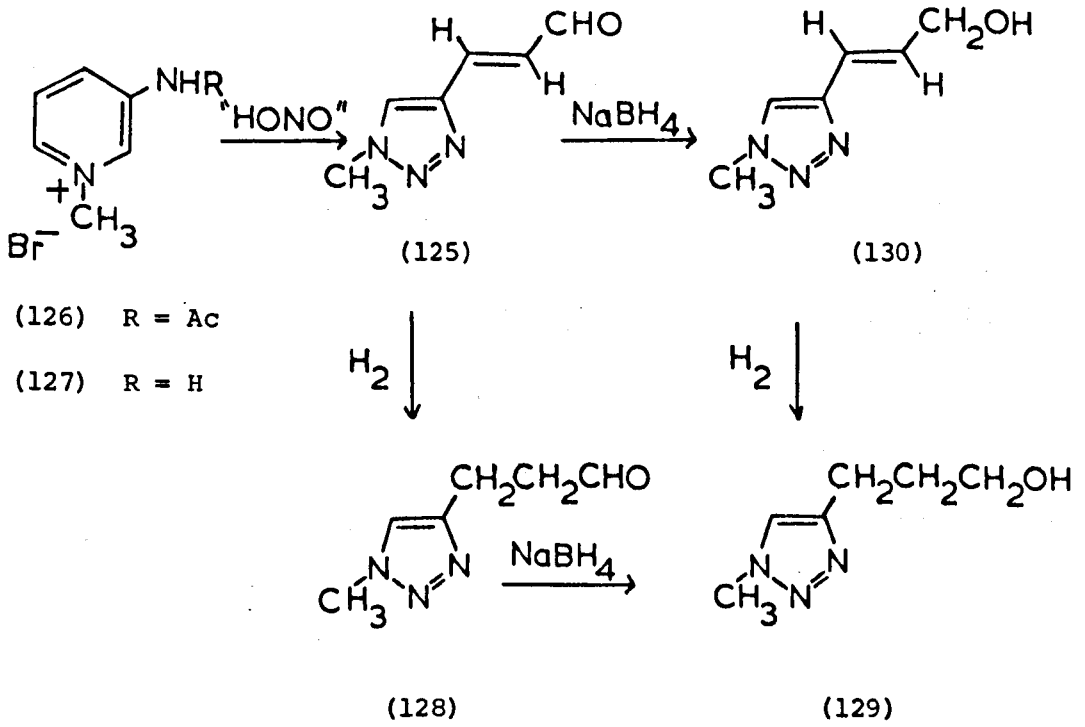
(51) (88) (123)

(124)

These were identified as 3-(3-v-triazolo[1,5-a]pyridyl)-2-methylpropanol (124) and 3-(3-v-triazolo[1,5-a]pyridyl)-2-methylpropionaldehyde (123). Partial purification of the aldehyde (123) was achieved by preparative layer chromatography. The n.m.r. spectrum showed an aldehyde singlet absorption at δ10.5 p.p.m. and a methyl doublet at δ1.25 p.p.m. (J = 7 Hz). Confirmation of the presence of the aldehyde was obtained by treatment with sodium borohydride in ethanol to give the 3-(3-v-triazolo[1,5-a]pyridyl)-2-methylpropanol (124).

3-(1-Methyl-v-triazolyl-4)-acraldehyde (125)[49] gave similar results. This was prepared by treating 3-acetamidopyridine[50] with dimethyl sulphate and then with concentrated hydrobromic acid

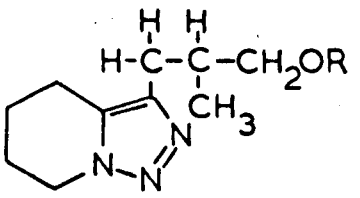
to give 3-acetamido-1-methylpyridinium bromide (126) which was hydrolysed to the amino derivative (127). Diazotisation with sodium nitrite in dilute hydrobromic acid followed by evaporation and extraction gave the v-triazolylacraldehyde (125).

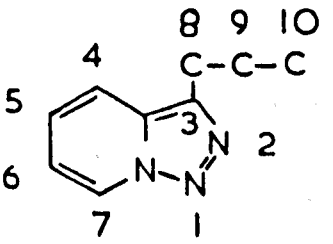


Catalytic hydrogenation of (125) gave 3-(1-methyl-v-triazolo-4)-propionaldehyde (128) contaminated with 3-(1-methyl-v-triazolo-4)-propanol. The n.m.r. spectrum of the purified material again showing an aldehyde absorption at δ9.8 p.p.m. as a singlet. However scale expansion of the n.m.r. spectrum showed that the

aldehyde proton was very weakly coupled and the absorption at δ9.8 was a broadened singlet. Treatment of this aldehyde (128) with sodium borohydride gave the propanol (129) also prepared by treatment of the acraldehyde (125) with sodium borohydride to give the 3-(1-methyl-v-triazolo-4)-allyl alcohol (130) followed by catalytic hydrogenation over palladium charcoal.

Hydrogenation of the trans-aldehyde (51) in glacial acetic acid over platinum oxide catalyst at 45-50° resulted in absorption of 4 molar equivalents of hydrogen. Evaporation gave a mixture identified from the n.m.r. spectrum as containing 3-(5,6,7,8-tetrahydro-v-triazolo[1,5-a]pyridyl-3)-2-methylpropanol (88) (also prepared by hydrogenation of alcohol (75) or (76)) and its acetyl derivative (131). Treatment of the mixture with sodium hydroxide gave the pure alcohol, also prepared by reduction of the aldehyde (51) in acetic acid using platinum oxide catalyst at room temperature.





(88) R = H

(131) R = Ac

N.m.r. details of v-Triazolo[1,5-a]pyridines*

Cpd.	Chemical shifts 4H	5H	6H	7H	8H	9H	10H	Other resonances	Coupling constants (in Hz) $J_{4,5}$	$J_{6,7}$	
48	7.78d	6.9 - 7.6		8.73d	6.9-7.6	6.12q	10.98d		9	8	$J_{8,9}$ 12 $J_{9,10}$ 7.5
49	7.78q	6.9 - 7.5		8.75d	6.9-7.5		10.9s	2.05s (CH_3)	9	6	$J_{4,6}$ 1 J_{8,CH_3} 1
50	7.78d	6.9 - 7.6		8.78d	6.9-7.6	6.99q	9.7d		9	7	$J_{8,9}$ 16 $J_{9,10}$ 7.5
51	7.78d	6.9 - 7.5		8.75d	6.9-7.5		9.6s	2.45s (CH_3)	9	6	
75	7.84d	6.9 - 7.6		8.8d	6.58s		4.5d	4.8-5.4(OH) 2.15d(CH_3)	9	8	J_{8,CH_3} 1.5
76	7.84d	6.9 - 7.6		8.8d	6.78s		4.38s	3.48sbr(OH) 2.25s(CH_3)	9	8	
77	7.9d	7.5m	7.2m	8.95d	6.7m		5.6s	2.1s(CH_3) 2.25($COCH_3$)	9	8	
78	7.9d	7.5m	7.2m	8.95d	6.83m		4.95s	2.22s(CH_3) 2.38($COCH_3$)	9	8	
86	7.95d	7.45m	7.17m	9.0d				8.3s (3-H)	8.5	6.5	$J_{4,6}$ 1
87	8.65q	8.0m	7.58m	9.25d	10.7s				8.5	6.5	$J_{4,6}$ 1
88	2.6-3.0	1.7 - 2.4		4.5t	2.6-3.0	1.7-2.4	3.62d	4.3s(OH) 0.95d(CH_3)			$J_{9,10}$ 6 J_{9,CH_3} 6
107	7.68d	7.0 - 7.5		8.5s	7.0-7.5		10.8s	2.4s(6-CH_3) 2.0s(9-CH_3)	9		
108	7.75d	7.1 - 7.5		8.5s	7.1-7.5		9.56s	2.4s(6-CH_3) 2.45(9-CH_3)	9		
111	8.04d	7.49t	7.13t	8.8d			9.67s	2.2s (CH_3)	8	6	
112	8.04d	7.49t	7.13t	8.8d			9.9s	2.19s (CH_3)	8	6	
114	7.8d	7.42t	7.07m	8.76d				2.05s (CH_3)	9	6	
115	7.8d	7.42t	7.07m	8.76d				2.45s (CH_3)	9	6	
118	7.75d	6.9 - 7.5		8.63d	6.9-7.5			2.2d(CH_3) 4.13q(OCH_2) 1.23t($CH_2\underline{CH}_3$)	9	7	
119	7.78d	6.9 - 7.5		8.75d	6.9-7.5			2.5s(CH_3) 4.42q(OCH_2) 1.4 t($CH_2\underline{CH}_3$)	9	7	
123	7.95d	7.0 - 7.6		8.95d	2.95 - 3.85		10.5s	1.25d (CH_3)	9	7	$J_{9,10}$ 6 J_{9,CH_3} 6
124	7.9d	6.9 - 7.6		8.85d	3.15m	1.9-2.5	3.65d	4.1s(OH) 1.0d(CH_3)	9	7	$J_{9,10}$ 6 J_{9,CH_3} 6

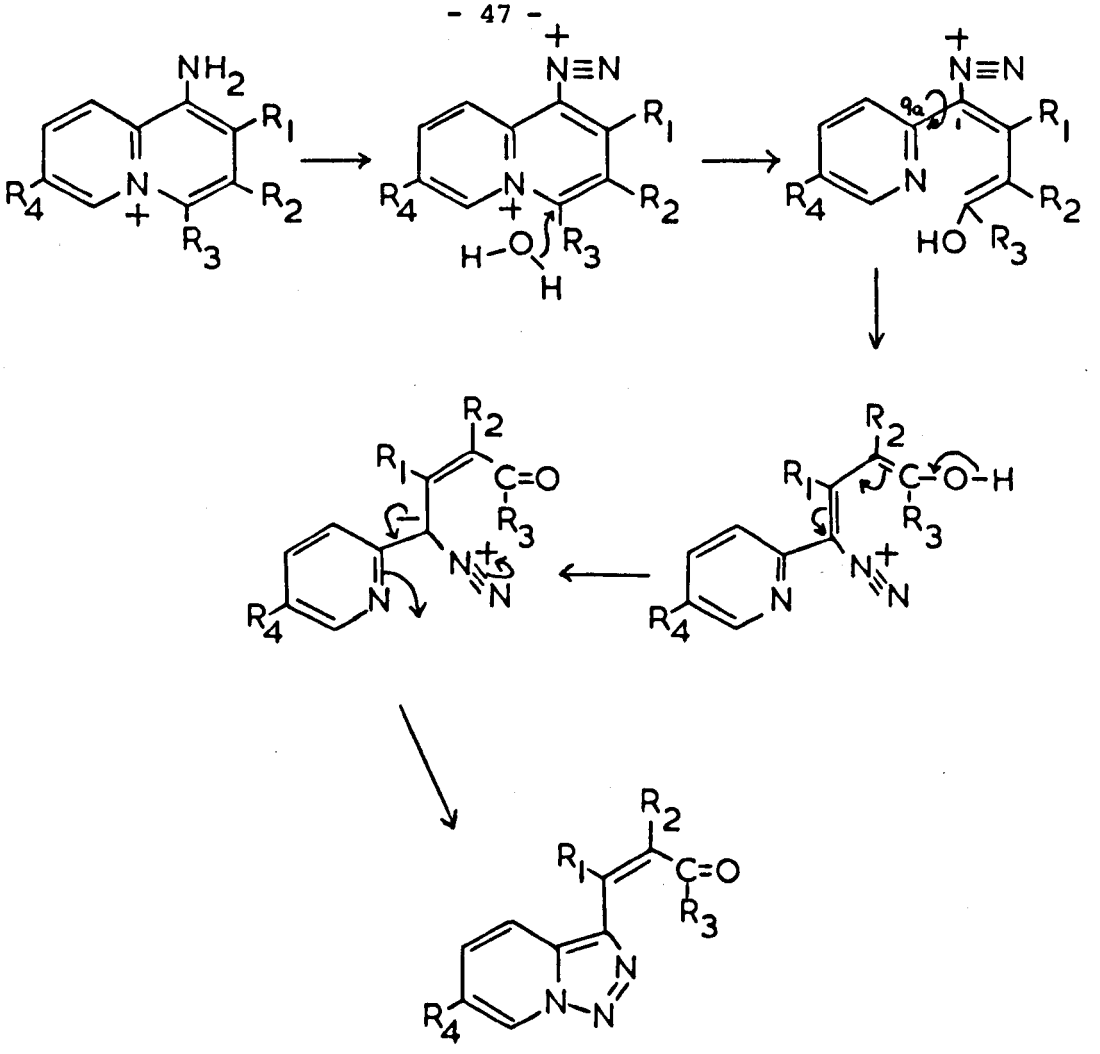
*All determined in $CDCl_3$ Values given are δ p.p.m. from $(CH_3)_4Si$

Table 1

The n.m.r. spectra (table 1) of the triazolopyridines described show some unusual features. The aromatic pattern is relatively simple and it is usually possible to distinguish between the protons at positions 4 and 7 which are doublets and to derive the coupling constants $J_{4,5}$ and $J_{6,7}$ which are consistently in the region of 9 and 6-8 Hz showing analogy with indolizine.[51] The downfield shifts shown by cis-aldehydes (48, 49, 107) relative to the trans isomers (50, 51, 108) have already been mentioned and these are attributed to the nitrogen (N-2) lone pair of electrons. Further evidence to support this is provided by the bromo-aldehyde (111). Here a peri-interaction between bromine and the 4-H causes the side-chain to move out of the plane of the aromatic ring and hence removes the aldehyde from the vicinity of the nitrogen at the 2-position. Confirmation is provided by the hypsochromic shift in the ultraviolet absorption of aldehydes (111) and (112) relative to other examples and by the increased barrier to cis-trans isomerism mentioned above. The downfield shift of the methylene protons at δ5.6 p.p.m. in cis-acetate (77) relative to the trans-acetate (78) at δ4.95 p.p.m. is explained in the same way, but the effect is not operating in the cis-alcohol (75). Here the alcohol is strongly hydrogen bonded to the nitrogen at position 2, shown by the broader -OH signal at δ4.8-5.4 p.p.m. and hence the methylene protons, absorbing at δ4.5 p.p.m., are held away from the lone pair. There is

thus no longer any large downfield shift relative to the trans-alcohol methylene protons absorption at δ4.38 p.p.m.

The mechanism of the rearrangement reaction of 1-amino-quinolizinium salts is thought to be similar to that by which 1-alkyl- or 1-aryl-3-aminopyridinium salts are converted into v-triazoles.[49,52] It is assumed that the 1-aminoquinolizinium salts are converted into 1-diazonium salts. This is known to occur in a non-aqueous medium[1] although attempts to obtain the intermediate diazonium salt from the 1-amino-3-methyl compound (16, X = Cl) under non-aqueous conditions proved unsuccessful, only starting material being isolated. It has been mentioned that quinolizinium salts can be attacked by nucleophiles with ring-opening[7,8,9] and with the electron withdrawal due to the diazonium group ring-opening results from attack by the solvent water at the 4-position. Rotation around the C(1)-C(9a) bond occurs with retention of configuration, since the cis-aldehyde is always isolated first under conditions which do not promote cis-trans isomerisation. Evidence for the diazo-derivative



as intermediate is provided by the rearrangement of the amino-ester (116) to the monocyclic vinylogous diazoketone (117) (page 37). The cyclisation of the diazo stage is expected and follows the pattern established by the work of Regitz.[26]

EXPERIMENTAL

Preliminary Notes

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

Infrared absorption spectra were measured on a Perkin-Elmer 257 spectrophotometer (dilution experiments were performed with a Unicam SP 700 spectrophotometer). The spectra of solids were determined as Nujol mulls, indicated as (Nujol) or in solution (e.g. $CHCl_3$). The spectra of liquids were determined as liquid films (film) or solutions (e.g. $CHCl_3$).

Ultraviolet spectra were recorded on a Unicam SP 800 instrument.

Nuclear magnetic resonance (n.m.r.) spectra were recorded on a Perkin-Elmer R10 60 MHz or Varian 100 MHz spectrometer and are quoted as 'delta' (δ) values in parts per million (p.p.m.) using a tetramethylsilane standard (δ0.00 p.p.m.). When spectra were determined in deuterium oxide or deuterosulphuric acid the standard was recorded externally in a solution of carbon tetrachloride. In all other cases the standard was used internally. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broadened.

Microanalyses were carried out on an F and M carbon/hydrogen/nitrogen analyser at the University of Keele.

Mass spectra were determined on an Hitachi-Perkin-Elmer RMU-6 and A.E.I. MS902 instruments.

Thin layer chromatography (t.l.c.) was carried out on 7.5 x 2.5 cm. microscope slides coated with Kieselgel PF_{254} (Merck). The components were visualised under ultraviolet light or developed in iodine vapour.

Preparative layer chromatography (p.l.c.) was carried out on 40 x 20 cm. glass plates coated with a 1.5 mm. layer of Kieselgel PF_{254}. The separated components, visualised as for t.l.c., were isolated by scraping off the silica and extraction with hot methanol. The filtered methanol solution was evaporated to leave a residue which contained silica. The residue was dissolved in chloroform filtered and evaporated.

Light petroleum refers to the fraction of b.p. 40-60^{o} unless otherwise indicated.

Photolytic work was performed using a Hanovia photochemical reactor (medium pressure mercury lamp) mainly transmitting light of 254, 265, 297, 313 and 366 nm. wavelength. Irradiations were through quartz under nitrogen unless otherwise indicated.

1-Aminoquinolizinium Chloride (7)

This was prepared by the method of Fozard and Jones,[2] described in the introduction to this thesis.

cis-3-(3-v-Triazolo[1,5-a]pyridyl)acraldehyde (48)

To a solution of 1-aminoquinolizinium chloride (7) (0.269g.) in water (5 ml.) at -5° was added an excess of saturated aqueous sodium nitrite. On addition of two drops of N hydrochloric acid a precipitate formed. Filtration gave cis-3-(3-v-triazolo-[1,5-a]pyridyl)acraldehyde (48) (0.111g., 43%), which crystallised from 95% ethanol as needles, m.p. 162-163°.

$C_9H_7N_3O$ requires: C, 62.3; H, 4.1; N, 24.5%

Found: C, 62.5; H, 3.75; N, 24.5%

$\delta(CDCl_3)$ 6.12 (1H, q, CHCHO) 6.9-7.6 (3H, m) 7.78 (1H, d) 8.73 (1H, d) 10.98 p.p.m. (1H, d, CHO).

$\nu_{max.}$ $(CHCl_3)$ 1672 $cm.^{-1}$

$\lambda_{max.}$ (EtOH) 285, 350sh nm. [log ε 3.79, (-)].

trans-3-(3-v-Triazolo[1,5-a]pyridyl)acraldehyde (50)

This was prepared by the method of Collicutt and Jones[1] described in the introduction and also by keeping a solution of the cis-acraldehyde (48) with piperidine in ethanol or chloroform for one hour at room temperature. Evaporation followed by crystallisation from water gave trans-3-(3-v-triazolo[1,5-a]pyridyl)acraldehyde (50),

m.p. 180°.

$\delta(CDCl_3)$	6.99 (1H, q, CHCHO) 6.9-7.6 (3H, m) 7.78 (1H, d) 8.78 (1H, d) 9.7 p.p.m. (1H, d, CHO).
$\nu_{max.}$ (Nujol)	1666 cm.$^{-1}$
$\lambda_{max.}$ (H_2O)	345 nm. [log ε 4.25].

1-Amino-3-methylquinolizinium Chloride (16, X = Cl)

This was prepared by the method of Hough and Jones,[3] described in the introduction to this thesis.

cis-2-Methyl-3-(3-v-triazolo[1,5-a]pyridyl)acraldehyde (49)

This was prepared by diazotisation of 1-amino-3-methylquinolizinium chloride (16, X = Cl) by the method of Hough and Jones.[16]

$\delta(CDCl_3)$	2.05 (3H, s, CH_3) 6.9-7.5 (3H, m) 7.78 (1H, q) 8.75 (1H, d) 10.9 p.p.m. (1H, s, CHO).
$\nu_{max.}$ ($CHCl_3$)	1672 cm.$^{-1}$
$\lambda_{max.}$ (EtOH)	224, 343 nm. [log ε 4.01, 4.19].
Mass spectrum m/e	187 (M^+), 159, 130, 104.

trans-2-Methyl-3-(3-v-triazolo[1,5-a]pyridyl)acraldehyde (51)

This was prepared by the method of Hough and Jones.[16]

$\delta(CDCl_3)$	2.45 (3H, s, CH_3) 6.9-7.5 (3H, m) 7.78 (1H, d) 8.75 (1H, d) 9.6 p.p.m. (1H, s, CHO)
$\nu_{max.}$ $(CHCl_3)$	1669 $cm.^{-1}$
$\lambda_{max.}$ (EtOH)	224, 314sh, 336 nm. [log ε 3.98, (-), 4.18].
Mass spectrum $^m/e$	187 (M^+), 159, 130, 104.

cis-2-Methyl-3-(3-v-triazolo[1,5-a]pyridyl)allyl Alcohol (75)

Sodium borohydride (0.11g.) was added to a solution of the cis-acraldehyde (49) (0.55g.) in ethanol. The mixture was allowed to stand at room temperature (3 hr.) with occasional swirling, filtered and the filtrate evaporated to dryness under reduced pressure. The residue was treated with dilute hydrochloric acid (20 ml.) and the aqueous solution extracted several times with chloroform. The combined extracts were dried (Na_2SO_4) and evaporation to dryness gave a solid (0.450g., 81%). Crystallisation from ethanol-water yielded the alcohol (75) as prisms, m.p. 113-114°.

$C_{10}H_{11}N_3O$ requires: C, 63.5; H, 5.82; N, 22.2%

Found: C, 63.7; H, 6.15; N, 22.3%

$\delta(CDCl_3)$	2.15 (3H, d, CH_3) 4.5 (2H, d, CH_2OH) 4.8-5.4 (1H, exchange with D_2O, OH) 6.58 (1H, s) 6.9-7.6 (2H, m) 7.84 (1H, d) 8.8 p.p.m. (1H, d).
$\nu_{max.}$ $(CHCl_3)$	3370 $cm.^{-1}$
$\lambda_{max.}$ (EtOH)	224, 262, 293, 320sh nm. [log ε 4.23, 4.10, 3.97, (-)].
Mass spectrum $^m/e$	189 (M^+), 160, 144, 132, 130, 118, 116, 104, 93, 78.

trans-2-Methyl-3-(3-v-triazolo[1,5-a]pyridyl)allyl Alcohol (76)

(a) This was prepared from the trans-acraldehyde (51) (0.77g.) as described above to give the alcohol (76) (0.67g., 86.3%). Crystallisation from ethanol-water gave the alcohol (76) as needles, m.p. 130-131°.

$C_{10}H_{11}N_3O$ requires: C, 63.5; H, 5.8; N, 22.2%

Found: C, 63.7; H, 5.8; N, 22.2%

$\delta(CDCl_3)$ 2.25 (3H, s, CH_3) 3.48 (1H, sbr, exchange with D_2O,OH) 4.38 (2H, s, $C\underline{H}_2OH$) 6.78 (1H, s) 6.9-7.6 (2H, m) 7.84 (1H, d) 8.8 p.p.m. (1H, d).

$\nu_{max.}$ (Nujol) 3350 $cm.^{-1}$

$\lambda_{max.}$ (EtOH) 224, 252, 259, 269, 293 nm. [log ε 4.22, 4.07, 4.08, 3.99].

Mass spectrum $^m/e$ 189 (M^+), 160, 144, 132, 130, 118, 116, 104, 93, 78.

(b) A solution of the cis-alcohol (75) in 10% aqueous sodium hydroxide was heated at 100° for one hour. The cooled solution was neutralised with hydrochloric acid and extracted with several portions of chloroform. The combined extracts were dried (Na_2SO_4) and evaporated to give a mixture of the trans-alcohol (76) 33% with the cis-alcohol (75) 66%.

cis-2-Methyl-3-(3-v-triazolo[1,5-a]pyridyl)allyl Acetate (77)

A solution of the cis-alcohol (75) (0.45g.) in acetic anhydride (25 ml.) was heated at 100° (3 hr.). Evaporation of the solution under reduced pressure followed by evaporation of absolute ethanol (10 ml.) from the residue gave the acetate (77) as a viscous yellow oil (0.440g., 80%), b.p. 200-205°/0.4 mm. which solidified on cooling and crystallised from ether, m.p. 54-55°.

$C_{12}H_{13}N_3O_2$ requires: C, 62.3; H, 5.6; N, 18.2%

Found: C, 62.4; H, 5.45; N, 18.1%

$\delta(CDCl_3)$ 2.1 (3H, s, CH_3) 2.25 (3H, s, $C\underline{H}_3CO$) 5.6 (2H, s, $C\underline{H}_2O$) 6.7 (1H, m) 7.2 (1H, m) 7.5 (1H, m) 7.9 (1H, d) 8.95 p.p.m. (1H, d).

$\nu_{max.}$ $(CHCl_3)$ 1735 $cm.^{-1}$

$\lambda_{max.}$ (EtOH) 221, 255sh, 264, 273sh, 292, 323sh nm. [log ε 4.24, (-), 4.08, (-), 3.95, (-)].

trans-2-Methyl-3-(3-v-triazolo[1,5-a]pyridyl)allyl Acetate (78)

This was prepared as described for the cis-derivative (77) from the trans-alcohol (53) (0.67g.) to give the trans-acetate (78) (0.569g., 69.5%) crystallised from ethanol-water m.p. 92-93°.

$C_{12}H_{13}N_3O_2$ requires: C, 62.3; H, 5.6; N, 18.2%

Found: C, 61.9; H, 5.55; N, 18.0%

$\delta(CDCl_3)$ 2.22 (3H, s, CH_3) 2.38 (3H, s $C\underline{H}_3CO$) 4.95 (2H, s, $C\underline{H}_2O$) 6.83 (1H, m) 7.2 (1H, m) 7.5 (1H, m) 7.9 (1H, d) 8.95 p.p.m. (1H, d).

$\nu_{max.}$ $(CHCl_3)$ 1734 $cm.^{-1}$

$\lambda_{max.}$ (EtOH) 221, 253sh, 261, 271, 291, 324sh nm. [log ε 4.22, (-), 4.10, (-), 3.94, (-)].

1-(2-Pyridyl)propan-2-one (81)

This was prepared from 2-picolyllithium and methyl acetate by the method of Goldberg, Barkley and Levine.[35]

1-Isonitroso-1-(2-pyridyl)propan-2-one (82)

1-(2-Pyridyl)propan-2-one (81) (4.1g.) was dissolved in absolute methanol (35 ml.) and anhydrous hydrogen chloride bubbled through the solution at a rate of three bubbles per second for 30 minutes while the solution was cooled in an ice-salt bath. Freshly distilled isopentyl nitrite (3.25g.) was added over 30 minutes and hydrogen chloride passed through the solution for a further hour. The methanolic solution was treated with an equal volume of ice-water with external cooling, the methanol removed under reduced pressure and the aqueous solution extracted several times with small portions of ether. The aqueous layer was neutralised with solid sodium bicarbonate and the precipitate collected by filtration. Crystallisation from chloroform gave the isonitroso-pyridylpropanone (82) as prisms (2.53g., 51%), m.p. 143-145°.

$C_8H_8N_2O_2$ requires: C, 58.2; H, 4.87; N, 17.0%

Found: C, 57.8; H, 4.82; N, 17.0%

$\delta(CDCl_3)$ 3.7 (3H, s, $C\underline{H}_3CO$) 7.6-8.7 (3H, m) 8.8 p.p.m. (1H, d).

$\nu_{max.}$ (Nujol) 1680 $cm.^{-1}$

1-Amino-1-(2-pyridyl)propan-2-one Dihydrochloride (83)

Concentrated hydrochloric acid (10 ml.) was added to a

additional 15 minutes with cooling. The mixture was extracted with several portions of chloroform and the combined extracts dried (Na_2SO_4) and evaporated under reduced pressure to leave an oil shown by t.l.c. to be a mixture. The oil had no diazo absorption in the i.r. spectrum.

(b) The above reaction was repeated. After addition of sodium nitrite solution the mixture was allowed to warm to room temperature and extracted with chloroform. Evaporation of the dried (Na_2SO_4) extracts gave a mixture as an oil with no diazo absorption in the i.r. spectrum.

(c) The reaction was repeated in a mixture of water-glacial acetic acid. After addition of sodium nitrite solution the mixture was stirred at 0° (3 hr.). Extraction as before gave an oil containing no diazo compound.

(d) Anhydrous hydrogen chloride was bubbled through a solution of 1-amino-1-phenylpropan-2-one hydrochloride (0.46g.) in absolute ethanol (50 ml.) over a period of 30 minutes. Freshly distilled pentyl nitrite (0.29g.) was added at 0° and the mixture stirred at 0° (1 hr.). Evaporation of the solvent under reduced pressure resulted in isolation of unreacted 1-amino-1-phenylpropan-2-one hydrochloride.

(e) 1-Diazo-1-phenylpropan-2-one was prepared from 1-(2-pyridyl)propan-2-one and p-toluenesulphonyl azide (prepared from

p-toluenesulphonyl chloride and sodium azide by the method of Doering and DePuy)[38] in the presence of sodium hydride following the synthesis of Hendrickson and Wolf.[38] The product had $\nu_{max.}$ (film) 2080 cm.$^{-1}$.

v-Triazolo[1,5-a]pyridine (86)

(a) A dispersion (50%) of sodium hydride in nujol (1.2g.) was slowly added to a stirred solution of 1-(2-pyridyl)propan-2-one (81) (1.35g.) in anhydrous tetrahydrofuran (50 ml.) After 30 minutes the mixture was cooled in an ice-salt bath and p-toluenesulphonyl azide (1.97g.) was added. The reaction mixture was allowed to warm to room temperature and stirred for an additional 15 minutes. The mixture was diluted with ether, filtered and evaporated to dryness. The residue was shaken with light petroleum and the residue was fractionally distilled to give the triazolo[1,5-a]pyridine (86) as an oil, b.p. 102°/0.75 mm. which solidified on cooling (0.786g., 66%), m.p. 34-35°.

$C_6H_5N_3$ requires: C, 60.49; H, 4.2; N, 35.3%

Found: C, 60.2; H, 4.15; N, 35.0%

$\delta(CDCl_3)$ 7.17 (1H, m) 7.45 (1H, m) 7.95 (1H, d)

8.3 (1H, s) 9.0 p.p.m. (1H, d).

(b) The triazolo[1,5-a]pyridine (86) was also prepared by oxidation of the hydrazone of pyridine-2-aldehyde by the method of Bower and Ramage.[18]

3-Formyl-v-triazolo[1,5-a]pyridine (87)

(a) trans-2-Methyl-3-(3-v-triazolo[1,5-a]pyridyl)allyl alcohol (76) (0.1g.) was dissolved in a mixture of water (80 ml.) and t-butanol (20 ml.). The pH of the solution was adjusted to 7.8 (indicator paper) by the addition of solid sodium carbonate. A solution of oxidant (75 ml.) [containing 20.98g. sodium meta-periodate and 167 ml. 0.01 M potassium permanganate per litre] was added with stirring (30 minutes). Stirring was maintained at room temperature until the purple colouration disappeared (1 hr.). The mixture was neutralised and filtered. The filtrate was extracted with chloroform and the extracts dried (Na_2SO_4). Evaporation to dryness yielded a crystalline solid (68.1 mg., 87%). Sublimation at 120°/0.2 mm. gave the aldehyde (87) (33.4 mg., 49%), m.p. 147-148° change of crystal form, needles to rods at 120-125°.

$C_7H_5N_3O$ requires: C, 57.1; H, 3.4; N, 28.5%

Found: C, 57.2; H, 3.3; N, 28.3%

$\delta(CDCl_3)$ 7.58 (1H, m) 8.0 (1H, m) 8.65 (1H, q) 9.25 (1H, d) 10.7 p.p.m. (1H, s, CHO).

$\nu_{max.}$ $(CHCl_3)$ 1680 $cm.^{-1}$

$\lambda_{max.}$ (EtOH) 258, 290sh, 313 nm. [log ε 3.59, (-), 4.13].

Mass spectrum $^m/_e$ 147 (M^+), 119, 91, 64.

(b) Similar oxidation of the cis-alcohol (75), cis-2-methyl-3-(3-v-triazolo[1,5-a]pyridyl)acraldehyde (49) or the trans-acraldehyde (51) gave the same aldehyde (87).

(c) A solution of cis-2-methyl-3-(3-v-triazolo[1,5-a]pyridyl)-acraldehyde (49) (0.1g.) in anhydrous acetone (50 ml.) was treated portion-wise with powdered potassium permanganate at 0° (3 hr.) until a purple colouration remained. The excess potassium permanganate was decomposed by addition of ethanol and the mixture filtered. Evaporation of the solvent gave 3-formyl-v-triazolo[1,5-a]-pyridine (87) (0.071g., 90%).

(d) Dimethylformamide (1.4g.) and phosphorus oxychloride (3g.) were mixed under dry nitrogen. After stirring at room temperature (15 minutes) ethylene dichloride (13g.) was added and the solution cooled to 0° when v-triazolo[1,5-a]pyridine (86) (1g.) dissolved in ethylene dichloride was added dropwise so that the temperature did not rise above 10°. After addition the reaction mixture was stirred at 0° for a further hour. Finely divided calcium carbonate was added and the mixture warmed until a violent reaction occurred which was moderated by external cooling. When the reaction had subsided the mixture was boiled (2 hr.), cooled and poured into a mixture of sodium acetate (12.5g.), water (12.5 ml.) and ice (2.5g.). The resulting mixture was diluted with chloroform (50 ml.), filtered, the organic layer separated and the filtrate extracted several times with chloroform. The combined organic extracts were dried (Na_2SO_4)

and evaporated to yield an oil (0.45g.) which was purified by p.l.c. using chloroform:ether (1:1). Extraction of one band yielded a gum (0.14g.). Purification by vacuum sublimation at 120°/0.2 mm. yielded needles (95 mg., 7.7%), m.p. 147-148° identical in all spectral details with 3-formyl-v-triazolo[1,5-a]-pyridine (87). A mixed melting point exhibited no depression.

Attempted Synthesis of trans-3-(3-v-triazolo[1,5-a]pyridyl)-acraldehyde (50)

A solution of 3-formyl-v-triazolo[1,5-a]pyridine (87) (94 mg.) in 95% ethanol (25 ml.) containing 2N sodium hydroxide solution (0.04 ml.) was treated at 0° with acetaldehyde (0.04 ml.) and the solution allowed to warm to room temperature overnight. The solution was evaporated to low bulk under reduced pressure and the residue diluted with water (10 ml.) and extracted with chloroform. The chloroform extracts were dried (Na_2SO_4) and evaporated to give unchanged 3-formyl-v-triazolo[1,5-a]pyridine (87).

Attempted Synthesis of trans-2-Methyl-3-(3-v-triazolo[1,5-a]pyridyl)-acraldehyde (51)

A solution of potassium hydroxide (60 mg.) in water (5 ml.) was added to a mixture of 3-formyl-triazolo[1,5-a]pyridine (87) (190 mg.) and propionaldehyde (70 mg.) in 95% ethanol (75 ml.) at 0°.

The mixture was stirred at 0° (2 hr.) and the temperature allowed to rise to room temperature and stirring continued for a further hour. On evaporation to low bulk a solid precipitated which was identified as unchanged 3-formyl-v-triazolo[1,5-a]pyridine (87).

3-(5,6,7,8-Tetrahydro-v-triazolo[1,5-a]pyridyl-3)-2-methylpropanol (88)

A solution of trans-2-methyl-3-(3-v-triazolo[1,5-a]pyridyl)-allyl alcohol (76) (0.38g.) in 95% ethanol was hydrogenated over platinum oxide catalyst (50 mg.) at ambient temperature and pressure. Absorption ceased when three molar equivalents of hydrogen were absorbed. Filtration and evaporation of the filtrate gave the alcohol (88) as a colourless oil, b.p. $178-185^{\circ}/0.4$ mm. (bulb-tube) (0.37g., 94%).

$C_{10}H_{17}N_3O$ requires: C, 61.5; H, 8.7; N, 21.5%

Found: C, 61.3; H, 8.85; N, 21.3%

$\delta(CDCl_3)$ 0.95 (3H, d, CH_3) 1.7-2.4 (5H, m) 2.6-3.0 (4H, m) 3.62 (2H, d $C\underline{H}_2OH$) 4.3 (1H, sbr, exchange with D_2O, OH) 4.5 p.p.m. (2H, t).

$\nu_{max.}$ (CCl_4) 3430 $cm.^{-1}$

$\lambda_{max.}$ (EtOH) 225 nm. [log ε 3.40].

3,5-Dimethylpyridine-1-oxide (90)

This was prepared from 3,5-dimethylpyridine and hydrogen peroxide by the method of Essery and Schofield.[42]

2-Cyano-3,5-dimethylpyridine (92)

Treatment of 3,5-dimethylpyridine-1-oxide with dimethyl sulphate at 100° gave 3,5-dimethyl-1-methoxypyridinium methosulphate (91). This was treated with sodium cyanide by the method of Feely and Beavers[43] to give 2-cyano-3,5-dimethylpyridine (92), m.p. 61-62° Lit.,[44] m.p. 64-65°.

2-Aminomethyl-3,5-dimethylpyridine (93)

A solution of 2-cyano-3,5-dimethylpyridine (92) (35.9g.) in anhydrous ether (100 ml.) was added with stirring to a slurry of lithium aluminium hydride (21.2g.) in anhydrous ether (250 ml.). After the addition the mixture was stirred at room temperature (2 hr.). The excess hydride was decomposed by the addition of a few drops of ethyl acetate followed by the careful dropwise addition of the minimum amount of water. The insoluble solids were removed by filtration and were extracted by trituration with three 50 ml. portions of hot benzene which were added to the filtrate. The solvent was evaporated and the resulting oil distilled under nitrogen to give the aminolutidine (93), b.p. 120-124°/12 mm. (18.9g., 51%).

$\delta(CCl_4)$ 2.3 (6H, s, $(CH_3)_2$) 2.6 (2H, sbr, NH_2, exchange with D_2O) 3.8 (2H, s, CH_2) 7.3 (1H, s) 8.25 p.p.m. (1H, s).

Treatment of the amine in ethanol with saturated ethanolic picric acid gave the picrate which crystallised from ethanol as needles, m.p. 90°.

$C_{14}H_{15}N_5O_7$ requires: C, 46.0; H, 4.11; N, 19.18%

Found: C, 46.1; H, 4.06; N, 19.0%

2-Acetamidomethyl-3,5-dimethylpyridine (94)

A solution of 2-aminomethyl-3,5-dimethylpyridine (93) (6.7g.) in a mixture of acetic anhydride (11.3 ml.) and glacial acetic acid (30 ml.) was heated at 100° with stirring for one hour. The acetic acid and excess acetic anhydride were removed under reduced pressure and the product distilled under nitrogen to yield a viscous oil, b.p. 140°-150°/0.1 mm. which solidified on cooling. Crystallisation from petroleum-ether (b.p. 60-80°) gave the amide (94) as colourless needles (6.5g., 74%), m.p. 77.5-78°.

$C_{10}H_{14}N_2O$ requires; C, 67.3; H, 7.94; N, 15.74%

Found: C, 67.9; H, 8.29; N, 15.9%

$\delta(CDCl_3)$ 2.15 (3H, s, CH_3CO) 2.3 (3H, s, CH_3) 2.35 (3H, s, CH_3) 4.5 (2H, d collapses to s with D_2O, CH_2) 7.4 (1H, s) 8.35 p.p.m. (1H, s).

$\nu_{max.}$ (Nujol) 1660 $cm.^{-1}$

2-Acetamidomethyl-1-carbethoxymethyl-3,5-dimethylpyridinium Bromide (95)

A solution of 2-acetamidomethyl-3,5-dimethylpyridine (94) (3.6g.) and ethylbromoacetate (5.5g.) in sulpholane (40 ml.) was kept at 35° (3 days). Ethyl acetate was added to the solution until a viscous oil separated and the solution was decanted. Although it was not possible to prepare a crystalline picrate from the oil the n.m.r. spectrum of the oil (95) in deuterium oxide confirmed its structure. The spectrum showed five singlets at δ5.8, 4.85, 2.75, 2.6, 2.1 p.p.m. corresponding to two methylene and three methyl groups respectively. A carbethoxy group was present with a methyl triplet centred at δ1.2 p.p.m. and a methylene quartet at δ4.5 p.p.m. There were two broadened singlets at δ8.6 and 8.8 p.p.m. corresponding to the pyridinium protons.

Attempted Synthesis of 1-Acetamido-3,7,9-trimethylquinolizinium Bromide (96)

A solution of 2-acetamidomethyl-1-carbethoxymethyl-3,5-dimethylpyridinium bromide (95) obtained as an oil from 2-acetamidomethyl-3,5-dimethylpyridine (94) (3.6g.) in ethanol (30 ml.) was boiled with 40% aqueous pyruvic aldehyde (3.6g.) and di-n-butylamine (1 ml.) for one hour. The solvent was evaporated under reduced pressure and excess water removed by evaporation of ethanol from

the residue. Trituration of the residue with ethyl acetate gave a solid identified as di-n-butylamine hydrobromide.

1-Acetamido-2,3,7,9-tetramethylquinolizinium Bromide (97)

A solution of 2-acetamidomethyl-1-carbethoxymethyl-3,5-dimethylpyridinium bromide (95) obtained as an oil from 2-acetamidomethyl-3,5-dimethylpyridine (94) (2.9g.) in ethanol (30 ml.) was boiled (1 hr.) with diacetyl (1.2g.) and di-n-butylamine (0.8 ml.). The solvent was evaporated under reduced pressure and excess water removed by evaporation of ethanol from the residue. The residue solidified in acetone and was crystallised from ethanol-ethyl acetate to give the salt (97) (0.45g., 8.6%), m.p. 293-294°.

$C_{15}H_{19}BrN_2O$ requires: C, 55.8; H, 5.9; N, 8.7%

Found: C, 55.7; H, 6.0; N, 8.4%

$\delta(D_2O)$ 2.4-2.6 (12H, m, $(CH_3)_4$) 2.85 (3H, s, CH_3CO) 8.05 (1H, s) 8.8 (1H, s) 8.95 p.p.m. (1H, s).

$\nu_{max.}$ (Nujol) 1680 $cm.^{-1}$

2-Bromo-5-methylpyridine (100)

This was prepared from 2-amino-5-methylpyridine (99) by the method of Case.[46]

2-Cyano-5-methylpyridine (101)

This was prepared from 2-bromo-5-methylpyridine (100) and cuprous cyanide by the method of Moynehan, Schofield, Jones and Katritzky.[47]

2-Aminomethyl-5-methylpyridine (102)

A solution of 2-cyano-5-methylpyridine (101) (28.4g.) in anhydrous ether (225 ml.) was added dropwise to a stirred slurry of lithium aluminium hydride (18.4g.) in anhydrous ether (100 ml.) at a rate sufficient to maintain gentle boiling. After the addition of the nitrile the mixture was stirred (1 hr.) at room temperature. The excess hydride was decomposed by careful dropwise addition of the minimum amount of water and the precipitate filtered. The solids were extracted by trituration with hot benzene (3 x 25 ml.). The combined organic solutions were dried (Na_2SO_4), the solvent removed by evaporation and the aminomethylmethylpyridine (102) distilled b.p. 102-105°/12 mm. (11.2g., 38%).

$\delta(CDCl_3)$ 1.7 (2H, sbr, NH_2) 2.35 (3H, s, CH_3) 4.0 (2H, s, CH_2) 7.3 (1H, d) 7.6 (1H, d) 8.55 p.p.m. (1H, s).

The picrate had m.p. 187-188°.

$C_{13}H_{13}N_5O_7$ requires: C, 44.4; H, 3.7; N, 19.9%

Found: C, 44.2; H, 3.55; N, 19.6%

2-Acetamidomethyl-5-methylpyridine (103)

2-Aminomethyl-3-methylpyridine (102) (10.3g.) with acetic anhydride (17.2 ml.) and glacial acetic acid were heated together (100°, 0.5 hr.). Evaporation of the solution under reduced pressure and distillation of the residue under nitrogen gave 2-acetamidomethyl-5-methylpyridine (103) b.p. 152-160°/0.2 mm. (12.9g., 93%).

$\delta(CDCl_3)$ 2.1 (3H, s, CH_3CO) 2.35 (3H, s, CH_3) 2.5 (2H, d collapses to s with D_2O, CH_2) 7.3 (1H, d) 7.6 (1H, d) 8.5 p.p.m. (1H, s).

2-Acetamidomethyl-1-carbethoxymethyl-5-methylpyridinium Bromide (104)

A solution of 2-acetamidomethyl-5-methylpyridine (103) (12.9g.) and ethylbromoacetate (19.8g.) in sulpholane (130 ml.) was kept at 35° (3 days). Addition of ethyl acetate precipitated a viscous oil (104), the n.m.r. spectrum of which in D_2O had the following characteristics δ1.4 (3H, t) 2.2 (3H, s) 2.65 (3H, s) 4.45 (2H, q) 5.7 (2H, s) 7.9-9 (3H, m) p.p.m. which confirmed its structure. The oil was used without purification for the next stage.

1-Acetamido-4-carbethoxy-3,7-dimethylquinolizinium Bromide (105)

A solution of the crude bromide from 2-acetamidomethyl-1-carbethoxymethyl-5-methylpyridinium bromide (104) (2.3g.), pyruvic aldehyde (1.9 ml., 40% aqueous solution) and di-n-butylamine (0.4 ml.) in ethanol (9 ml.) was boiled for one hour. Evaporation to dryness and trituration of the residue with ethyl acetate-acetone gave a solid. Crystallisation from acetone-methanol gave the 1-acetamido-4-carbethoxy-3,7-dimethylquinolizinium bromide (0.8g., 15.5% from 2-acetamidomethyl-5-methylpyridine), m.p. 184-185° with decomposition.

$C_{16}H_{19}BrN_2O_3$ requires: C, 52.3; H, 5.27; N, 7.6%

Found: C, 52.6; H, 5.27; N, 7.6%

$\delta(D_2O)$ 1.65 (3H, t) 2.55 (3H, s) 2.78 (6H, sbr) 4.82 (2H, m, obscured by HDO) 8.2-8.7 (3H, m) 8.9 p.p.m. (1H, sbr).

$\nu_{max.}$ (Nujol) 1720, 1690 $cm.^{-1}$

1-Amino-3,7-dimethylquinolizinium Bromide (106, X = Br)

A solution of 1-acetamido-4-carbethoxy-3,7-dimethylquinolizinium bromide (105) (5g.) in hydrobromic acid (100 ml., 48%) was boiled for one hour. Evaporation under reduced pressure followed by successive evaporation of two 30 ml. portions of absolute ethanol gave a gum which solidified in ethyl acetate (3.0g.,

87%). The salt (106, X = Br) was crystallised from 95% ethanol as yellow prisms, m.p. >330°.

$C_{11}H_{13}BrN_2$ requires: C, 52.2; H, 5.15; N, 11.1%

Found: C, 52.3; H, 5.2; N, 10.9%

$\delta(CF_3CO_2H)$ 2.68 (6H, s) 8.0-8.9 p.p.m. (5H, m).

1-Amino-3,7-dimethylquinolizinium Chloride (106, X = Cl)

A solution of the bromide (106, X = Br) in ethanol was percolated through an ion-exchange resin, Amberlite IRA 400 (Cl^-). Evaporation of the eluate gave 1-amino-3,7-dimethylquinolizinium chloride (106, X = Cl).

cis-2-Methyl-3-(6-methyl-3-v-triazolo[1,5-a]pyridyl)acraldehyde (107)

A solution of 1-amino-3,7-dimethylquinolizinium chloride (106, X = Cl) (1.27g.) in water (15 ml.), to which two drops of dilute hydrochloric acid were added, was treated at room temperature with an excess of saturated aqueous sodium nitrite solution. A precipitate formed and was filtered. Crystallisation from ethanol gave cis-2-methyl-3-(6-methyl-3-v-triazolo[1,5-a]pyridyl)acraldehyde (107) as needles (0.73g., 60%), m.p. 150-151°.

$C_{11}H_{11}N_3O$ requires: C, 65.65; H, 5.5; N, 20.9%

Found: C, 65.5; H, 5.55; N, 20.9%

$\delta(CDCl_3)$ 2.0 (3H, s, 9-CH_3) 2.4 (3H, s, 6-CH_3) 7.0-7.5 (3H, m) 7.68 (1H, d) 8.5 (1H, s) 10.8 p.p.m. (1H, s, CHO).

$\nu_{max.}$ $(CHCl_3)$ 1660 $cm.^{-1}$

$\lambda_{max.}$ (EtOH) 233.5, 297sh, 308sh, 343 nm. [log ε 4.17, (-), (-), 4.19].

trans-2-Methyl-3-(6-methyl-3-v-triazolo[1,5-a]pyridyl)acraldehyde (108)

A solution of the cis-acraldehyde (107) (0.1g.) in ethanol (20 ml.) was treated with piperidine (1 ml.) and the mixture stood at room temperature (1 hr.). Evaporation to dryness gave trans-2-methyl-3-(6-methyl-3-v-triazolo[1,5-a]pyridyl)acraldehyde (108) which crystallised from absolute ethanol as needles (94 mg., 94%), m.p. 165.5-167°.

$C_{11}H_{11}N_3O$ requires: C, 65.65; H, 5.45; N, 20.9%

Found: C, 65.6; H, 5.55; N, 20.8%

$\delta(CDCl_3)$ 2.4 (3H, s, 6-CH_3) 2.45 (3H, s, 9-CH_3) 7.1-7.5 (3H, m) 7.75 (1H, d) 8.5 (1H, s) 9.56 p.p.m. (1H, s, CHO).

$\nu_{max.}$ $(CHCl_3)$ 1670 $cm.^{-1}$

$\lambda_{max.}$ (EtOH) 235, 296sh, 314sh, 343 nm. [log ε 4.19, (-), (-), 4.39].

Attempted Synthesis of 1-Acetamido-2,3-diphenylquinolizinium Bromide (109)

(a) Benzil (3g.) and di-n-butylamine (2 ml.) were added to a solution of 2-acetamidomethyl-1-carbethoxymethylpyridinium bromide (10) (4.4g.) in 95% ethanol (30 ml.) and the mixture boiled for one hour. Evaporation to dryness and trituration of the residue with acetone gave di-n-butylamine hydrobromide and a tarry residue which could not be purified.

(b) To a solution of the quaternary compound (10) (2.4g.) in absolute ethanol (25 ml.) was added benzil (1.5g.) and 2N ammonia (2 ml.) and the mixture boiled for one hour. Evaporation under reduced pressure and trituration of the residue with ethyl acetate-acetone gave ammonium bromide and a tar from which no pure material could be obtained.

Attempted Synthesis of 15-Acetamidophenanthro[9,10-b]quinolizinium Bromide (110)

Sodium bicarbonate (0.57g.) and 9,10-phenanthraquinone (1.3g.) were added to a solution of 2-acetamidomethyl-1-carbethoxymethylpyridinium bromide (10) in acetone-absolute ethanol (1:1 60 ml.) and the mixture was boiled (1.25 hr.). Dilute hydrobromic acid (4 ml.) was added and the solution evaporated to dryness. Extraction with absolute ethanol left unreacted 9,10-phenanthraquinone. The ethanolic solution was evaporated to dryness and the residue shaken with

chloroform and water mixture. Evaporation of the dried (Na_2SO_4) chloroform solution gave a tar which could not be purified. Evaporation of the aqueous solution gave only sodium bromide.

1-Amino-2-bromo-3-methylquinolizinium Chloride (37, X = Cl)

This was prepared by the action of bromine on 1-amino-3-methylquinolizinium bromide (16, X = Br) and converted to the chloride with Amberlite IRA 400 (Cl^-) by the method of Hough and Jones.[16]

cis-3-Bromo-2-methyl-3-(3-v-triazolo[1,5-a]pyridyl)acraldehyde (111)

(a) A solution of 1-amino-2-bromo-3-methylquinolizinium chloride (37, X = Cl) (0.6g.) in dilute hydrochloric acid (10 ml.) was treated with an excess of saturated aqueous sodium nitrite solution at 0°. A precipitate formed and was filtered. The n.m.r. spectrum indicated the product was a mixture of the cis and trans isomers from the absorptions at $\delta(CDCl_3)$ 9.67 and 9.9 p.p.m. Attempts to separate the isomers by p.l.c. were unsuccessful.

(b) A solution of the aminoquinolizinium salt (37, X = Cl) 0.6g. in water (10 ml.) was treated with an excess of saturated aqueous nitrite solution at 0°. No reaction was observed until dilute hydrochloric acid (1 ml.) was added when a precipitate formed. The reaction mixture was allowed to warm to room temperature and the

precipitate filtered to give the cis-bromoacraldehyde (111) (0.5g., 85.6%) which crystallised from absolute ethanol as needles, m.p. 192-193°.

$C_{10}H_8BrN_3O$ requires: C, 45.1; H, 3.0; N, 15.9%

Found: C, 45.0; H, 3.0; N, 15.7%

$\delta(CDCl_3)$ 2.2 (3H, s, CH_3) 7.13 (1H, t) 7.49 (1H, t) 8.04 (1H, d) 8.8 (1H, d) 9.67 p.p.m. (1H, s, CHO).

$\nu_{max.}$ $(CHCl_3)$ 1667 cm.$^{-1}$

$\lambda_{max.}$ (EtOH) 232, 292, 320 nm. [log ε 4.43, 4.04, 4.03].

Mass spectrum $^m/_e$ 267, 265 (M^+); 239, 237; 210, 208; 158, 130, 104, 78, 51.

trans-3-Bromo-2-methyl-3-(3-v-triazolo[1,5-a]pyridyl)acraldehyde (112)

A solution of cis-3-bromo-2-methyl-3-(3-v-triazolo[1,5-a]-pyridyl)acraldehyde (111) (0.3g.) in glacial acetic acid was heated (100°, 1.5 hr.). Evaporation to dryness under reduced pressure followed by crystallisation from absolute ethanol gave the trans-isomer (112) as rods (0.25g., 89%), m.p. 189-190°.

$C_{10}H_8BrN_3O$ requires: C, 45.1; H, 3.0; N, 15.9%

Found: N, 45.3; H, 3.1; N, 15.7%

$\delta(CDCl_3)$ 2.19 (3H, s, CH_3) 7.13 (1H, t) 7.49 (1H, t) 8.04 (1H, d) 8.8 (1H, d) 9.9 p.p.m. (1H, s, CHO).

$\nu_{max.}$ $(CHCl_3)$ 1667 cm.$^{-1}$

$\lambda_{max.}$ (EtOH) 216, 253sh, 320 nm. [log ε 4.16, (-), 3.20].

1-Amino-2,4-dibromo-3-methylquinolizinium Chloride (38, X = Cl)

This was prepared by the action of bromine on 1-amino-3-methylquinolizinium bromide (16) and converted to the chloride with Amberlite IRA 400 (Cl^-) by the method of Hough and Jones.[16]

Attempted nitrosation of 1-Amino-2,4-dibromo-3-methylquinolizinium Chloride (38, X = Cl)

An excess of saturated aqueous sodium nitrite solution was added to a solution of the aminodibromoquinolizinium chloride (38, X = Cl) (0.5g.) in 2N hydrochloric acid (20 ml.) at room temperature. The mixture was stirred at room temperature overnight. The solution was extracted with chloroform. Evaporation of the dried (Na_2SO_4) extracts gave a tar from which no pure material could be isolated.

1-Amino-2,4-dideutero-3-methylquinolizinium Chloride (113)

1-Amino-3-methylquinolizinium chloride (16, X = Cl) (1.0g.) was dissolved in concentrated deuterosulphuric acid (2.5 ml.) and the black solution heated at 150° (24 hr.) in a sealed-tube. The n.m.r. spectrum of a sample of the reaction mixture indicated that exchange (D for H) had occurred at the 2 (100%) and 4 (80%) positions.

$\delta(D_2SO_4)$ 2.8 (3H, s, CH_3) 8.1-8.7 (3H, m) 9.1 p.p.m. (1H, d).

cis-1,3-Dideutero-2-methyl-3-(3-v-triazolo[1,5-a]pyridyl)-acraldehyde (114)

The solution of predominantly 1-amino-2,4-dideutero-3-methylquinolizinium chloride (113) in concentrated deuterosulphuric acid from the above reaction was diluted with water (40 ml.) and the resulting solution treated with an excess of saturated aqueous sodium nitrite solution at room temperature. The resulting precipitate was filtered and crystallised from ethanol to give the predominantly cis-1,3-dideutero-2-methyl-3-(3-v-triazolo[1,5-a]-pyridyl)acraldehyde (114).

$\delta(CDCl_3)$ 2.05 (3H, s, CH_3) 7.07 (1H, m) 7.42 (1H, t) 7.8 (1H, d) 8.76 p.p.m. (1H, d).

trans-1,3-Dideutero-2-methyl-3-(3-v-triazolo[1,5-a]pyridyl)-acraldehyde (115)

Treatment of the cis-deuterated acraldehyde in ethanolic solution with piperidine at room temperature (1 hr.) gave trans-1,3-dideutero-2-methyl-3-(3-v-triazolo[1,5-a]pyridyl)acraldehyde (115).

$\delta(CDCl_3)$ 2.45 (3H, s, CH_3) 7.07 (1H, m) 7.42 (1H, t) 7.8 (1H, d) 8.76 p.p.m. (1H, d).

Mass spectrum $^m/_e$ 189 (M^+), 188, 160, 131, 104.

1-Acetamido-4-carbethoxy-3-methylquinolizinium Bromide (15)

This was prepared by the method of Hough and Jones[3] described in the introduction to this thesis.

1-Amino-4-carbethoxy-3-methylquinolizinium Bromide (116, X = Br)

A solution of 1-acetamido-4-carbethoxy-3-methylquinolizinium bromide (15) (7g.) in N hydrochloric acid (50 ml.) was heated at 95-100° for one hour. The solution was evaporated to dryness under reduced pressure and excess water removed by evaporation from the residue of absolute ethanol (25 ml. twice). The black granular solid was extracted (soxhlet) with chloroform. Evaporation of the solvent gave a brown tar which on trituration with acetone gave 1-amino-4-carbethoxy-3-methylquinolizinium bromide (116) as a yellow powder (4.35g., 70.5%), m.p. 171-172° (dec.). This had $\delta(D_2O)$ 1.3 (3H, t, $CH_2\underline{CH}_3$) 2.1 (3H, s, CH_3) 4.4 (2H, q, $\underline{CH}_2CH_3$)6.7 (1H, s) 7.7 (3H, m) 8.46 p.p.m. (1H, d,) and $\nu_{max.}$ (Nujol) 1710 cm.$^{-1}$ which confirmed its structure.

1-Amino-4-carbethoxy-3-methylquinolizinium Chloride (116, X = Cl)

A solution of 1-amino-4-carbethoxy-3-methylquinolizinium bromide (116, X = Br) in 95% ethanol (250 ml.) was percolated through Amberlite IRA 400 (Cl^-). Evaporation of the eluate followed by trituration with acetone yielded the quinolizinium chloride (116, X = Cl) as yellow powder (0.825g., 82.5%).

Ethyl cis-3-Methyl-2-oxo-4-(3-v-triazolo[1,5-a]pyridyl)but-3-enoate (118)

A solution of 1-amino-4-carbethoxy-3-methylquinolizinium chloride (116, X = Cl) (0.825g.) in water (25 ml.) was treated with an excess of saturated aqueous sodium nitrite solution at room temperature. No reaction was observed until dilute hydrochloric acid (1 ml.) was added when a yellow precipitate formed. This was filtered, washed with water and dried. The solid had the following spectral characteristics: $\delta(CDCl_3)$ 2.05 (d, CH_3) 8.63 p.p.m. (d) and $\nu_{max.}$ ($CHCl_3$) 2270 cm.$^{-1}$ (N≡N) assigned to the monocyclic diazo compound (117) which was 24% of the mixture. Crystallisation from methanol gave the pure cis-keto-ester (118) as yellow needles (0.7g., 87%), m.p. 126-127°.

$C_{13}H_{13}N_3O_3$ requires: C, 60.2; H, 5.05; N, 16.2%

Found: C, 60.6; H, 5.25; N, 16.5%

$\delta(CDCl_3)$ 1.23 (3H, t, $CH_2\underline{CH_3}$) 2.2 (3H, d, CH_3) 4.13 (2H, q, $\underline{CH_2}CH_3$) 6.9-7.5 (3H, m) 7.75 (1H, d) 8.63 p.p.m. (1H, d).

$\nu_{max.}$ ($CHCl_3$) 1730, 1673 cm.$^{-1}$

$\lambda_{max.}$ (EtOH) 221, 346 nm. [log ε 4.25, 4.15].

Ethyl trans-3-Methyl-2-oxo-4-(3-v-triazolo[1,5-a]pyridyl)-but-3-enoate (119)

A solution of cis-keto-ester (118) (0.2g.) and piperidine (1 ml.) in chloroform was evaporated after one hour at room temperature to give the trans-keto-ester (119) (0.19g., 95%) which crystallised from methanol as needles, m.p. 170-171°.

$C_{13}H_{13}N_3O_3$ requires: C, 60.2; H, 5.05; N, 16.2%

Found: C, 60.6; H, 5.2; N, 16.3%

$\delta(CDCl_3)$ 1.4 (3H, t, $CH_2\underline{CH_3}$) 2.5 (3H, s, CH_3) 4.42 (2H, q, $\underline{CH_2}CH_3$) 6.9-7.5 (3H, m) 7.78 (1H, d) 8.75 p.p.m. (1H, d).

$\nu_{max.}$ $(CHCl_3)$ 1734, 1672 $cm.^{-1}$

$\lambda_{max.}$ (EtOH) 221, 349 nm. [log ε 4.13, 4.14].

Mass spectrum $^m/_e$ 259 (M^+), 231, 186, 158, 130, 103, 78.

3-Methyl-1-(2-pyridyl)but-3-en-1-yne (120)

A solution of cis-2-methyl-3-(3-v-triazolo[1,5-a]pyridyl)-allyl alcohol (75) (1g.) in N hydrochloric acid (25 ml.) was heated at 100° for one hour. The cooled solution was basified with solid sodium bicarbonate and extracted with chloroform (3 x 25 ml.). The combined extracts were dried (Na_2SO_4) and evaporated at room temperature to give a crude oil (0.250g.). This was purified by p.l.c. using chloroform to give an oil (0.085g., 11.3%) which was

unstable above room temperature. The oil had absorptions in the n.m.r. spectrum at $\delta(CDCl_3)$ 2.0 (3H, d, CH_3) 5.4 (1H, s) 5.35 (1H, m) 7-7.7 (3H, m) 8.5 p.p.m. (1H, d) and $\nu_{max.}$ (film) 2220 $cm.^{-1}$ which confirmed the structure of the acetylene (120).

$\lambda_{max.}$ (EtOH) 260, 285 nm. [log ε 3.04, 3.06].

$\lambda_{max.}$ (EtOH/HCl) 258, 298, 315 nm. [log ε 2.86, 2.98, 2.99].

3-Methyl-1-(2-pyridyl)butane (121)

(a) A solution of 3-methyl-1-(2-pyridyl)but-3-en-1-yne (120) (85mg.) in ethanol (30 ml.) was hydrogenated over palladium on charcoal (10%) catalyst (25 mg.) at ambient temperature and pressure. Absorption of hydrogen ceased after three molar equivalents of hydrogen were absorbed. The filtered solution was evaporated to leave a yellow oil. Bulb distillation gave the alkylpyridine (121) as an oil b.p. 95-103°/17 mm. (75 mg., 85%). Treatment of this oil with saturated ethanolic picric acid gave the picrate which crystallised from ethanol-ether as yellow needles, m.p. 105-106°.

(b) The alkylpyridine (121) synthesised by the method of Osuch and Levine[48] from picolyllithium and isobutyl bromide was identical with the sample obtained above. A mixed melting point determination of the picrates exhibited no depression.

Attempted Bromination of trans-2-Methyl-3-(3-v-triazolo[1,5-a]-pyridyl)acraldehyde (51)

(a) A solution of trans-2-methyl-3-(3-v-triazolo[1,5-a]-pyridyl)acraldehyde (51) (1.0g.) in chloroform (100 ml.) was treated with bromine (0.85g.) and the mixture boiled (12 hr.). Evaporation gave an intractable tar from which no pure material could be isolated.

(b) A solution of the trans-acraldehyde (51) (0.39g.) in chloroform, containing diethylamine (2 ml.) was treated with bromine (0.7g.) and the mixture stirred at room temperature overnight. Evaporation to dryness followed by extraction of the residue with chloroform gave, on removal of the solvent, trans-acraldehyde (51).

Hydrogenation of trans-2-Methyl-3-(3-v-triazolo[1,5-a]pyridyl) acraldehyde (51)

(a) 3-(3-v-Triazolo[1,5-a]pyridyl)-2-methylpropionaldehyde.

A solution of trans-2-methyl-3-(3-v-triazolo[1,5-a]pyridyl)-acraldehyde (51) (2.0g.) in 95% ethanol (600 ml.) was hydrogenated at ambient temperature and pressure over palladium on charcoal (10%) catalyst (0.5g.). Absorption ceased when approximately three molar equivalents of hydrogen were absorbed. Filtration and evaporation gave a mixture which was extracted with ether to leave a residue of unreacted trans acraldehyde (51) (0.52g.). The ether solution was evaporated to yield an oil (1.24g.) whose n.m.r. spectrum indicated it

was a mixture of 3-(5,6,7,8-tetrahydro-v-triazolo[1,5-a]pyridyl-3)-2-methylpropanol (88), 3-(3-v-triazolo[1,5-a]pyridyl)-2-methylpropanol (124) and 3-(3-v-triazolo[1,5-a]pyridyl)-2-methylpropionaldehyde (123). Attempts to separate the mixture by p.l.c. using chloroform-ether (9:1) were only partially successful. The only component separated being the propionaldehyde (123) (0.32g., 21.3%) which had $\delta(CDCl_3)$ 1.25 (3H, d, CH_3) 2.95-3.85 (3H, m, CH_2CH) 7.0-7.6 (2H, m) 7.95 (1H, d) 8.95 (1H, d) 10.5 p.p.m. (1H, s, CHO) and $\nu_{max.}$ (film) 1723 $cm.^{-1}$.

(b) 3-(5,6,7,8-Tetrahydro-v-triazolo[1,5-a]pyridyl-3)-2-methylpropanol (88)

Platinum oxide catalyst (0.1g.) was added to a solution of trans-acraldehyde (51) (1.1g.) in glacial acetic acid (200 ml.) (purified by distillation from chromium trioxide) and the mixture hydrogenated at 45-50° and ambient pressure. Absorption ceased when four molar equivalents of hydrogen were absorbed. The filtered solution was evaporated to dryness under reduced pressure and the residue dissolved in chloroform and made neutral to moist litmus with aqueous sodium bicarbonate. The dried (Na_2SO_4) chloroform solution was evaporated to give an oil which was shown by its n.m.r. spectrum to be a mixture of the alcohol (88) and its acetyl derivative. The oil was dissolved in a mixture of ethanol-water (1:1, 20 ml.) containing sodium hydroxide (0.2g.) and the mixture boiled (0.5 hr.). The cooled mixture was diluted with water and extracted with

chloroform. The chloroform extracts were dried (Na_2SO_4) and evaporated to yield the alcohol (65) (0.6g., 53%) which was identical to that obtained by hydrogenation of trans-2-methyl-3-(3-v-triazolo[1,5-a]pyridyl)allyl alcohol (76).

(c) trans-2-Methyl-3-(3-v-triazolo[1,5-a]pyridyl)acraldehyde (51) (0.68g.) in purified glacial acetic acid (125 ml.) was hydrogenated over platinum oxide catalyst (83 mg.) at ambient temperature and pressure. Work up as in (b) above gave the alcohol (88) (0.63g., 89%).

3-(3-v-Triazolo[1,5-a]pyridyl-)2-methylpropanol (124)

A solution of 3-(3-v-triazolo[1,5-a]pyridyl)-2-methyl-propionaldehyde (123) (0.1g.) in 95% ethanol was treated with sodium borohydride (30 mg.) and the mixture allowed to stand at room temperature overnight. The filtered solution was evaporated under reduced pressure and the residue extracted with chloroform. Evaporation gave the propanol (124) as an oil (72 mg., 71%).

$\delta(CDCl_3)$ 1.0 (3H, d, CH_3) 1.9-2.5 (1H, m, CH) 3.15 (2H, m, CH_2) 3.65 (2H, d, CH_2OH) 4.1 (1H, s, exchange with D_2O, OH) 6.9-7.6 (2H, m) 7.9 (1H, d) 8.85 p.p.m. (1H, d).

$\nu_{max.}$ (film) 3380 $cm.^{-1}$

3-Acetamidopyridine

This was prepared from 3-aminopyridine and acetic anhydride by the method of Farley and Eliel.[50]

3-Acetamido-1-methylpyridinium Bromide (126)

This was prepared from 3-acetamidopyridine, dimethyl sulphate and hydrobromic acid by the method of König, Coenen, Bahr, May and Bassl.[49]

trans-3-(1-Methyl-v-triazolyl-4)-acraldehyde (125)

This was prepared by the method of König, Coenen, Bahr, May and Bassl[49] from 3-acetamido-1-methylpyridinium bromide.

$\delta(CDCl_3)$	4.15 (3H, s, NCH_3) 6.75 (1H, q, CHCHO) 7.5 (1H, d, CHCHCHO) 7.9 (1H, s) 9.63 p.p.m. (1H, d, CHO)
$\nu_{max.}$ $(CHCl_3)$	1679 cm.$^{-1}$
$\lambda_{max.}$ (EtOH)	278 nm. [log ε 3.04].
$\lambda_{max.}$ (20% H_2SO_4)	265 nm. [log ε 3.33].
Mass spectrum m/e	137.0589 (M^+, $C_6H_7N_3O^+$ requires 137.0589) 109.0638 ($C_5H_7N_3^+$ requires 109.0640) 108.0449 ($C_6H_6NO^+$ requires 108.0449) 80.0499 ($C_5H_6N^+$ requires 80.0500) 68.0260 ($C_4H_4O^+$ requires 68.0262).

3-(1-Methyl-v-triazolyl-4)-propionaldehyde (128)

Palladium on charcoal (10%) catalyst (0.1g.) was added to a solution of 3-(1-methyl-v-triazolyl-4)-acraldehyde (0.5g.) in 95% ethanol (50 ml.) and the mixture hydrogenated at ambient temperature and pressure. Absorption ceased when approximately one molar equivalent of hydrogen was absorbed. The filtered solution was evaporated to give an oil which was purified by p.l.c. using ethyl acetate (2 elutions). Extraction of the main band gave the propionaldehyde (128) as an oil, b.p. 125-130°/0.04 nm. which solidified on cooling (0.19g., 37.4%).

$\delta(CDCl_3)$ 2.8-3.1 (4H, m, CH_2CH_2) 4.0 (3H, s, NCH_3) 7.4 (1H, s) 9.8 p.p.m. (1H, sbr, CHO).

$\nu_{max.}$ (film) 1710 $cm.^{-1}$

$\lambda_{max.}$ (EtOH) 216 nm. [log ε 3.62].

$\lambda_{max.}$ (EtOH / HCl) 218 nm. [log ε 3.66].

Mass spectrum $^m/e$ 139.0721 (M^+, $C_6H_9N_3O^+$ requires 139.0746) 111.0795 ($C_5H_9N_3^+$ requires 111.0797) 110.0604 ($C_6H_8NO^+$ requires 110.0606) 110.0715 ($C_5H_8N_3^+$ requires 110.0718) 82.0658 ($C_5H_8N^+$ requires 82.0657) 68.0499 ($C_4H_6N^+$ requires 68.0500).

3-(1-Methyl-v-triazolyl-4)-allyl Alcohol (130)

Sodium borohydride (0.1g.) was added to a solution of 3-(1-methyl-v-triazolyl-4)acraldehyde (125) (0.5g.) in 95% ethanol (50 ml.) and the reaction mixture allowed to stand at room temperature (2 hr.). The filtered solution was evaporated to dryness and the residue treated with dilute hydrochloric acid with cooling. The mixture was evaporated to dryness. Extraction of the residue with chloroform and evaporation of the solvent gave 3-(1-methyl-v-triazolyl-4)-allyl alcohol (130) as an oil, b.p. 167-172°/0.005 mm. (0.436g., 86%).

$\delta(CDCl_3)$ 3.0 (1H, sbr, exchange with D_2O, OH) 4.0 (3H, s, NCH_3) 4.27 (2H, d, CH_2OH) 6.55 (2H, d, CH.CH) 7.47 p.p.m. (1H, s).

$\nu_{max.}$ (film) 3370 $cm.^{-1}$

$\lambda_{max.}$ (EtOH) 231 nm. [log ε 3.06].

Mass spectrum m/e 139 (M^+) 110, 94, 82, 80, 68.

3-(1-Methyl-v-triazolyl-4)-propanol (129)

(a) A solution of 3-(1-methyl-v-triazolo-4)-allyl alcohol (130) (0.24g.) in 95% ethanol (25 ml.) was hydrogenated at ambient temperature and pressure over palladium on charcoal (10%) catalyst (50 mg.). Absorption ceased when one molar equivalent of hydrogen was absorbed. The filtered solution was evaporated to give the alcohol (129) as an oil, b.p. 171-175°/0.002 mm. (0.2g., 84%).

$\delta(CDCl_3)$	1.6-2.1 (2H, m, $CH_2\underline{CH_2}CH_2$) 2.78 (2H, t, $\underline{CH_2}CH_2CH_2OH$) 3.65 (2H, t, $\underline{CH_2}OH$) 3.9 (1H, sbr, exchange with D_2O, OH) 4.0 (3H, s, NCH_3) 7.4 p.p.m. (1H, s).
$\nu_{max.}$ (film)	3380 $cm.^{-1}$
$\lambda_{max.}$ (EtOH)	220 nm. [log ε 2.56].
Mass spectrum m/e	141 (M^+) 140, 83, 69, 59.

(b) A solution of 3-(1-methyl-v-triazolyl-4)-propionaldehyde (128) (0.1g.) in ethanol (20 ml.) was treated with sodium borohydride (0.05g.) and the mixture allowed to stand at room temperature (2 hr.). The filtered solution was evaporated to dryness and the residue was treated with dilute hydrochloric acid with cooling. The mixture was evaporated to dryness and the residue extracted with chloroform. Evaporation of the solvent gave the alcohol (129) as an oil (79 mg., 78%).

Attempted Diazotisation of 1-Amino-3-methylquinolizinium Chloride (16, X = Cl)

(a) An excess of freshly distilled pentyl nitrite was added to a solution of 1-amino-3-methylquinolizinium chloride (16, X = Cl) (0.16g.) in 95% ethanol (20 ml.) at 0°. The solution was allowed to warm to room temperature and stirred for a further three hours. A positive alkaline β-naphthol test could not be obtained. The solution was stirred at room temperature overnight. Filtration of the resulting precipitate resulted in isolation of trans-2-methyl-

3-(3-v-triazolo[1,5-a]pyridyl)acraldehyde (51) (75 mg., 49%).

(b) Pentyl nitrite (2 ml.) was added to a solution of 1-amino-3-methylquinolizinium chloride (16, X = Cl) (0.16g.) in absolute ethanol (20 ml.) saturated with anhydrous hydrogen chloride at 0^{o}. The mixture was stirred at 0^{o} (1 hr.) and allowed to warm to room temperature and stirred overnight. Evaporation to dryness gave only unreacted quinolizinium chloride (16, X = Cl).

Thermal Rearrangement of v-Triazolo[1,5-a]pyridylacraldehydes

The facile isomerisation of cis-(v-triazolo[1,5-a]pyridyl) acraldehydes to the trans isomers has already been discussed and it was found that the cis- (49) and trans-aldehydes (51) had identical mass-spectra (fig. 8). The major fragmentation showed loss of 28 units followed by 29 units. High resolution studies have shown these correspond to loss of N_2 or CO followed by N_2H or CHO. It was thought that thermal rearrangement of compound (49) to (51) might be occurring in the heated inlet of the mass spectrometer. Accordingly the cis-aldehyde (49) was briefly heated above its melting point to 180-185°. Gas evolution was noted and by direct evacuation into the mass spectrometer shown to be a mixture of nitrogen and carbon monoxide. The pyrolysis mixture was rapidly cooled and the starting cis-aldehyde (49) was shown to have been completely consumed during the reaction by the absence of an absorption at δ10.9 p.p.m. in the n.m.r. spectrum of the crude product. The melt was taken up in chloroform and extracted with dilute hydrochloric acid. Evaporation of the dried chloroform solution gave the trans-aldehyde (51) (6.4%).

On neutralisation of the acidic extracts a mixture was obtained. Extraction with sodium hydroxide left a red oil as residue which solidified on trituration with light petroleum. This was the major product of the reaction (56%) and after

Mass spectrum of 4-formyl-3-methyl-5-(2-pyridyl)pyrazole (132) also observed for cis- (49) and trans-2-methyl-3-(3-v-triazolo[1,5-a]pyridyl)acraldehyde (51)

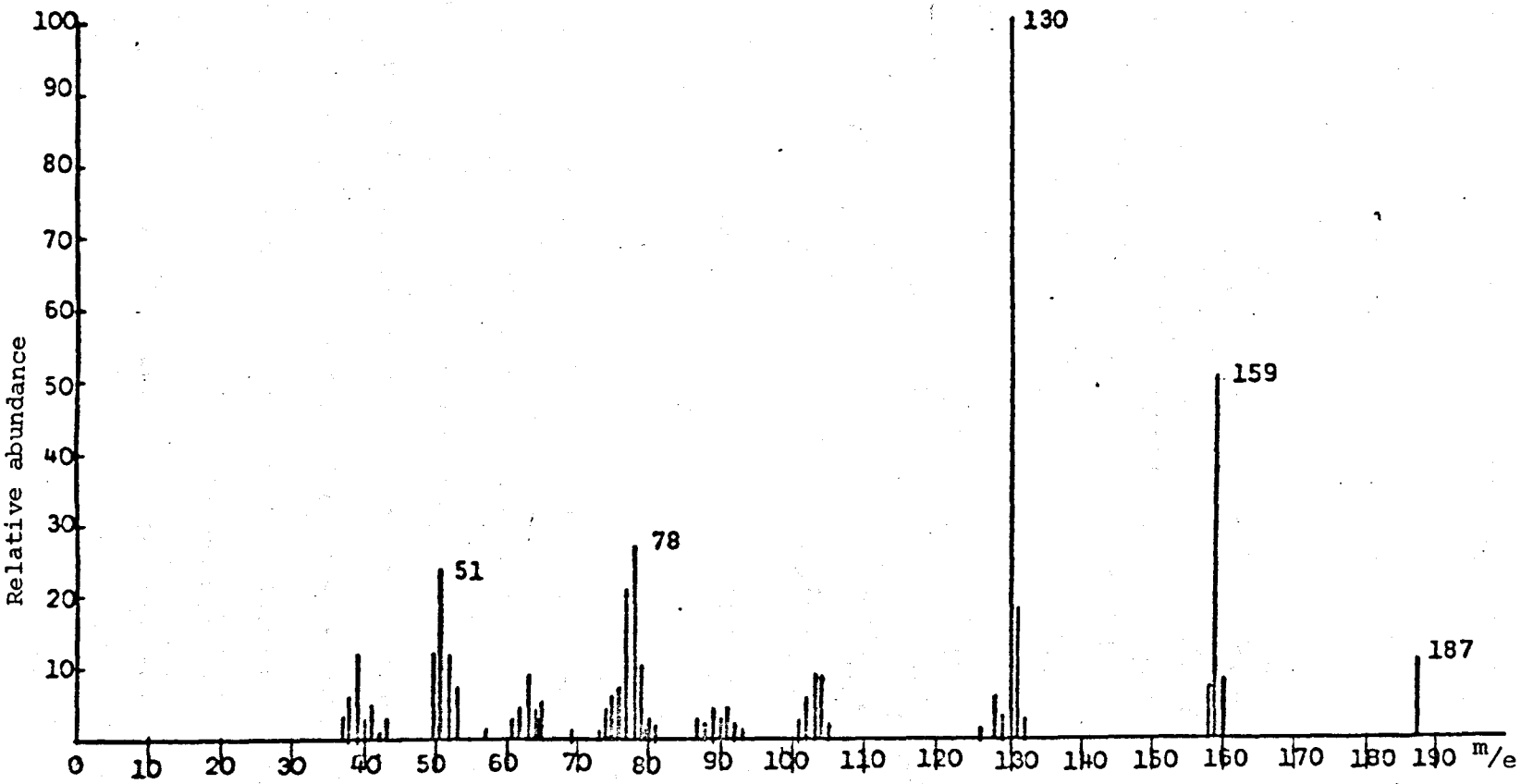
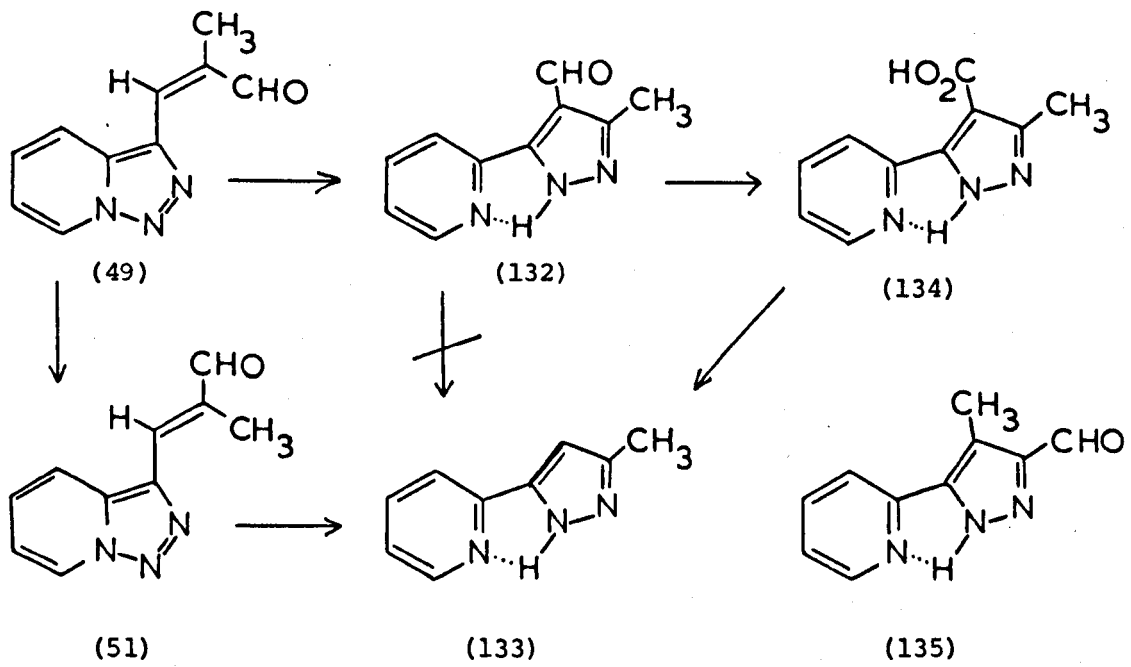


Figure 8

purification by vacuum sublimation was shown to have the formula $C_9H_9N_3$.



Neutralisation of the sodium hydroxide extract followed by extraction gave a minor product (35%) which was shown by elemental analysis to be isomeric with the cis- and trans-aldehydes (49) and (51). When the reaction was repeated and the temperature not allowed to rise above 170°, the proportion of the trans-aldehyde (51) isolated increased to 40% with 25% of the decarbonylated material and 21% of the isomeric product being obtained. It was necessary to heat the trans-aldehyde (51) to 205-208° before any reaction was

observed and here the only identified product was the decarbonylated material (41%) together with unreacted starting material (16%).

The isomeric minor product obtained by heating the cis-aldehyde (49), which was shown to be the pyridylpyrazole (132), had an identical mass spectral fragmentation pattern to those obtained for the aldehydes (49) and (51), and since these were determined using heated inlet temperatures at which decomposition and isomerisation occurred, it appeared that it was the breakdown (fig.8) of compound (132) which was observed in all three cases. Loss of N_2 followed by HCO or loss of CO followed by N_2H by an alternative pathway led to only consideration of structures containing these fragments for the minor product.

The n.m.r. spectrum showed features which were important in determining the structure. Notably an aldehyde singlet absorption at δ10.5 p.p.m. confirmed by an absorption at 1675 $cm.^{-1}$, and a singlet methyl absorption at δ2.45 p.p.m. attributed to a methyl group attached to an aromatic or unsaturated system. The absorptions due to a 2-substituted-pyridine ring and the reported[53] solubility of formyl-pyrazoles in sodium hydroxide solution without alteration virtually confirmed the structure as 4-formyl-3-methyl-5-(2-pyridyl)pyrazole (132). The absence of a resonance peak for N-H in the n.m.r. spectrum was confirmed by the results of Habraken and co-workers[54] which showed this was not unusual for pyrazoles. This phenomena was ascribed to

hydrogen bonding and coupling with the quadrupole moment of the nitrogen atom.

The ultraviolet spectrum showed a large bathochromic shift in the band of longest wavelength (277 nm. to 306 nm.) on acidification. A similar shift has been reported[55] between the neutral and quaternary forms of some 3-(4-pyridyl)pyrazoles.

Oxidation of the aldehyde (132) was achieved with potassium permanganate in acetone at room temperature to give the corresponding acid (134). This proved difficult to decarboxylate but heating at 190-200° over a period of 30 minutes resulted in evolution of carbon dioxide (lime-water). Purification of the product by preparative layer chromatography using chloroform-methanol followed by vacuum sublimation gave 3-methyl-5-(2-pyridyl)pyrazole (133) (33%), which was identical with the major product resulting from the pyrolysis of the cis-aldehyde (49) at 180-185°. The n.m.r. spectrum (fig.9) of the pyrazole (133) showed a one proton singlet at δ6.56 p.p.m. in good agreement with that expected for a pyrazole H-4.[56,57] This and the difficulty of decarboxylation of the acid (134)[58] led to the formula (133) for the major product which confirmed the structure of the minor product as the aldehyde (132) rather than (135).

Further proof of the structure of the 3-methyl-5-(2-pyridyl)-pyrazole (133) was provided by an independent synthesis as outlined below. The Grignard compound formed from 2-bromopyridine (136) and magnesium, by the method of entrainment with the Grignard reagent of

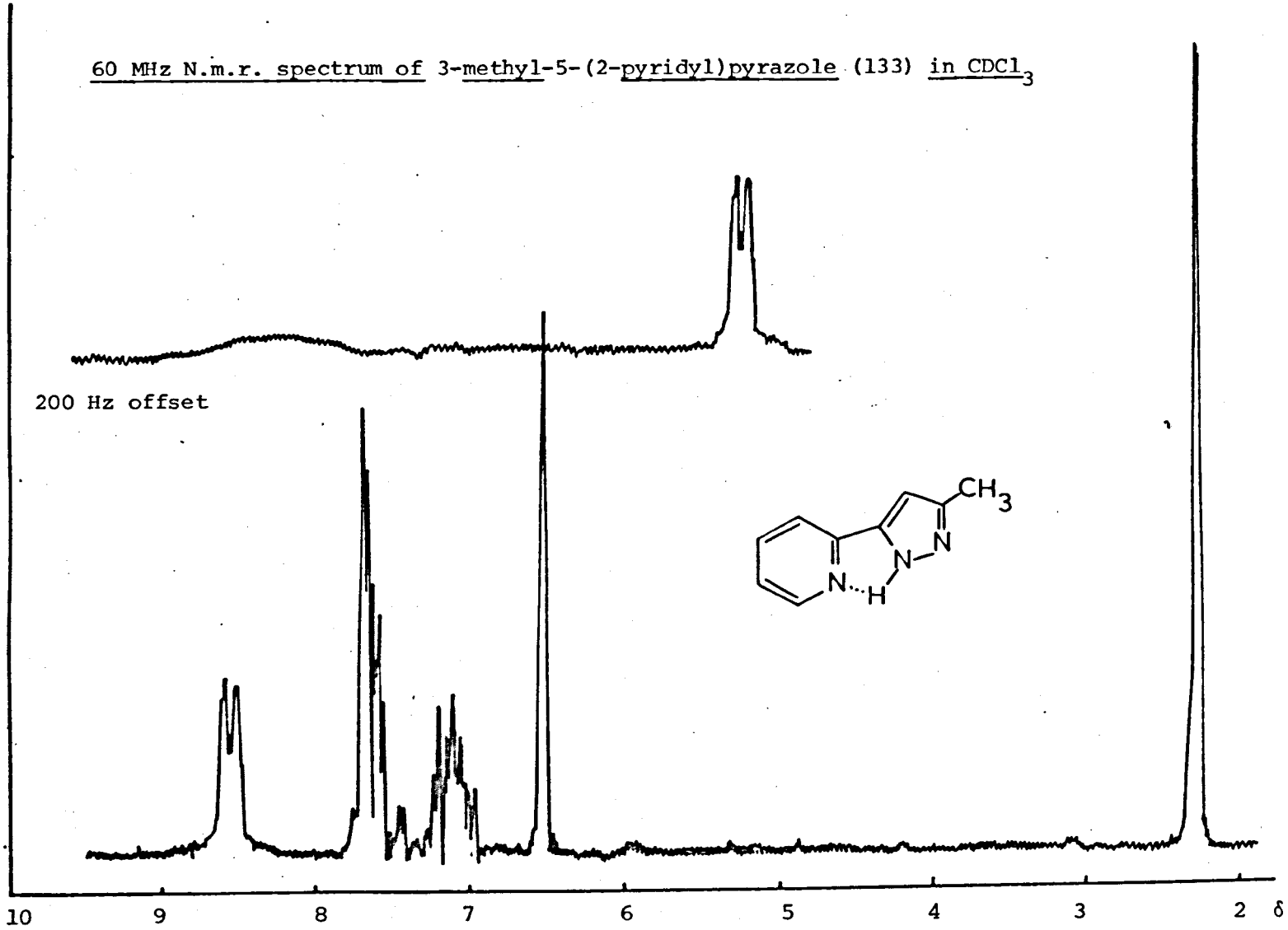
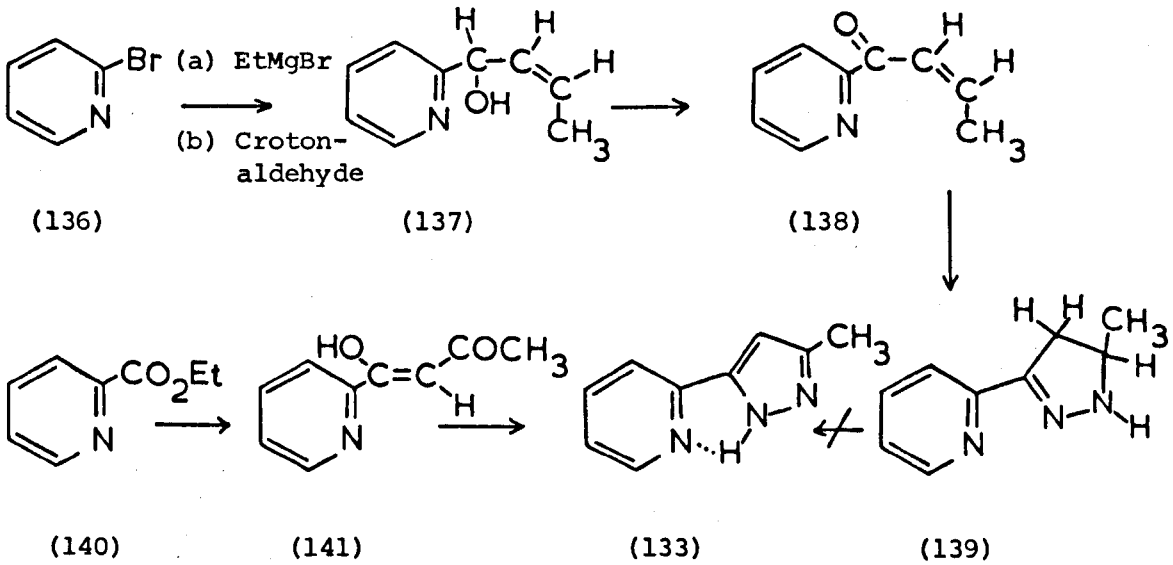

60 MHz N.m.r. spectrum of 3-methyl-5-(2-pyridyl)pyrazole (133) in $CDCl_3$
200 Hz offset
CH_3
N
N
N
H
10
9
8
7
6
5
4
3
2
δ

Figure 9

ethyl bromide,[59] was treated with crotonaldehyde. Hydrolysis with ammonium chloride in ammonium hydroxide gave 1-(2-pyridyl)but-2-en-1-ol (137) which on oxidation with active manganese dioxide[60] in acetone gave 1-(2-pyridyl)but-2-en-1-one (138).

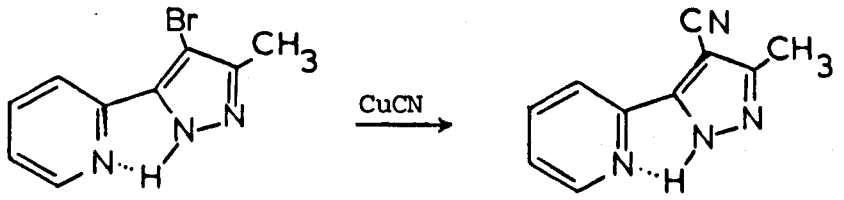


Treatment of this unsaturated ketone with hydrazine hydrate in ethanol gave 5-methyl-3-(2-pyridyl)pyrazoline (139). This compound was very unstable in air and attempts to oxidise it with bromine in carbon tetrachloride, potassium permanganate in acetone, dichlorodicyanobenzoquinone in boiling benzene, or lead tetraacetate in glacial acetic acid to the pyridylpyrazole (133) proved unsuccessful. Preparation of the pyrazole (133) was achieved by treatment of

1-(2-pyridyl)butan-1,3-dione (141),[61] prepared from ethyl picolinate (140) and acetone in the presence of sodium ethoxide, with hydrazine hydrate in ethanol. The synthetic material was identical in all respects with the compound (133) isolated after pyrolysis of the cis-aldehyde (49).

An attempt to formylate the pyrazole (133) using the Vilsmeier reagent, phosphorus oxychloride in dimethylformamide proved unsuccessful and it has been reported[62] that it is not possible to introduce a formyl group in the pyrazole nucleus if there is no substituent other than hydrogen at N-1.

Bromination of the pyrazole (133) was achieved using bromine in chloroform to give 4-bromo-3-methyl-5-(2-pyridyl)pyrazole (142). An attempt to convert this compound to the pyrazole-4-carboxylic



(142) (143)

acid (134) using n-butyllithium and solid carbon dioxide in tetrahydrofuran was unsuccessful, only starting material being isolated.

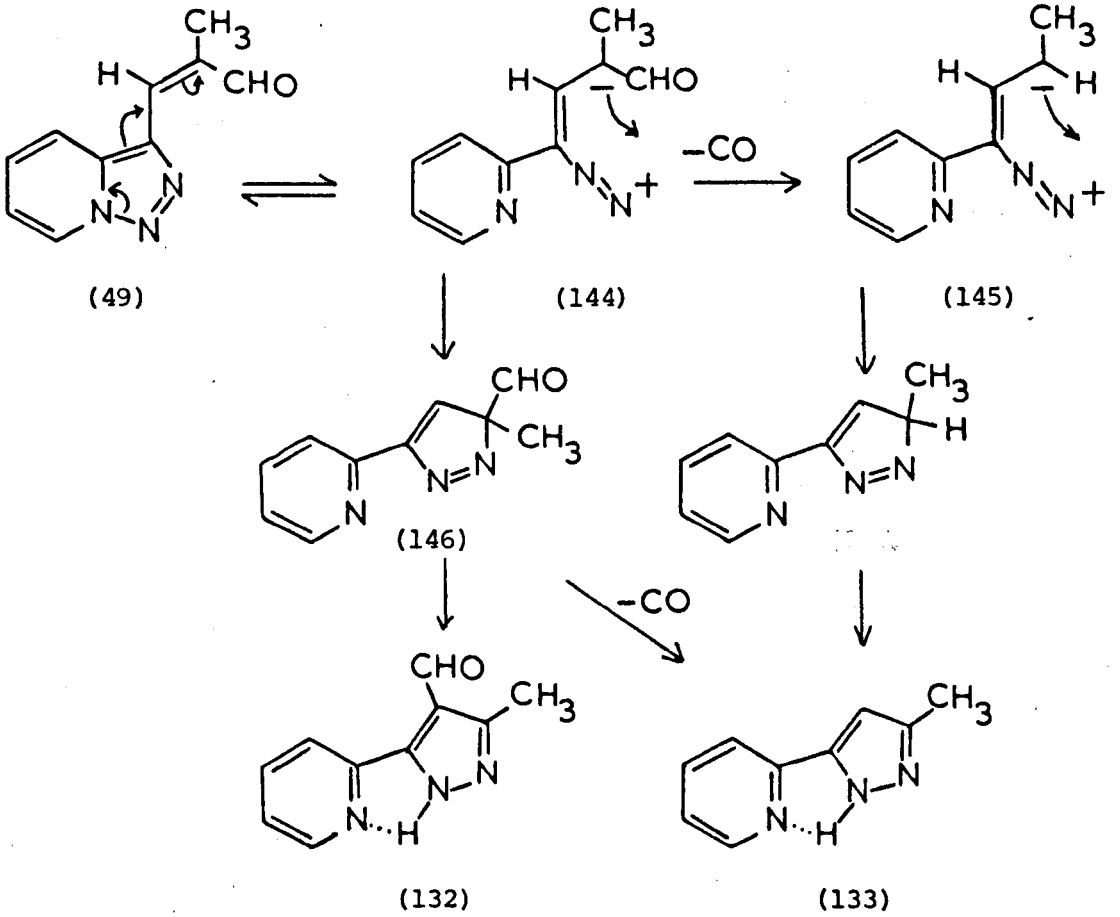
Dry distillation of an intimate mixture of the bromopyrazole

(142) and cuprous cyanide under reduced pressure gave a mixture of the 4-cyano (143) and starting 4-bromo-3-methyl-5-(2-pyridyl)-pyrazoles which it proved impossible to separate. The two compounds co-crystallised from several solvents, co-distilled, co-sublimed and ran as one spot on a thin layer chromatogram in several solvent systems. The isolated material was shown to be a mixture in each case by the cyanide absorption at 2230 $cm.^{-1}$ and the pair of peaks at $^{m}/e$ 237 and 239 in the mass spectrum characteristic of the isotopic distribution of bromine in brominated compounds.

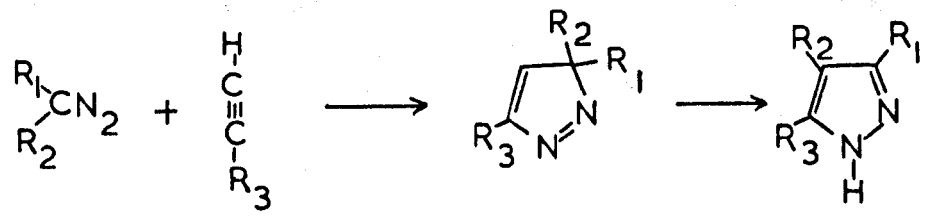
Hydrolysis of the bromo-cyano mixture (142) and (143) to the acid (134) using strong acid or base proved unsuccessful. In each case either no reaction or decomposition was observed depending on the conditions employed.

The rearrangement mechanism is supposed to proceed via the monocyclic diazo-aldehyde (144). From this the trans-aldehyde (51) can result by cis-trans isomerisation and recyclisation, or the diazo-aldehyde (144) can cyclise to give the 3H-pyrazole (146).

Heating the formylpyrazole (132) to 220° produced no decomposition so the loss of carbon monoxide must occur from an intermediate stage, either from the diazo-aldehyde (144) followed by cyclisation to give the pyrazole (133), or during the rearrangement of the 3H-pyrazole (146).

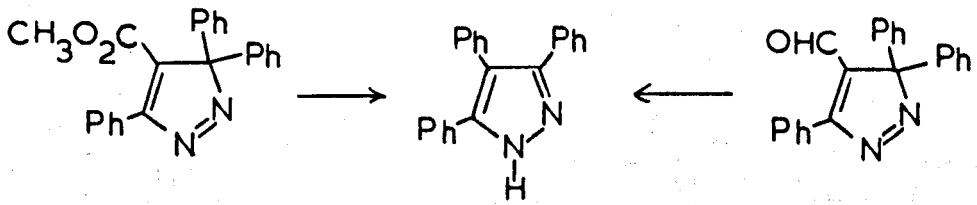


Isopyrazoles or 3H-pyrazoles with two substituents on position 3 (149) have also been prepared by the addition of di-substituted diazomethanes (147) to compounds containing a triple bond (148). Such compounds (149) on treatment with various agents (mineral or organic acids, heat, alkalies, heating in the presence of maleic anhydride) isomerise to pyrazoles (150).[63,64,65]

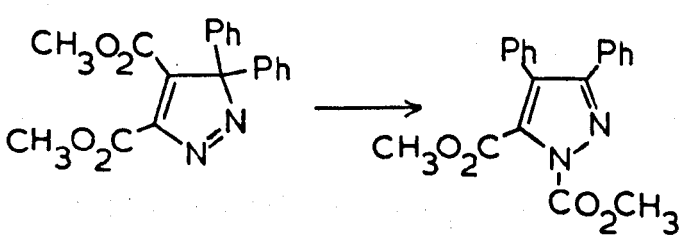


(147) (148) (149) (150)

In a few examples[66] the rearranged pyrazole was obtained directly. When position-4 in the 3H-pyrazole (149) was substituted the rearrangement took place with elimination of this group or its migration to position-1.[63,66,67]

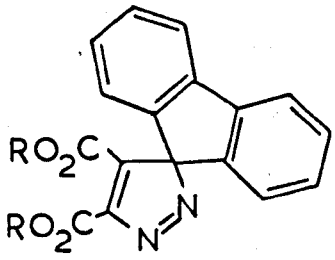


(151) (152) (153)

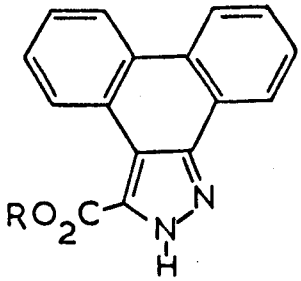


(154) (155)

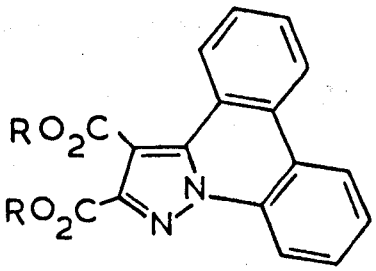
Sometimes migration of one of the geminal substituents to the neighbouring nitrogen atom was observed.[68]



(156)

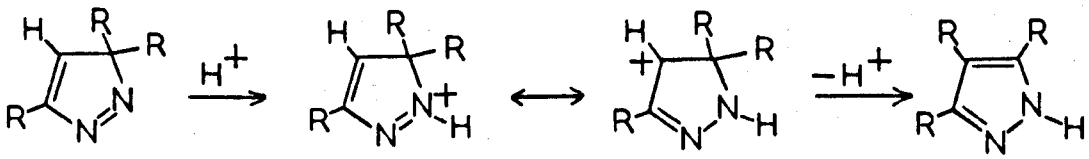


(157)



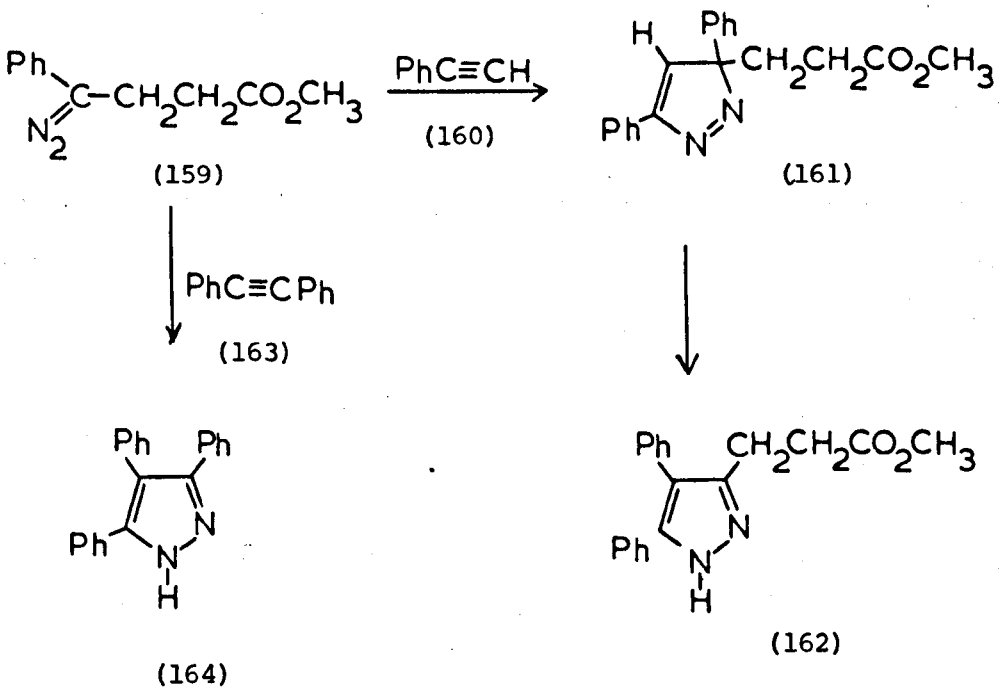
(158)

Data for various alkyl and aryl substituted 3H-pyrazoles established the following migratory series:[63] p-dimethylaminophenyl≫ phenyl>p-bromophenyl≫methyl. This is in agreement with a carbonium ion mechanism.



The positive charge is stabilised at C_4 by electron donation from the substituent R.

Rearrangement of 3H-pyrazoles with elimination or migration of the 4-substituent does not always occur. Moritani, Hosokawa, and Obata[69] have reported that although the pyrazole formed from 4-diazo-4-phenylbutyrate (159) and phenylacetylene (160) gave 3-(2-carbomethoxyethyl)-3,5-diphenyl-3H-pyrazole (161) which thermally rearranged to 3-(2-carbomethoxyethyl)-4,5-diphenylpyrazole (162), the adduct from (159) and diphenylacetylene (163) gave 3,4,5-triphenylpyrazole (164).

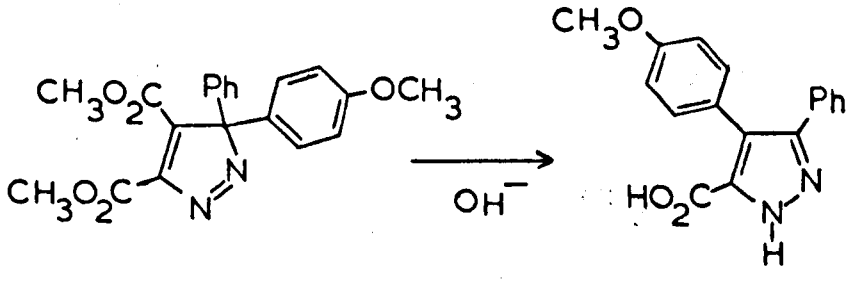


(159) (160) (161) (163) (164) (162)

This was ascribed to the difference in the substituents at the C_4 position of the intermediate 3H-pyrazole. In the case of (161) the phenyl migration produced an intermediate which could transform into a stable pyrazole derivative by a simple prototropic rearrangement. The intermediate formed from (159) and (163) cannot be stabilised in this way and eliminated methylacrylate to give pyrazole (164).

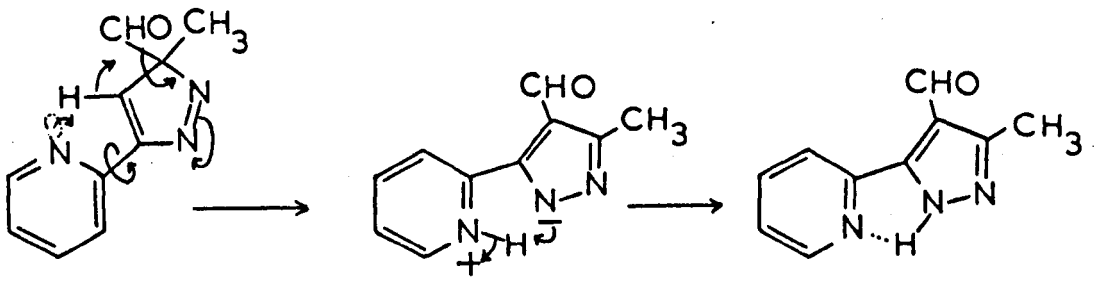
It was difficult to understand how the carbonium ion mechanism (page 99) could be applied to the migration of the formyl group in the formation of the 4-formyl-3-methyl-5-(2-pyridyl)pyrazole (132) in preference to the methyl group, since this would involve migration of an electron-deficient carbon atom to a site of positive charge at position C-4.

However there is a report[63] of the rearrangement of dimethyl 3-(4-methoxyphenyl)-3-phenyl-3H-pyrazole-4,5-dicarboxylate (165) in basic media to 4-(4-methoxyphenyl)-3-phenylpyrazole-5-carboxylic acid (166). This was supposed to proceed via a carbanion intermediate.



(165) (166)

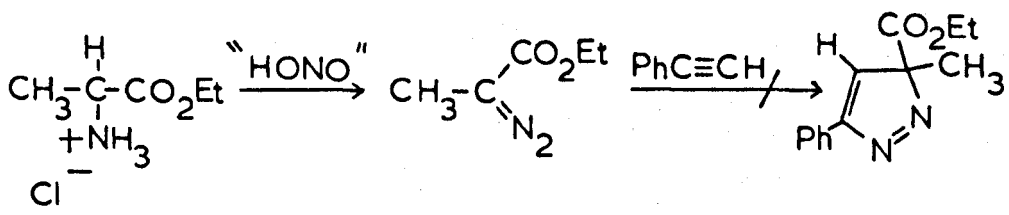
A negatively charged intermediate is also thought to be involved in the rearrangement of the 3H-pyrazole (146).



(146) (132)

The pyridine lone pair of electrons abstracts the pyrazole H-4 and the developing negative charge is attacked by the electron deficient carbon atom of the carbonyl group with formyl transfer and localisation of the negative charge on the pyrazole N-1. Rotation around the pyridine-pyrazole bond leads to transfer of the proton with formation of the pyridylpyrazole (132).

In order to study the rearrangement of another 3H-pyrazole with an electron withdrawing group at position C-3, attempts were made to prepare 3-carbethoxy-3-methyl-4-phenyl-3H-pyrazole (169) following the method Kirmse and Horner[70] have derived for the preparation of 3-carbethoxy-5-phenylpyrazole from ethyl diazoacetate. However the reaction between ethyl diazopropionate (168)[71] prepared from alanine ethyl ester hydrochloride (167) and phenylacetylene (160) resulted in loss of molecular nitrogen from the mixture and no pyrazole could be isolated.



(167) (168) (169)

EXPERIMENTAL

Pyrolysis of cis-2-Methyl-3-(3-v-triazolo[1,5-a]pyridyl)-acraldehyde (49)

(a) cis-2-Methyl-3-(3-v-triazolo[1,5-a]pyridyl)acraldehyde (49) (0.5g.) in a pyrex tube was slowly heated in an oil-bath past its melting point (165°) to 185° when a vigorous effervescence occurred. The reaction mixture was rapidly cooled and the residue dissolved in chloroform (50 ml.). The chloroform solution was extracted with 2N hydrochloric acid (25 ml. twice) and the chloroform solution dried (Na_2SO_4). Evaporation of the solvent left trans-2-methyl-3-(3-v-triazolo[1,5-a]pyridyl)acraldehyde (51) (32 mg., 6.4%).

The acidic extracts were basified with solid sodium bicarbonate the mixture extracted with chloroform (3 x 20 ml.) and the combined chloroform extracts shaken with 2N sodium hydroxide solution (25 ml. twice). The chloroform solution was washed with water (20 ml.), dried (Na_2SO_4) and evaporated to leave a red oil which solidified on trituration with light petroleum. Sublimation at 112-115°/0.3 mm. gave 3-methyl-5-(2-pyridyl)pyrazole (133) as prisms (0.293g., 56.2%), m.p. 115-116°.

$\delta(CDCl_3)$	2.26 (3H, s, CH_3) 6.56 (1H, s) 7.0-7.3 (1H, m) 7.56-7.86 (2H, m) 8.6 (1H, d) 11.1-11.6 p.p.m. (1H, sbr, exchange with D_2O, NH).
$\nu_{max.}$ $(CHCl_3)$	3450 $cm.^{-1}$
$\lambda_{max.}$ (EtOH)	248, 282 nm. [log ε 3.06, 2.95].
$\lambda_{max.}$ (EtOH/HCl)	247, 309 nm. [log ε 2.95, 2.01].

Mass spectrum $^{m}/e$ 159 (M^+), 130, 104, 103, 78.

The picrate crystallised from absolute ethanol as prisms, m.p. 172-174°.

$C_{15}H_{12}N_6O_7$ requires: C, 46.4; H, 3.12; N, 21.65%

Found: C, 46.7; H, 3.13; N, 21.4%

The sodium hydroxide extract of the pyrolysis residue of cis-2-methyl-3-(3-v-triazolo[1,5-a]pyridyl)acraldehyde (49) was neutralised to pH8 with hydrochloric acid and extracted with chloroform. The chloroform extracts were dried (Na_2SO_4) and evaporated to give 4-formyl-3-methyl-5-(2-pyridyl)pyrazole (132) (0.175g., 35%) which crystallised from methanol as prisms, m.p. 167-168°.

$C_{10}H_9N_3O$ requires: C, 64.15; H, 4.85; N, 22.45%

Found: C, 64.5; H, 5.22; N, 22.8%

$\delta(CDCl_3)$ 2.45 (3H, s, CH_3) 7.75 (1H, t) 8.16 (2H, m) 8.65 (1H, d) 10.5 p.p.m. (1H, s, CHO).

$\delta(CF_3CO_2H)$ 2.83 (3H, s, CH_3) 7.9-8.25 (1H, m) 8.5-9 (3H, m) 9.92 p.p.m. (1H, s, CHO).

$\nu_{max.}$ ($CHCl_3$) 3440, 1675 $cm.^{-1}$

$\lambda_{max.}$ (EtOH) 228, 258, 277sh nm. [log ε 3.20, 3.04 (-)].

$\lambda_{max.}$ (EtOH/HCl) 225, 257, 306 nm. [log ε 3.16, 2.89, 3.02].

$\lambda_{max.}$ (EtOH/NaOH) 238, 274s, 293 nm. [log ε 3.12, (-), 3.10].

Mass spectrum $^{m}/e$ 187.0746 (M^+ requires 187.0746) 159.0794 ($C_9H_9N_3^+$ requires 159.0796) 159.0682 ($C_{10}H_9NO^+$ requires 159.0684) 130.0656 ($C_9H_8N^+$ requires 130.0657) 104.

(b) cis-2-Methyl-3-(3-v-triazolo[1,5-a]pyridyl)acraldehyde (49) (0.5g.) in a pyrex tube was heated under nitrogen for one hour at 165-170°. Extraction and separation as before gave trans-2-methyl-3-(3-v-triazolo[1,5-a]pyridyl)acraldehyde (51) (0.2g., 40%) 3-methyl-5-(2-pyridyl)pyrazole (133) (0.102g., 24.8%) and 4-formyl-3-methyl-5-(2-pyridyl)pyrazole (132) (0.107g., 21.3%).

Pyrolysis of trans-2-Methyl-3-(3-v-triazolo[1,5-a]pyridyl)-acraldehyde (51)

trans-2-Methyl-3-(3-v-triazolo[1,5-a]pyridyl)acraldehyde (51) (0.3g.) in a pyrex tube was heated in an oil bath under nitrogen at 205-208°. Gas was evolved when the compound melted and the mixture was quickly cooled and dissolved in chloroform (15 ml.). The chloroform solution was poured into anhydrous ether (150 ml.), the mixture filtered and the filtrate evaporated to leave a solid residue. Extraction with hot ether left unreacted trans-2-methyl-3-(3-v-triazolo[1,5-a]pyridyl)acraldehyde (51) (49 mg., 16.2%). Evaporation of the ether extracts gave 3-methyl-5(2-pyridyl)-pyrazole (133) (0.104g., 40.9%).

3-Methyl-5-(2-pyridyl)pyrazole-4-carboxylic Acid (134)

Powdered potassium permanganate was added in portions to a stirred solution of 4-formyl-3-methyl-5-(2-pyridyl)pyrazole (132) (0.552g.) in anhydrous acetone (150 ml.) at room temperature over a

period of 3 days until a purple colouration remained. The precipitate was filtered, washed with acetone and extracted with hot water (50 ml.). The aqueous solution was adjusted to pH 6.9 with hydrochloric acid (indicator paper) and the solution evaporated to dryness. The residue was extracted with hot ethanol and the ethanolic solution evaporated to dryness to give 3-methyl-5-(2-pyridyl)pyrazole-4-carboxylic acid (134) which crystallised from aqueous ethanol (0.454g., 76%), m.p. 229-231°.

$C_{10}H_9N_3O_2$ requires: C, 59.1; H, 4.43; N, 20.7%

Found: C, 58.6; H, 4.29; N, 20.8%

$\delta(CF_3CO_2H)$	2.22 (3H, s, CH_3) 8-8.4 (1H, m) 8.4-9 p.p.m. (3H, m).
$\nu_{max.}$ ($CHCl_3$)	3420, 3208, 1668 $cm.^{-1}$
$\lambda_{max.}$ (EtOH)	250, 286 nm. [log ε 3.0, 3.04].
$\lambda_{max.}$ (EtOH/HCl)	250, 294 nm. [log ε 2.88, 3.03].
$\lambda_{max.}$ (EtOH/HCl)	235, 285 nm. [log ε 2.85, 2.94].
Mass spectrum m/e	203 (M^+), 185, 159, 130.

Grignard Reagent of 2-Bromopyridine

This was prepared from 2-bromopyridine and magnesium by the method of Tilford, Shelton and Van Campen.[59]

1-(2-Pyridyl)but-2-en-1-ol (137)

Freshly distilled crotonaldehyde (8.75g.) was slowly added

to a solution of 2-pyridyl magnesium bromide (from 12g. 2-bromopyridine) in anhydrous ether (50 ml.) at 0° (1.5 hr.). The mixture was stirred for a further hour at 0° and the Grignard compound decomposed by addition of a saturated solution of ammonium chloride in ammonium hydroxide. The organic layer was separated and the aqueous solution was extracted with ether (3 x 50 ml.). The combined organic extracts were dried (Na_2SO_4) and fractionated to give 1-(2-pyridyl)but-2-en-1-ol (137) as a colourless oil, b.p. 77-78°/0.2 mm. (3.25g., 28.7%).

$C_9H_{11}NO$ requires: C, 72.5; H, 7.38; N, 9.4%

Found: C, 72.1; H, 7.32; N, 9.2%

$\delta(CCl_4)$ 1.7 (3H, d, CH_3) 4.4 (1H, sbr, exchange with D_2O, OH) 5.0 (1H, d, CHOH) 5.6 (2H, m, CH=CH) 6.95-7.8 (3H, m) 8.4 p.p.m. (1H, d).

$\nu_{max.}$ (film) 3350 $cm.^{-1}$

$\lambda_{max.}$ (EtOH) 260 nm. [log ε 2.51].

$\lambda_{max.}$ (EtOH/HCl) 264 nm. [log ε 2.82].

Active Manganese Dioxide

This was prepared by the method of Attenburrow, Cameron, Chapman, Evans, Hems, Jansen and Walker.[60]

1-(2-Pyridyl)but-2-en-1-one (138)

Active manganese dioxide (25g.) was added to a solution of 1-(2-pyridyl)but-2-en-1-ol (137) (2.0g.) in anhydrous acetone (100 ml.), and the mixture was shaken at room temperature overnight. The filtered solution was evaporated to yield 1-(2-pyridyl)-but-2-en-1-one as a mobile liquid (1.92g., 97.3%), b.p. 147-152°/17 mm.

C_9H_9NO requires: C, 73.45; H, 6.12; N, 9.5%

Found: C, 73.5; H, 6.01; N, 9.4%

$\delta(CCl_4)$ 2.05 (3H, d, CH_3) 6.9-8.2 (5H, m) 8.6 p.p.m. (1H, d).

$\nu_{max.}$ (film) 1675 $cm.^{-1}$

$\lambda_{max.}$ (EtOH) 252, 268sh nm. [log ε 3.08, (-)].

5-Methyl-3-(2-pyridyl)Δ^2pyrazoline (139)

Hydrazine hydrate (100%, 5 ml.) was added to a solution of 1-(2-pyridyl)but-2-en-1-one (138) (1.5g.) in 95% ethanol (20 ml.) and the solution was boiled for two hours. The ethanol was removed under reduced pressure and the oil which separated from the aqueous residue was extracted with ether. The ether extracts were dried (Na_2SO_4) and evaporated to give the pyrazoline (139) as an oil, b.p. 105-110/0.1 mm. (1.15g., 70%).

$\delta(CCl_4)$ 1.25 (3H, d, CH_3) 2.4-3.4 (2H, m, CH_2) 3.7-4.2 (1H, m, CH) 5.5 (1H, sbr, exchange with D_2O, NH) 6.9-8 (3H, m) 8.45 p.p.m. (1H, d).

$\nu_{max.}$ (film) 3280 cm.$^{-1}$

$\lambda_{max.}$ (EtOH) 300 nm. [log ε 2.97].

$\lambda_{max.}$ (EtOH/HCl) 235, 307, 363 nm. [log ε 2.58, 2.70, 2.81].

Mass spectrum $^{m}/e$ 161 (M^{+}), 146, 117.

Attempted Synthesis of 3-Methyl-5-(2-pyridyl)pyrazole (133)

(a) Bromine (2.6 ml.) was added at room temperature to a solution of 3-methyl-5-(2-pyridyl)pyrazoline (139) (0.5g.) in carbon tetrachloride (15 ml.), containing calcium carbonate (2g.) as a suspension. The precipitate was separated extracted with water and the resulting aqueous solution was basified with solid sodium bicarbonate and the product extracted with chloroform. Evaporation of the dried (Na_2SO_4) extracts gave a tar which was shown by t.l.c. and its n.m.r. spectrum to be a mixture containing no pyrazole (133).

(b) Powdered potassium permanganate was added to a solution of pyrazoline (139) (0.16g.) in anhydrous acetone (15 ml.). The mixture was boiled under reflux (2.5 hr.). Filtration and evaporation gave unreacted pyrazoline (139).

(c) A solution of the pyrazoline (139) (0.5g.) in benzene (50 ml.) containing dichlorodicyanobenzoquinone (0.9g.) was boiled under reflux (1 hr.). Evaporation of the solvent gave an intractable tar which could not be purified.

(d) A solution of the pyrazoline (139) (0.5g.) in glacial acetic acid (10 ml.) was treated with lead tetraacetate (1.38g.)

at room temperature with cooling. The reaction mixture was allowed to stand at room temperature (1 hr.), poured into water, and basified with solid sodium bicarbonate. The product was extracted with chloroform and the dried (Na_2SO_4) extracts evaporated to give an oil shown by its n.m.r. spectrum to be a complex mixture containing no pyrazole (133).

1-(2-Pyridyl)butan-1,3-dione (141)

This was prepared by the method of Levine and Sneed[61] from ethyl picolinate and acetone in the presence of sodium ethoxide.

3-Methyl-5-(2-pyridyl)pyrazole (133)

(a) Hydrazine hydrate (100%, 5.5 ml.) was added to a solution of 1-(2-pyridyl)butan-1,3-dione (141) (1.5g.) in ethanol (20 ml.) and the mixture was boiled under reflux for 45 minutes. The solution was evaporated to low bulk and the oil which separated from the aqueous residue extracted with chloroform. The chloroform extracts were dried (Na_2SO_4) and evaporated to leave a red oil which solidified when triturated with light petroleum. Sublimation at 90°/0.01 mm. gave 3-methyl-5-(2-pyridyl)pyrazole (133) (1.5g., 75%), m.p. 115-116°. A mixed m.p. determination with a sample obtained by pyrolysis of cis-2-methyl-3-(3-v-triazolo[1,5-a]pyridyl)acraldehyde

(49) showed no depression.

(b) 3-Methyl-5-(2-pyridyl)pyrazole-4-carboxylic acid (134) (0.1g.) in a pyrex tube was heated in an oil bath at 190-200° until CO_2 (lime-water) ceased to be evolved (0.5 hr.). The cooled product was purified by p.l.c. using chloroform-methanol (19:1) followed by sublimation at 90-95°/0.25 mm. to give 3-methyl-5-(2-pyridyl)pyrazole (133) (26 mg., 33.2%).

Attempted Synthesis of 4-Formyl-3-methyl-5-(2-pyridyl)pyrazole (132)

A mixture of 3-methyl-5-(2-pyridyl)pyrazole (133) (1.0g.) and anhydrous dimethylformamide (1.15g.) was warmed to 95-100° and phosphorus oxychloride (0.75 ml.) added dropwise. The mixture was heated (100°, 2 hr.) cooled to 10° and hydrolysed by the addition of water. The resulting solution was neutralised with solid sodium bicarbonate and extracted with chloroform. Evaporation of the dried (Na_2SO_4) extracts gave an oil shown by the n.m.r. spectrum to be crude unreacted pyridylpyrazole (133).

4-Bromo-3-methyl-5-(2-pyridyl)pyrazole (142)

A stirred solution of 3-methyl-5-(2-pyridyl)pyrazole (133) (5g.) in chloroform (100 ml.), containing calcium carbonate (5g.) as a suspension, was treated dropwise with a solution of bromine (1.7 ml.) in chloroform (50 ml.) over the period of one hour. After

the addition was completed the mixture was stirred for an additional hour at room temperature. The mixture was filtered and the chloroform solution washed with saturated aqueous sodium bicarbonate solution. The dried (Na_2SO_4) chloroform solution was evaporated to leave a solid residue. This crystallised from carbon tetrachloride to give the bromopyrazole (142) as needles (2.3g., 30.8%), m.p. 165-166°.

$C_9H_8N_3Br$ requires: C, 45.4; H, 3.60; N, 17.65%

Found: C, 45.3; H, 3.40; N, 17.4%

$\delta(CDCl_3)$ 2.25 (3H, s, CH_3) 7.15 (1H, m) 7.7 (1H, t) 8.2 (1H, d) 8.55 (1H, sbr) 10.65 p.p.m. (1H, sbr, exchange with D_2O, NH).

$\nu_{max.}$ ($CHCl_3$) 3430 $cm.^{-1}$

$\lambda_{max.}$ (EtOH) 242, 280 nm. [log ε 2.95, 2.94].

$\lambda_{max.}$ (EtOH/HCl) 245, 306 nm. [log ε 2.86, 3.02].

$\lambda_{max.}$ (EtOH/NaOH) 266, 295 nm. [log ε 2.94, 2.96].

Mass spectrum $^m/_e$ 239 237 (M^+), 130, 103, 78.

Attempted Synthesis of 3-Methyl-5-(2-pyridyl)pyrazole-4-carboxylic Acid (134)

A solution of n-butyllithium in hexane (15%, 1.8 ml.) was added slowly to a solution of 4-bromo-3-methyl-5-(2-pyridyl)pyrazole (142) (1.0g.) in anhydrous tetrahydrofuran (25 ml.) cooled in a dry ice/1,2-dichloroethane bath (-30 to -35°) under nitrogen. The mixture was

stirred (1 hr.), cooled in an acetone-dry ice bath (-70°) and powdered dry ice (5g.) quickly added. The mixture was stirred for a further hour at -70° and allowed to warm to room temperature. The resulting solution contained only unreacted starting material shown by t.l.c. using chloroform-methanol (19:1).

Attempted Synthesis of 4-Cyano-3-methyl-5-(2-pyridyl)pyrazole (143)

A mixture of 4-bromo-3-methyl-5-(2-pyridyl)pyrazole (142) (0.5g.) and cuprous cyanide (0.188g.) were intimately mixed by grinding and placed in a bulb-tube. The pressure in the bulb-tube was reduced (200 mm.) and the bulb-tube heated cautiously with a luminous flame. After the mixture melted a vigorous reaction occurred, the pressure was immediately reduced (15 mm.) and the product distilled to give a solid (0.25g.), shown to be a mixture by peaks in the mass spectrum due to the bromopyrazole (142) at $^{m}/_{e}$ 239, 237 and an i.r. cyano absorption at 2230 $cm.^{-1}$. Repeated crystallisation from carbon tetrachloride or chloroform, distillation, sublimation, p.l.c. failed to separate the cyanopyrazole from the starting bromopyrazole (142). Attempts to prepare a pure picrate from the mixture were also unsuccessful.

Attempted Synthesis of 3-Methyl-5-(2-pyridyl)pyrazole-4-carboxylic Acid (134)

(a) Sodium hydroxide (0.2g.) was added to a solution of crude

4-cyano-3-methyl-5-(2-pyridyl)pyrazole (143) (60 mg.) in ethanol-water (1:1, 20 ml.) and the mixture boiled under reflux (2 hr.). The ethanol was removed under reduced pressure and the resulting aqueous solution adjusted to pH 6.5 (indicator paper) using concentrated hydrochloric acid. The solution was evaporated to dryness under reduced pressure and the residue extracted with absolute ethanol. Evaporation of the ethanolic solution resulted in isolation of unreacted cyano-bromo mixture.

(b) Potassium hydroxide solution (30%, 10 ml.) was added to a solution of crude cyanide (143) (0.26g.) in butan-2-ol (20 ml.) and the solution boiled under reflux (50 hr.) neutralisation followed by evaporation and extraction as before gave unreacted starting material.

(c) A solution of crude cyanide (143) (0.2g.) in ethanol (10 ml.) and aqueous sodium hydroxide (40%, 10 ml.) was heated in a sealed tube (140°, 18 hr.). Neutralisation, evaporation and extraction as before gave a tar which had no cyanide or carbonyl i.r. absorption.

(d) A solution of crude cyanide (143) (60 mg.) in concentrated hydrochloric acid (25 ml.) was heated (100°, 1 hr.). The solution was adjusted to pH 6.9 with solid sodium bicarbonate and the solution evaporated to dryness. Extraction with ethanol and evaporation gave only unreacted starting material.

(e) A solution of the crude cyanide (143) (83 mg.) in concentrated hydrobromic acid (15 ml.) was boiled under reflux (3 hr.). Neutralisation, evaporation, extraction with ethanol and evaporation gave a tar which appeared to be the decomposition product of the cyanide with no cyanide or carbonyl i.r. absorptions.

Ethyl 2-Diazo-propionate (168)

A solution of alanine ethyl ester hydrochloride (167) (10g.) and sodium acetate (0.2g.) in water (10 ml.) was placed in a three-necked flask fitted with a separating funnel and stirrer. A stopper in the third neck of the flask carried a glass tube that reached to the bottom of the flask. The solution was cooled to 2° and a cold solution of sodium nitrite (5.4g.) in water (6 ml.) was added and the mixture stirred until the temperature fell to 0°. The temperature was maintained below 2° during all the following operations. Ether (20 ml.) was added and 2N sulphuric acid (0.2 ml.). After 5 minutes the reaction mixture was blown by nitrogen pressure into a separating funnel, the aqueous layer returned to the reaction flask and the ether extract quickly transferred to a separating funnel containing sodium carbonate solution (10%). The ether layer was separated and dried (Na_2SO_4). A further portion of ether (20 ml.) and acid (0.5 ml.) were added and the mixture stirred. After 5 minutes the ether layer was separated as before. This process was

repeated until the ether extract was no longer coloured (ten times). Evaporation of the ether extracts gave the crude diazo-ester.

$\nu_{max.}$ (CCl_4) 2080 cm.$^{-1}$ Lit.,[71] $\nu_{max.}$ ($CHCl_3$) 2105 cm.$^{-1}$

An attempt to purify a sample by p.l.c. using benzene as eluent resulted in decomposition of the diazo-ester.

Attempted Synthesis of 3-Carbethoxy-3-methyl-5-phenylpyrazole (169)

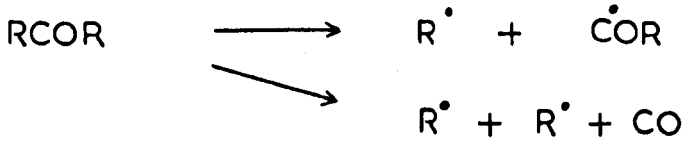
Crude ethyl 2-diazo-propionate (168) (1.0g.) and phenyl acetylene (160) (0.72g.) were mixed and heated in a sealed tube (105°, 20 hr.). A gas was evolved when the tube was opened and the n.m.r. spectrum of the reaction mixture indicated unreacted phenyl acetylene and decomposition products of the diazo-ester were present. There was no evidence for diazo compound or pyrazole formation.

PHOTOCHEMICAL STUDIES ON β-SUBSTITUTED-ACRALDEHYDES

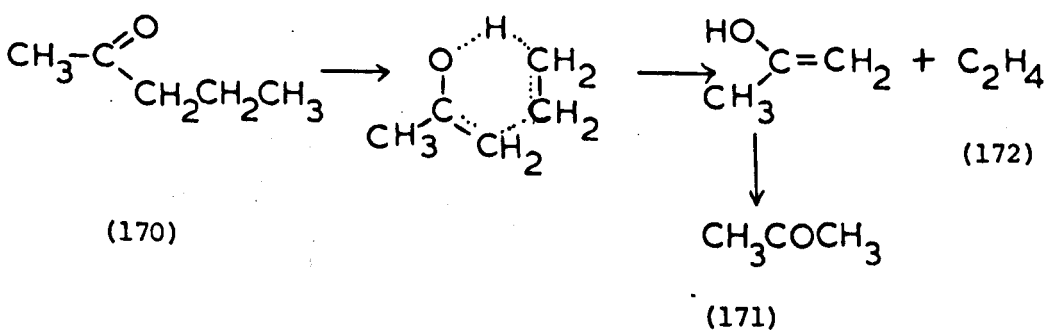
SURVEY OF PREVIOUS WORK

The photochemistry of α,β-unsaturated aldehydes has been relatively little studied compared to unsaturated ketones. Ultraviolet irradiation of acraldehyde[72] and trans-crotonaldehyde[73] led to polymer formation. Cinnamaldehyde either was unaffected[74] or also gave polymeric material,[75] while unsaturated ketones, for example trans-methylpropenylketone[76] was converted to the cis-isomer as the only significant photo-reaction.

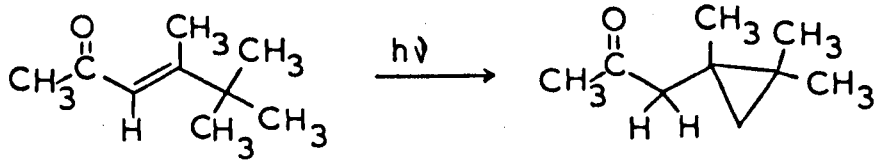
The photodecomposition of ketones and aldehydes into free radicals is referred to as the "Type I" split. The



Norrish "Type II" split is a mode of intramolecular decomposition of aliphatic ketones and aldehydes having a γ-hydrogen atom on the alkyl chain. For example propan-2-one (170) is converted to acetone (171) and ethylene (172).

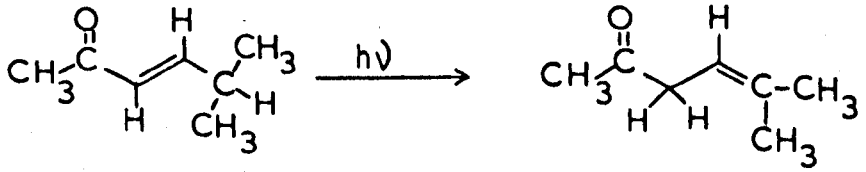


Jorgenson and Yang[77] have shown that when an α,β-unsaturated ketone has a quaternary carbon atom at the γ-position (173) irradiation led to cyclisation of the chain to give a cyclopropane derivative (174).

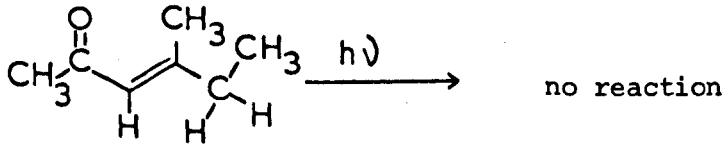


(173) (174)

Irradiation of α,β-unsaturated aliphatic ketones having no γ-quaternary carbon (175) resulted in isomerisation to the β,γ-unsaturated isomer (176) or no reaction.[78]

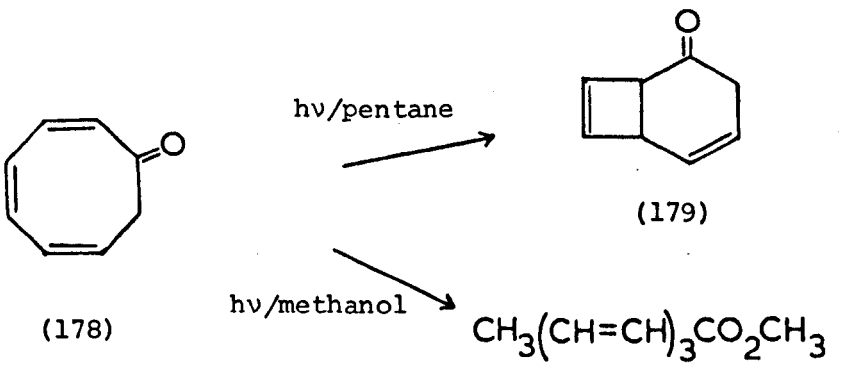


(175) (176)



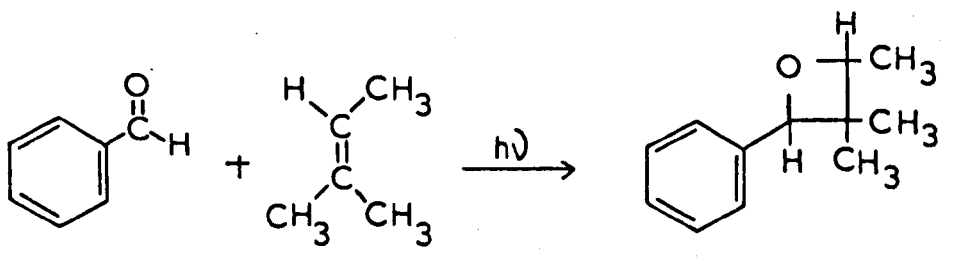
(177)

Photoisomerisations of cyclic ketones involving conversion of monocyclic into bicyclic structures and vice versa have been reported to occur in the liquid phase.[79] Irradiation of 2,4,6-cyclooctatriene (178) in pentane solution led to a bicyclic ketone (179). In methanol solution methyl 2,4,6-octatrienoate (180) was obtained.



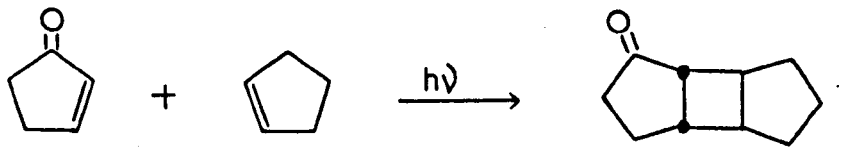
(178) (179) (180)

Büchi and co-workers[80] have shown that olefin molecules can form addition products with carbonyl compounds photochemically, giving rise to oxetanes as can be seen in the addition of benzaldehyde (181) to 2-methyl-2-butene (182) to give the oxetane (183). Cis-trans isomerisation of the olefin may accompany the cycloaddition reaction.



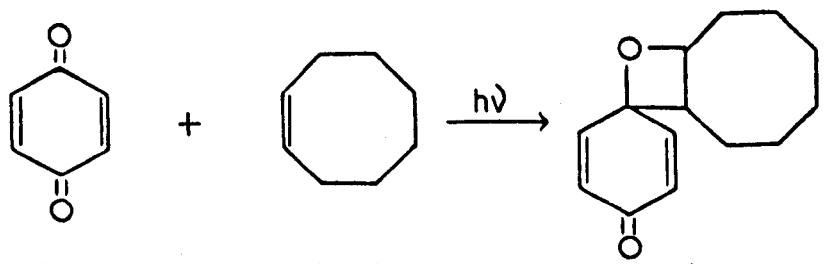
(181) (182) (183)

Simple α,β-unsaturated carbonyl compounds undergo photocycloaddition to olefins in a different fashion. Rather than addition of the carbonyl group to the olefin a cyclobutane derivative is formed. For example cyclopentenone (184) and cyclopentene (185) gave on irradiation a cyclobutane[81] (186).



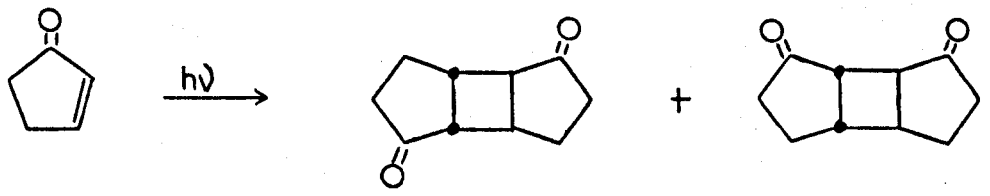
(184) (185) (186)

Benzoquinone (187) was reported[82] to add to cyclooctene (188) to give the oxetane (189) rather than a cyclobutane derivative.



(187) (188) (189)

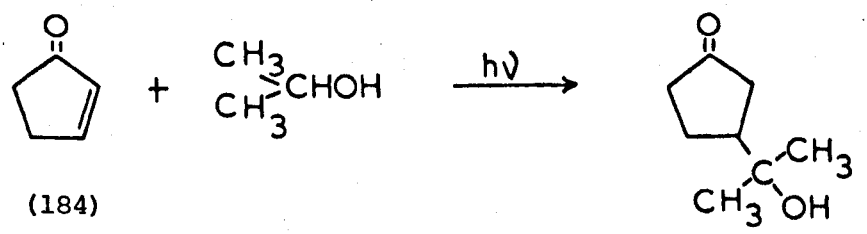
Photocyclodimerisation to give cyclobutane derivatives has long been known for α,β-unsaturated carbonyl compounds,[83] for example cyclopentenone (184) photodimerised to give trans-head-to-tail (190) and trans-head-to-head dimers (191) in equal yields.[84]



(184) (190) (191)

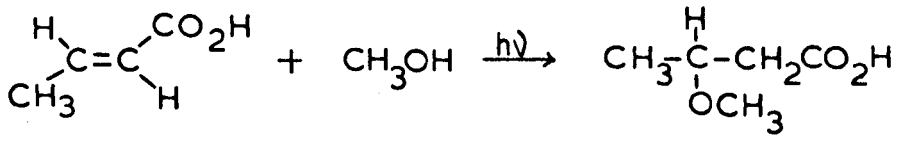
The difference in the mode of photocycloaddition of carbonyl compounds to olefins is thought to reflect differences in the nature of their excited states.

Addition of alcohols to olefins under ultraviolet irradiation occurs in two modes; the addition takes place at the carbon atom to which the hydroxyl function is attached or the addition takes place at the hydroxyl group. The photoaddition of isopropanol to cyclopentenone (184)[85] in the presence of benzophenone yielded 1:1 adducts (192).



(184) (192)

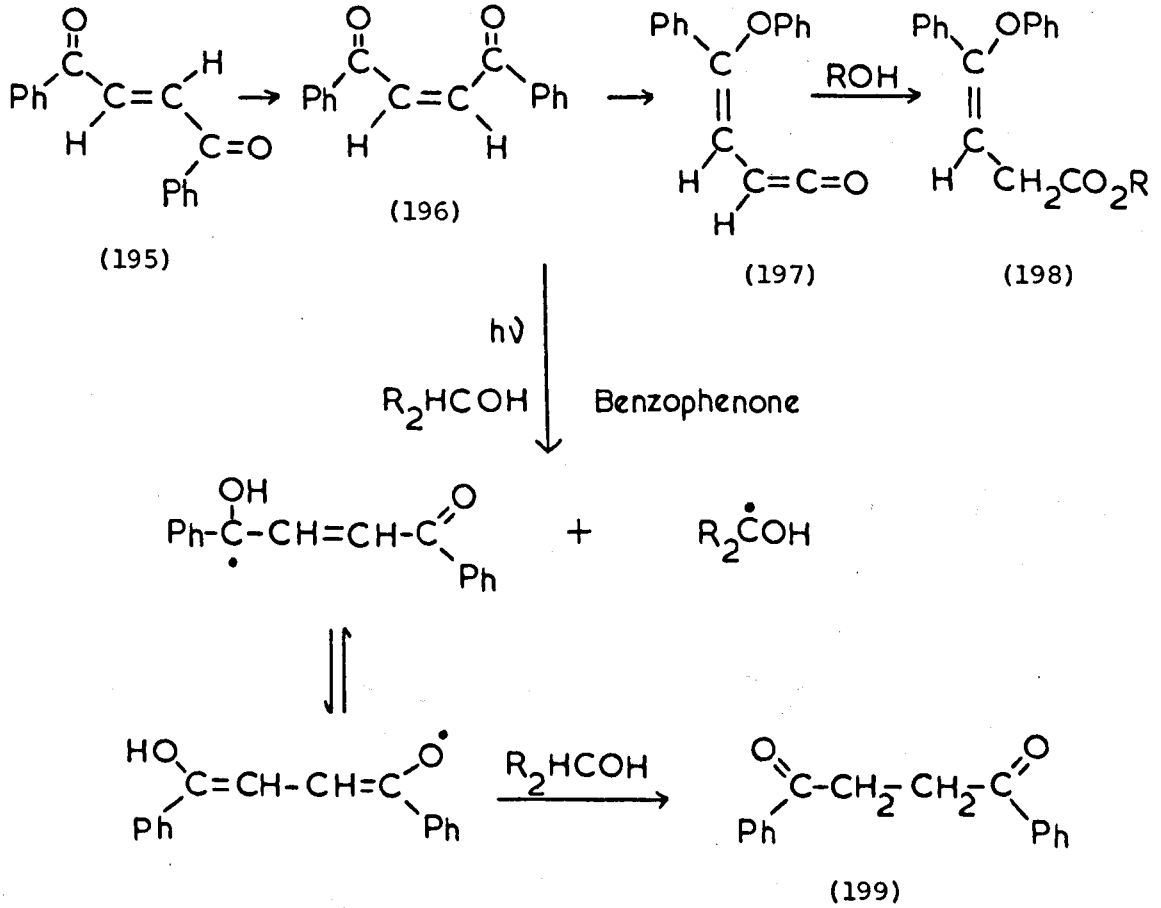
The other mode of addition where the hydroxyl group adds across a double bond is less common. The photoaddition of methanol to crotonic acid (193) to give the ether (194) was reported by Stoermer and Stockman.[86]



(193) (194)

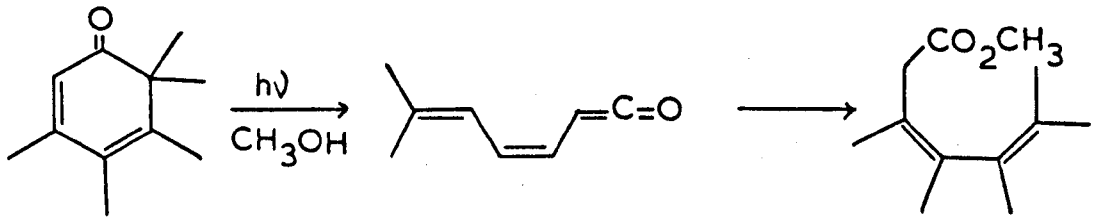
A free radical mechanism is thought to operate in the reactions where addition takes place at the carbon atom of the alcohol, while polar intermediates are involved where ethers are obtained by addition.

The ability of a photo-excited ketone or aldehyde to abstract a hydrogen atom from a good hydrogen donor in the solution phase has long been known.[87] The efficiency of this process depends on the reactivity of the hydrogen donor the structure of the abstracting carbonyl compound and the solvent. This was shown by the photochemical reactions of trans-dibenzoylethylene (195) in alcoholic solvents.[88] Short irradiation in alcohol gave the cis-isomer (196) (94%) plus the ester (198) (5%). On longer irradiation the ester (198) was produced in 36% yield.

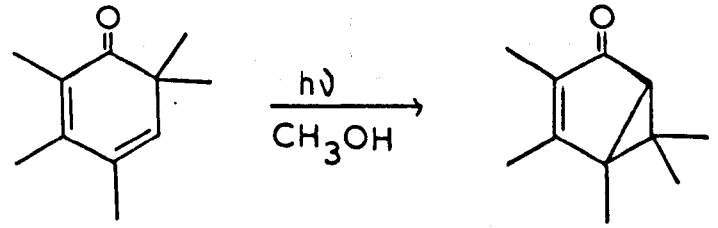


Griffin and O'Connell[89] have shown that irradiation of the cis isomer (196) in alcoholic solvents involved an excited singlet state which mainly underwent 1,5-phenyl migration followed by addition of alcohol to the ketene intermediate (197) to give the ester (198). Sensitisation by benzophenone produced the olefin (196) in its triplet state which was subsequently photoreduced via intermolecular hydrogen atom transfer from the solvent to give the diketone (199).

Many photochemical reactions of unsaturated ketones have been considered to involve ketenes as transient intermediates. Photolysis of the dienone (200) in methanol gave solely the acyclic ester (202) whereas under identical conditions the isomeric dienone (203) gave solely the bicyclohexenone (204).[90]



(200) (201) (202)

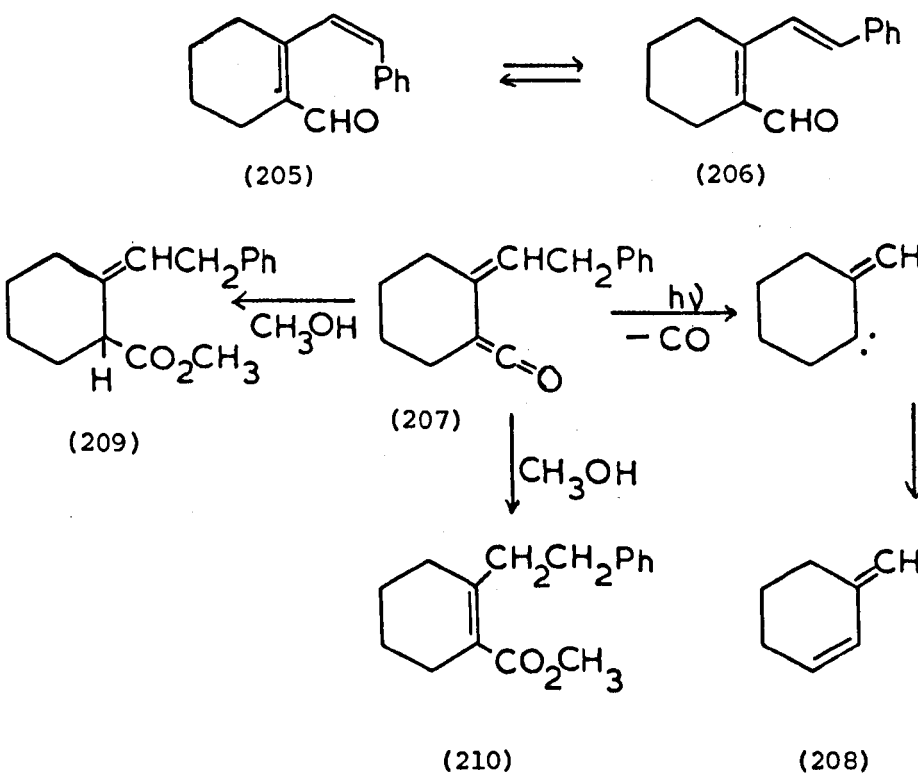


(203) (204)

Direct spectroscopic evidence has been obtained from photolyses at -100° of the presence of the diene-ketenes (201).[91] The ketene from the dienone (203) apparently cyclised so rapidly that it could not be trapped by weak nucleophiles such as alcohols. More potent nucleophiles, amines for example were better able to compete with cyclisation and gave acyclic amides. Quinkert,[92] Hobson[93] and Chapman[94] and their respective co-workers also report spectroscopic evidence for ketene intermediates in low temperature

photolyses.

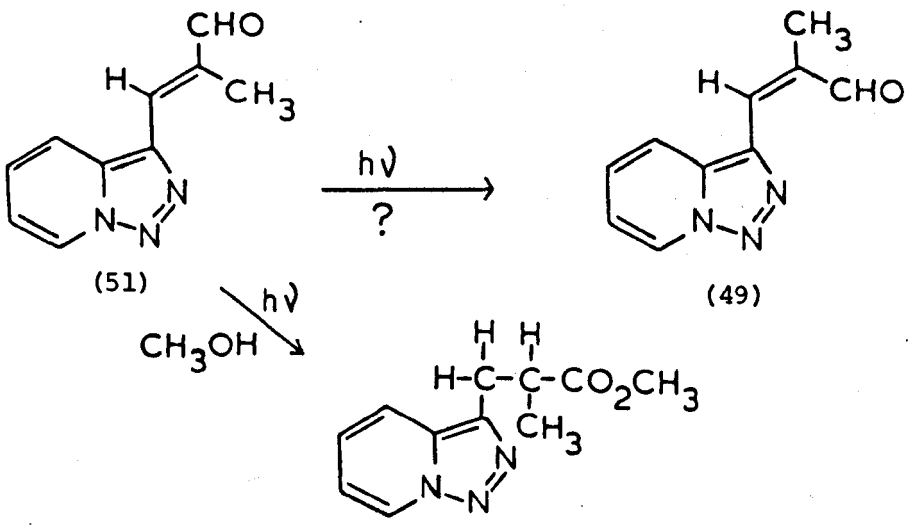
Schiess and Suter have reported[95] that irradiation of pentadienealdehyde (205) or (206) also led to a ketene in high yield through a 1,5-hydrogen shift shown by an absorption at 2100 cm.$^{-1}$ (C=C=O) at -20°. The ketene was photolabile forming the



hydrocarbon (208) on further irradiation. The ketene could also decompose at room temperature to pentadienealdehyde (206) or form addition products with nucleophiles, for example methanol to give a mixture of (209) and (210), with the unconjugated isomer (209) predominating.

DISCUSSION

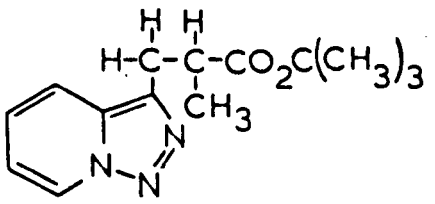
Although the cis-triazolopyridylacraldehyde (49) was easily isomerised to the trans-isomer (51) the reverse isomerisation was not observed and several attempts were made to induce the change trans- to cis- photochemically.



(211)

Due to the insoluble nature of the acraldehyde (51) in hydrocarbons (e.g. benzene, pentane, hexane), the normal solvents for photolysis were not available. Irradiation of the trans-acraldehyde (51) in dioxane (3 hr.) or chloroform (1 hr.) under nitrogen at room temperature using a Hanovia medium pressure lamp through quartz resulted in decomposition and polymer formation with no evidence for trans-cis isomerisation. Irradiation in methanolic solution of the

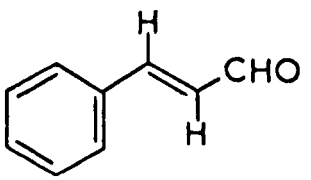
acraldehyde (51) for one hour resulted in conversion into a single product (74%) showing a saturated ester absorption at 1735 $cm.^{-1}$ and disappearance of aldehyde and vinyl proton absorptions in the n.m.r. spectrum. This ester was identified as methyl 3-(3-v-triazolo[1,5-a]pyridyl)-2-methylpropionate (211). There was no evidence for the presence of any cis-aldehyde (49). Similar irradiation, over a period of 1.5 hours, of the cis-acraldehyde (49) gave the same ester (211) in 85% yield. The reaction was shown to be general for alcohols by irradiation of the trans-aldehyde (49) in tertiary-butanol to give the tertiary-butyl ester (212).



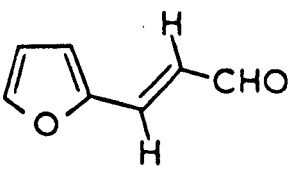
(212)

Irradiation through quartz of cinnamaldehyde (213) was reported to give either no reaction[74] or polymer formation.[75] Irradiation in methanol also gave polymer formation showing that the photochemical addition reaction was not general for 3-arylacraldehydes. Irradiation of cinnamaldehyde (213) in methanol through pyrex gave after one hour conversion to the cis-isomer (20%) indicated by the

appearance of the cis-aldehyde signal at δ9.9 p.p.m. in the n.m.r. spectrum with no ester formation. Irradiation of 3-(2-furyl)-acraldehyde (214)[96] (prepared from furfural and acraldehyde by the action of sodium) in methanol for 19 hours also failed to give any ester as shown by the absence of an ester-carbonyl absorption in the product mixture. The n.m.r. spectrum indicated a high proportion of starting material, a small amount of the cis-isomer and decomposition products which were not identified.



(213)

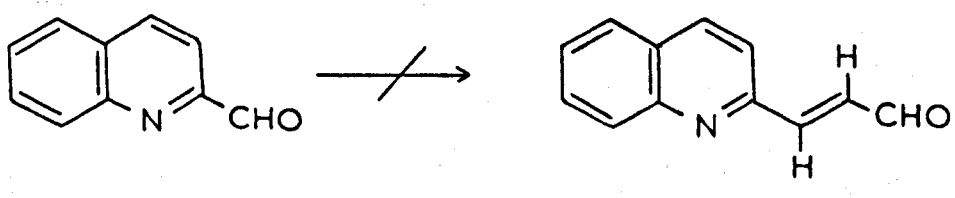


(214)

It was suspected that the adjacent nitrogen lone pair played a critical part in the photochemical addition and so efforts were made to provide analogous acraldehydes which might undergo the same photoaddition.

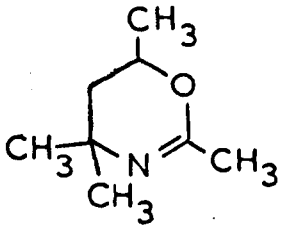
Quinoline-2-aldehyde (215)[97] was prepared by the treatment of 2-methylquinoline with selenium dioxide. Attempted aldol condensation of this aldehyde (215) with acetaldehyde to form 3-(2-quinolyl)acraldehyde (216) using Amberlite resin (IR4B) or sodium hydroxide resulted either in isolation of starting material or

condensation products of quinoline-2-aldehyde respectively. Similarly the attempted condensation between quinoline-2-aldehyde and propionaldehyde in the presence of phosphorus oxychloride resulted in isolation of starting material.

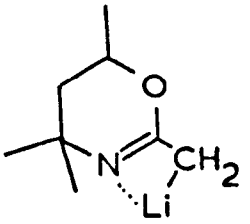


(215) (216)

Due to the failure of the normal aldol condensation with quinoline-2-aldehyde an attempt was made to synthesise the quinolylacraldehyde (216) using a method reported by Meyers and his co-workers.[98] This synthetic route[99] was used in attempts to synthesise several substituted α,β-unsaturated aldehydes. It involved preparation of 2,4,4,6-tetramethyl-5,6-dihydro-1,3-oxazine (217)[100] from acetonitrile and 2-methyl-2,4-pentane-diol in the presence of concentrated sulphuric acid. Treatment of this oxazine (217) in anhydrous tetrahydrofuran under nitrogen at -70° (acetone-dry ice) with a solution of n-butyllithium in hexane gave the anion of the oxazine (218). Reaction of this anion with quinoline-2-aldehyde (215) at -70° in anhydrous tetrahydrofuran followed by

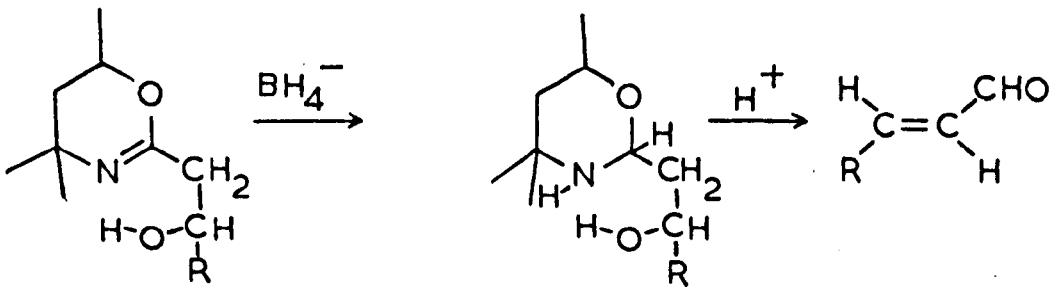


(217)



(218)

hydrolytic work up produced an almost quantitative yield of the oxazinyl alcohol (219, R = 2-quinolyl).

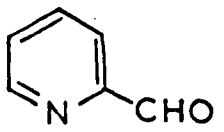


(219) (220)

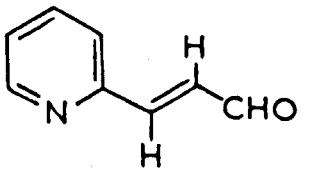
Reduction with sodium borohydride of the crude adduct in tetrahydrofuran-ethanol-water solution gave the expected alkylated-tetrahydro-1,3-oxazine (220, R = 2-quinolyl). The oxazines studied by Meyers[98] cleaved under the action of hot aqueous oxalic acid to give α,β-unsaturated aldehydes but the 2-quinolyloxazine (220, R = 2-quinolyl) proved resistant to cleavage with oxalic acid, even boiling with concentrated hydrochloric acid proved unsuccessful. The unreacted tetrahydro-1,3-oxazine was isolated on neutralisation in each case.

Although the treatment of pyridine-2-aldehyde (221) with

acetaldehyde in the presence of Amberlite resin (IR4B) following the method of Ohta and Isowa[101] resulted in the formation of some 3-(2-pyridyl)acraldehyde (222) the yield was very poor and several different synthetic approaches to the acraldehyde (222) were attempted.



(221)



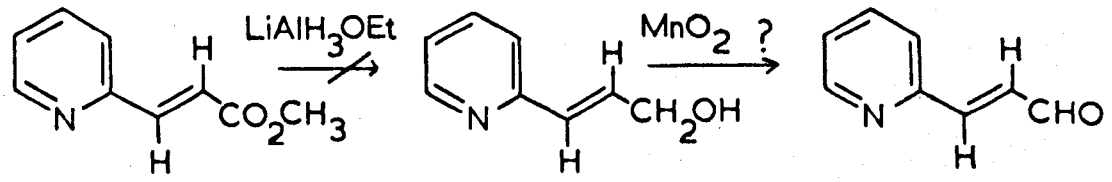
(222) R = H

(223) R = CH_3

Cinnamaldehyde (213) was reported[102] to be formed on treatment of styrene with the Vilsmeier formylating agent, phosphorus oxychloride in dimethylformamide. It was thought that 2-vinylpyridine (67) might react analogously, but on work up of the product only starting material was isolated.

The reported use of lithium aluminium monoethoxyhydride as a selective reducing agent of α,β-unsaturated esters to the corresponding primary allylic alcohols[103] together with the use of active manganese dioxide[60] as an oxidising agent to convert primary allylic alcohols to conjugated aldehydes,[104] without further oxidation to carboxylic acids, led to the attempted synthetic route to the

pyridylacraldehyde (222) outlined below.



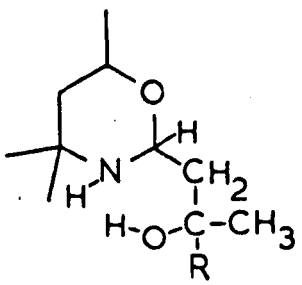
(224) (225) (222)

However treatment of methyl pyridylacrylate (224)[105] with lithium aluminium monoethoxyhydride in ether solution both at room temperature and at -35° to -45° gave on hydrolysis pyridyl propanol,[106] reduction of the double bond and the ester group having occurred.

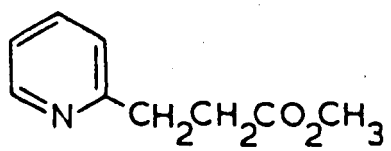
In the attempted synthesis of the acraldehyde (222) from pyridine-2-aldehyde (221) large quantities of the condensation product pyridoin were observed and it appeared that the difficulty might lie in the use of the basic Amberlite resin because the base used might be catalysing the condensation of pyridine-2-aldehyde with itself faster than the aldol condensation. It has been reported[107] that potassium-2,6-di-t-butylphenoxide proved more effective than potassium t-butoxide in catalysing the reaction of trialkylboranes with some α-bromoketones to give the corresponding α-monoalkylated ketones in good yields. Accordingly the aldol condensation of pyridine-2-aldehyde (221) with acetaldehyde was attempted in the presence of potassium 2,6-di-t-butylphenoxide prepared from

2,6-di-t-butylphenol and potassium, at 0^{o} in tetrahydrofuran. Hydrolytic work up gave only decomposition products of pyridine-2-aldehyde and no pyridylacraldehyde (222).

An attempt was made to synthesise 3-(2-pyridyl)-3-methylacraldehyde (223) following the method devised by Meyers.[98] Although the alkylated tetrahydro-1,3-oxazine (226, R = 2-pyridyl) was obtained in good yield it was not possible to induce cleavage of the oxazine ring to give the acraldehyde (223) even with boiling hydrobromic acid.



(226, R = 2-pyridyl)

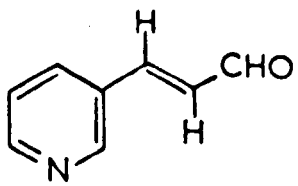


(227)

Following the failure of all the modifications the original synthesis due to Ohta and Isowa[101] was repeated several times to furnish a supply of the pyridylacraldehyde (222).

Irradiation of this aldehyde (222) in methanol for one hour gave after purification by preparative layer chromatography a poor yield of methyl 2-pyridylpropionate (227)[108] also synthesised by hydrogenation of methyl 2-pyridylacrylate (224)[102] over palladium on charcoal catalyst.

To determine whether the nitrogen lone pair had to be in an adjacent position to the acraldehyde side-chain the preparation of the isomers 3-(3-pyridyl)- and 3-(4-pyridyl)acraldehyde was undertaken. The synthesis of 3-pyridylacraldehyde (228) by aldol condensation of pyridine-3-aldehyde and acetaldehyde was reported[109] to proceed in less than 1% yield so an attempt was made to synthesise the acraldehyde (228) following the synthesis and decomposition of the alkylated tetrahydro-1,3-oxazine (220, R = 3-pyridyl) devised by Meyers and co-workers.[98]



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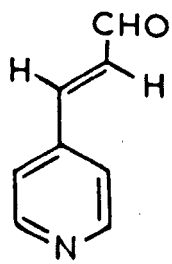


(229)

Cleavage of the oxazine was achieved using boiling oxalic acid. Neutralisation and extraction gave a poor yield of practically pure 3-(3-pyridyl)acraldehyde (228). Similarly the 3-(4-pyridyl)-acraldehyde (229) was prepared.

A methanolic solution of 3-pyridylacraldehyde (228) was irradiated for one hour. The n.m.r. spectrum of an evaporated sample showed, from the integral of the aldehyde absorptions at δ9.69 (trans) and δ9.9 p.p.m. (cis), that isomerisation to the cis-isomer (22% conversion) had occurred. Further irradiation (1 hr.) resulted

in a 35% conversion to the cis-isomer with some polymer formation. There was no evidence for ester formation. Attempts to separate the cis and trans isomers formed were unsuccessful, the cis-compound being converted to the trans-isomers on heating above room temperature.

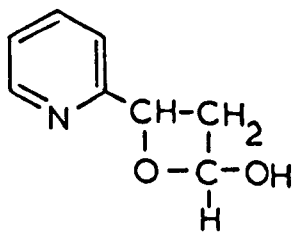
Irradiation of 4-pyridylacraldehyde (229) in methanol (1 hr.) also gave conversion to the cis-isomer as shown by the n.m.r. aldehyde absorptions at δ9.69 (trans) and δ9.9 p.p.m. (cis). Further irradiation again resulted in polymer formation.

Although there is a similarity in reactivity of the 2- and 4-positions of the pyridine ring the fact that the photoaddition fails with the 4-pyridylacraldehyde excludes the necessity of a suitable electronic configuration of the aromatic ring for the formation of the reaction intermediate as sole prerequisite for the photoreaction. This together with the failure of 3-pyridylacraldehyde in the reaction, where the aldehyde group is unable sterically to approach the nitrogen lone pair of electrons, appears to confirm the requirement of an adjacent nitrogen lone pair.

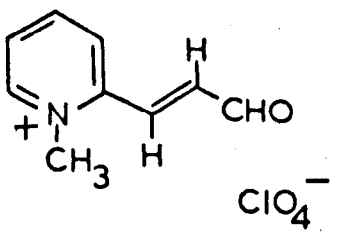
The high dilutions (1 g. in 800 ml. methanol) used for the photolyses of the pyridylacraldehydes prevented intermolecular catalysis of the photoaddition by a nitrogen lone pair. This was not necessary for the 2-isomer where intramolecular reaction was possible. In an attempt to promote intermolecular reaction cinnamaldehyde (213), and 4-pyridylacraldehyde, were irradiated in a methanol-triethylamine mixture (1:1). Polymerisation resulted in

each case.

Irradiation of 2-pyridylacraldehyde (222) in 1% sulphuric acid for one hour followed by neutralisation and extraction of the product gave a solid which proved difficult to purify. Comparison of the spectra of this and 2-pyridylpropionic acid[110] obtained by alkaline hydrolysis of methyl 2-pyridylpropionate (227) showed no similarity. The product had absorptions in the n.m.r. spectrum at δ2.8-3.4 ($CHCH_2$), 5.2-5.6 (CHOH) 5.8 p.p.m. (OH exchange with D_2O) and absorptions due to the protons of a 2-substituted pyridine ring. The presence of the hydroxyl group was confirmed by an absorption at 3200 $cm.^{-1}$. The compound had a molecular ion $^m/e$ 151 in the mass spectrum shown by high resolution to correspond to $C_8H_9NO_2$ and the compound was assigned the structure of the oxetane (230).



(230)



(231)

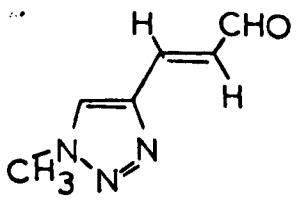
The quaternary compound 2-(3-acrolyl)-1-methylpyridinium iodide formed from boiling a solution of 2-pyridylacraldehyde with methyl iodide in acetone was converted to the perchlorate salt (231) by passage down a perchlorate loaded ion exchange resin column. This was irradiated in methanol solution for one hour. Evaporation gave a

tar whose n.m.r. spectrum showed no conversion to the ester, only decomposition products of the acraldehyde.

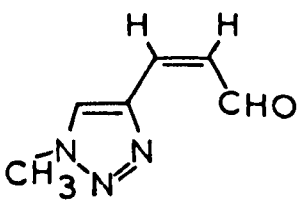
That the two pyridylacraldehydes in which the nitrogen lone pair of electrons were prevented from participation in formation of the photochemical intermediate by protonation and quaternisation failed to produce any pyridylpropionate clearly justified the necessity of an adjacent lone pair of electrons.

Although the results obtained appeared conclusive the poor stability of 2-pyridylacraldehyde in the atmosphere resulting in low yields observed in the reactions performed, it was decided to repeat some of them on a readily available acraldehyde in which the photochemical addition product was isolable in better yield. The acraldehyde used was 3-(1-methyl-v-triazolyl-4)-acraldehyde (125).[49]

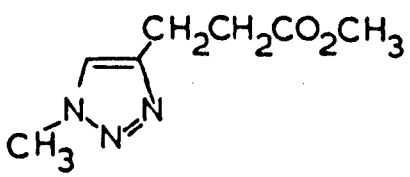
Irradiation through quartz of this aldehyde (125) in methanol solution gave after one hour an almost quantitative yield of methyl 3-(1-methyl-v-triazolyl-4)-propionate (233).



(125)



(232)



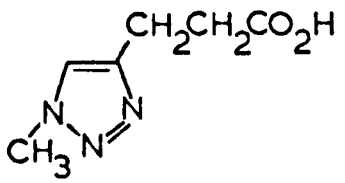
(233)

Irradiation through pyrex in methanol solution gave a mixture identified by the n.m.r. spectrum which showed the presence of the triazolylpropionate (233) (79%), trans-v-triazolylacraldehyde (125) δ9.6 p.p.m. (trans-CHO) (21%) and cis-v-triazolylacraldehyde (232) δ10.6 p.p.m. (cis-CHO) (6%). This was the first evidence for any trans-cis isomerisation in photolysis reactions in which esters were produced. Attempts to isolate the cis-v-triazolylacraldehyde (232) or the reaction intermediate by irradiation of the trans-isomer (125) in inert solvents such as tetrahydrofuran through quartz and pyrex, and benzene (quartz) proved unsuccessful. Evaporation of the solvent gave a tar in each case, shown by n.m.r. and thin layer chromatography to be a complex mixture.

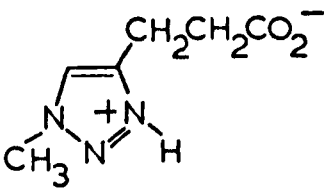
Attempts to isolate the cis-v-triazolylacraldehyde by diazotisation of 3-amino-1-methylpyridinium bromide (127) in nearly neutral medium also failed, the trans-isomer being obtained in all cases. This was ascribed to the solubility of the acraldehydes (125) and (232) in the aqueous reaction mixture. The insolubility of the triazolopyridylacraldehyde (49) enabled it to be filtered from the reaction mixture and be quickly removed from contact with the acidic medium thus preventing acid catalysed isomerisation to the trans-isomer (51). The simple triazolylacraldehyde (232) presumably isomerised to (125) during the isolation procedure.

Irradiation of the acraldehyde (125) in aqueous medium gave the propionic acid (234) (28% conversion after 1 hour). Protonation

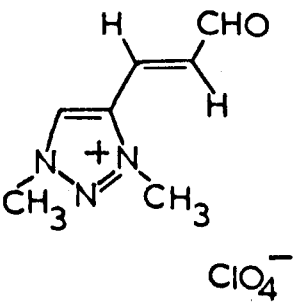
of the triazole (125) was achieved in 20% sulphuric acid, shown by the change in the ultraviolet absorption from λ280 nm. in aqueous solution to λ265 nm. There was no further shift of absorption maximum in 30% sulphuric acid solution. Irradiation of the acraldehyde (125) in 20% sulphuric acid solution also gave the propionic acid isolated as the zwitterion (235) by neutralisation



(234)



(235)



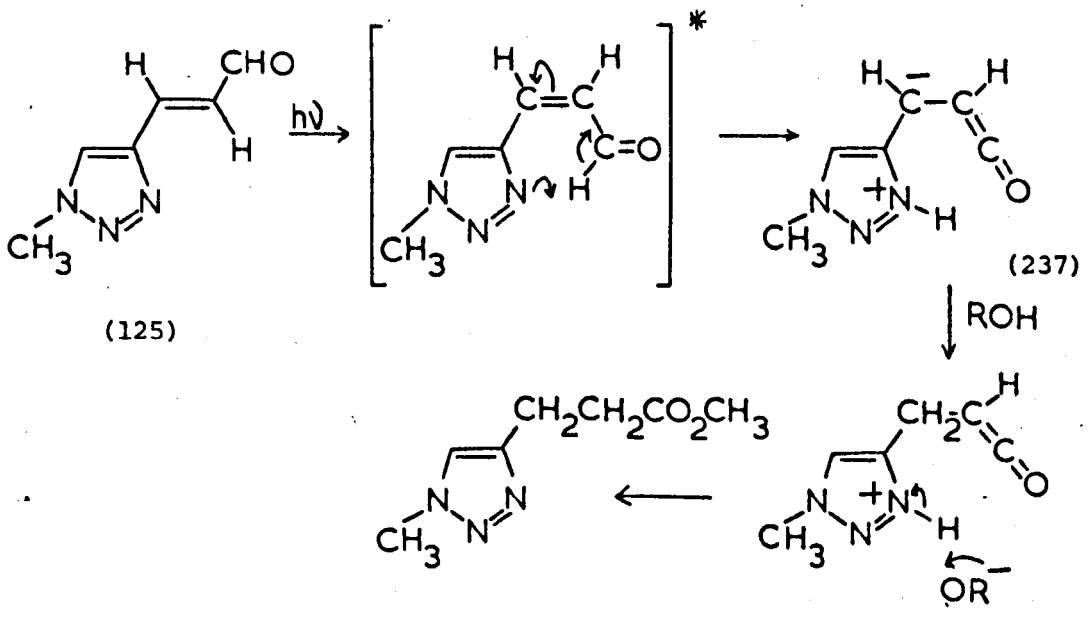
(236)

and extraction (16% after 1 hour). Attempts to isolate the free amino acid (234) as the product from photolysis in acidic solution by neutralisation to different pH values were unsuccessful. The formation of the propionic acid was unexpected in view of the failure of the photolysis of protonated 2-pyridylacraldehyde (222) to give 2-pyridylpropionic acid. However in the triazole it is not established whether protonation occurs exclusively at the 3-nitrogen atom or if there is an equilibrium situation between protonation at positions 2 and 3 with some of the triazole molecules having free nitrogen lone

pairs at position-3 thus enabling them to participate in formation of the photochemical intermediate.

That irradiation of the quaternary salt (236) (formed in analogous manner to 2-(3-acrolyl)-1-methylpyridinium perchlorate (231)) in methanol gave no trace of the saturated ester clearly established the participation of the lone pair of electrons on the nitrogen atom adjacent to the acraldehyde side chain.

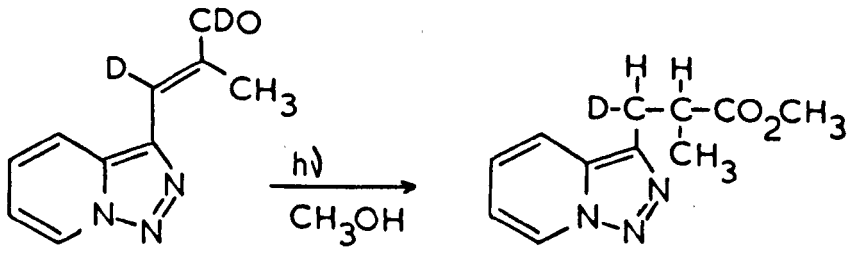
The mechanism proposed for the reaction is outlined below:



(125) (237) (233)

Evidence to support this is provided by irradiations of suitably deuterium labelled compounds.

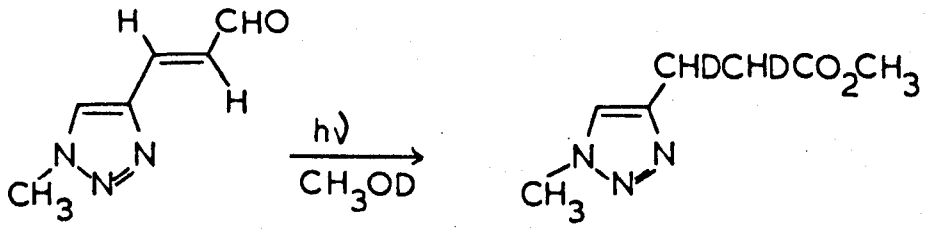
Irradiation of the predominately trans-1,3-dideutero-2-methyl-3-(3-v-triazolo[1,5-a]pyridyl)acraldehyde (115) in methanol gave methyl 3-deutero-3-(3-v-triazolo[1,5-a]pyridyl)-2-methylpropionate (238). The mass spectrum and n.m.r. spectrum indicated the product was monodeuterated on the 3-carbon atom of the side chain, the aldehyde deuterium atom having been exchanged during the photochemical reaction as required by the proposed mechanism.



(115) (238)

An attempt to prepare the analogous deuterated triazolylacraldehyde via treatment of 3-amino-1-methylpyridinium bromide (127) with concentrated deuterosulphuric acid to give the 2,4,6-trideutero derivative (239) proved unsuccessful. Exchange of H-2 occurred in concentrated deuterosulphuric acid at room temperature as shown by the n.m.r. spectrum but heating at 150° (20 hr.) failed to provide further exchange.

Irradiation of v-triazolylacraldehyde (125) in CH_3OD solution gave a dideuterated ester (240) whose n.m.r. and mass spectra indicated incorporation of deuterium atoms at carbon atoms 2 and 3.



(125) (240)

Irradiation of 2-pyridylacraldehyde (222) in CH_3OD solution also gave a dideuterated ester, thus supporting the outlined mechanism.

EXPERIMENTAL

Photolytic work was performed using a Hanovia photochemical reactor (medium pressure mercury lamp) mainly transmitting light of 254, 265, 297, 313 and 366 nm. wavelength. Irradiations were through quartz under nitrogen unless otherwise indicated.

Attempted Photochemical Isomerisation of trans-2-Methyl-3-(3-v-triazolo[1,5-a]pyridyl)acraldehyde (51)

(a) A solution of trans-2-methyl-3-(3-v-triazolo[1,5-a]pyridyl)-acraldehyde (51) (0.7g.) in dioxane (800 ml.) was irradiated (3 hr.). Evaporation gave a brown tar which was extracted with hot carbon tetrachloride. Evaporation of the extracts gave a yellow oil shown by t.l.c. to be a complex mixture. There was no evidence for the presence of the cis-isomer (49) in the n.m.r. spectrum of the product mixture.

(b) A solution of the trans-acraldehyde (51) (50 mg.) in chloroform (50 ml.) was irradiated for one hour. Evaporation gave a polymeric tar from which no pure material could be obtained.

Methyl 3-(3-v-Triazolo[1,5-a]pyridyl)-2-methylpropionate (211)

(a) A solution of trans-2-methyl-3-(3-v-triazolo[1,5-a]pyridyl)-acraldehyde (51) (1.5g.) in methanol (800 ml.) was irradiated (1 hr.)

and the solvent removed under reduced pressure. Extraction the residue with hot carbon tetrachloride left unreacted starting material (0.2g., 13.3%). Evaporation of the carbon tetrachloride extracts gave a pale yellow oil (1.32g., 74%) which was distilled to give methyl 3-(3-v-triazolo[1,5-a]pyridyl)-2-methylpropionate (211), b.p. 160-164°/0.2 mm.

$C_{11}H_{13}N_3O_2$ requires: C, 60.3; H, 5.90; N, 19.5%

Found: C, 60.1; H, 6.0; N, 19.0%

$\delta(CCl_4)$ 1.25 (3H, d, CH_3) 3-3.6 (3H, m, CH_2CH) 3.7 (3H, s, OCH_3) 6.95-7.55 (2H, m) 7.9 (1H, d) 8.95 p.p.m. (1H, d).

$\nu_{max.}$ (film) 1735 $cm.^{-1}$

$\lambda_{max.}$ (EtOH) 215, 225sh, 281, 310sh nm. [log ε 4.07, (-), 3.73, (-)].

Mass spectrum $^m/e$ 219 (M^+), 191, 159, 149, 132, 130, 117, 78.

(b) A solution of cis-2-methyl-3-(3-v-triazolo[1,5-a]pyridyl)-acraldehyde (49) (0.502g.) in methanol (800 ml.) was irradiated (1.5 hr.). The solvent was evaporated under reduced pressure and the residue distilled to give the ester (170), b.p. 140-150°/0.15 mm. (0.498g., 85%).

t-Butyl 3-(3-v-Triazolo[1,5-a]pyridyl)-2-methylpropionate (212)

A solution of trans-2-methyl-3-(3-v-triazolo[1,5-a]pyridyl)-acraldehyde (51) (0.5g.) in t-butanol (800 ml.) was irradiated (1 hr.)

at 30°. Evaporation of the solvent and distillation gave the t-butyl ester (212) as an oil, b.p. 128-133°/0.005 mm. (0.412g., 59%).

$C_{14}H_{19}N_3O_2$ requires: C, 64.35; H, 7.3; N, 16.1%

Found: C, 64.2; H, 7.6; N, 15.6%

$\delta(CDCl_3)$ 2.25 (3H, d, CH_3) 2.35 (9H, s, $OC(CH_3)_3$) 2.7-3.3 (3H, m, CH_2CH) 6.8-7.4 (2H, m) 7.8 (1H, d) 8.7 p.p.m. (1H, d)

$\nu_{max.}$ (film) 1720 $cm.^{-1}$

Photolysis of Cinnamaldehyde (213)

(a) A solution of cinnamaldehyde (213) (0.5g.) in methanol (25 ml.) was irradiated (4 hr.). Evaporation of the solvent gave a residue which was a mixture of cinnamaldehyde and polymeric material.

(b) A solution of cinnamaldehyde (213) (0.5g.) in methanol (25 ml.) was irradiated through pyrex (1 hr.). Evaporation of the solvent at room temperature gave an oil shown to be a mixture of starting trans-cinnamaldehyde (80%) and the cis-isomer (20%) by the n.m.r. spectrum.

$\delta(CDCl_3)$ 6.15 (q, cis-C<u>H</u>CHO) 6.65 (q, trans-C<u>H</u>CHO) 7.2-7.7 (6H, m) 9.65 (d, trans-CHO) 9.9 p.p.m. (d, cis-CHO).

3-(2-Furyl)acraldehyde (214)

This was prepared from furfural and acraldehyde in the presence of sodium by the method of Grandberg, Kost and Sibiryakova.[96]

Attempted Synthesis of Methyl 3-(2 Furyl)propionate

A solution of 3-(2-furyl)acraldehyde (214) (2.0g.) in methanol (800 ml.) was irradiated (19 hr.). Evaporation of the solvent left a brown oil as residue. The n.m.r. spectrum indicated this was predominantly starting material with small amounts of the cis-isomer and decomposition products which were not identified. The absence of an ester carbonyl absorption in the i.r. spectrum confirmed that no furyl ester was formed during the photolysis.

Quinoline-2-aldehyde (215)

Selenium Dioxide (30g.) was dissolved in dioxane (250 ml.) containing water (10 ml.) by warming and vigorous shaking. 2-Methylquinoline (17g.) was added and the mixture vigorously shaken. The mixture was boiled under reflux (2.5 hr.), the cooled mixture filtered and the dark red solution steam distilled. After removal of the dioxane distillate, the steam distillate was collected. Quinoline-2-aldehyde (215) crystallised from the cooled distillate as rods (4.45g., 23.9%), m.p. 69-70° Lit.,[97] m.p. 71°.

Attempted Synthesis of 3-(2-Quinolyl)acraldehyde (216)

(a) A solution of acetaldehyde (0.72 ml.) in water (0.7 ml.) was slowly added to a stirred solution of quinoline-2-aldehyde (215) (2.0g.) in 95% ethanol containing Amberlite resin IR4B (0.7g.) at 0°. After addition the mixture was stirred at 0° (1 hr.) and then at $35-40^{\circ}$ (0.5 hr.). Filtration and evaporation gave quinoline-2-aldehyde (215).

(b) Acetaldehyde (0.7 ml.) was added to a stirred solution of quinoline-2-aldehyde (2.0g.) in 95% ethanol at 0° and sodium hydroxide solution (0.2 ml.) added dropwise. The black solution was neutralised and evaporated to give a residue which was extracted with chloroform. The chloroform extracts were evaporated to dryness to give a residue the n.m.r. spectrum of which showed that no acraldehyde was present and that the residue was mainly condensation products of quinoline-2-aldehyde.

Attempted Synthesis of 2-Methyl-3-(2-quinolyl)acraldehyde

Quinoline-2-aldehyde (215) (0.7g.), propionaldehyde (0.2 ml.) and phosphorus oxychloride (0.2 ml.) were dissolved in benzene (10 ml.) and the solution stirred at room temperature (16 hr.). Ice-water (20 ml.) was added and the aqueous layer separated and washed with benzene (2 x 20 ml.). The aqueous layer was neutralised with solid sodium bicarbonate and extracted with

chloroform. Evaporation of the dried (Na_2SO_4) chloroform extracts gave quinoline-2-aldehyde (215).

2,4,4,6-Tetramethyl-5,6-dihydro-1,3-oxazine (217)

This was prepared from acetonitrile and 2-methyl-2,4-pentane-diol by the method of Meyers.[100]

General Procedure for Preparation of Alkylated Dihydro-1,3-oxazines (219)[99]

A 500 ml. three-necked flask, equipped with magnetic stirring bar, two 100 ml. addition funnels each with a rubber septum and a three-way stopcock with a gas-bubbler, was evacuated and flushed with nitrogen. Anhydrous tetrahydrofuran (100 ml.) and 2,4,4,6-tetramethyl-5,6-dihydro-1,3-oxazine (217) (14.1g., 0.1 mole) were added from a syringe through the rubber septum in one funnel to the flask. The stirred solution was cooled in a dry ice-acetone bath to -70° and a solution of n-butyllithium (15%, 46.8 ml.) in hexane was injected into the other funnel and the n-butyllithium was added dropwise (1 hr.). Approximately one hour after addition a yellow precipitate was formed which indicated complete anion formation. The mixture was stirred for an additional two hours and then the heterocyclic carbonyl compound (quinoline-2-aldehyde, 2-acetylpyridine, pyridine-3-aldehyde and pyridine-4-aldehyde were

used) (0.11 mole) in anhydrous tetrahydrofuran (25 ml.) was injected into the addition funnel and added over 30 minutes whilst the temperature was maintained at -70°. After addition was complete the reaction mixture was allowed to warm to room temperature overnight. The mixture was poured into ice-water (100 ml.) and acidified (pH 2-3) with concentrated hydrochloric acid. The acidic solution was extracted with pentane (3 x 75 ml.) and made basic with 40% sodium hydroxide solution with the addition of ice to keep the solution cool. The resulting red oil was extracted with ether (3 x 75 ml.). The combined ether extracts were dried (K_2CO_3) and evaporated under reduced pressure to give the crude alkylated dihydro-1,3-oxazine (219).

Reduction of Dihydro-1,3-oxazine (219) to Tetrahydrooxazine (220)

Tetrahydrofuran (100 ml.), ethanol (100 ml.), and the crude dihydrooxazine (219) were added to a 600 ml. beaker and the mixture was cooled between -35 and -40° with an acetone bath to which dry ice was added as needed. Concentrated hydrochloric acid was added to the magnetically stirred solution until an approximate pH of 7 was obtained. The pH was monitored by periodic checks with pH paper. A solution of sodium borohydride (3.78g.) in water (7 ml.), to which one drop of 40% sodium hydroxide solution was added, was prepared. The sodium borohydride solution and the

concentrated hydrochloric acid solution were added to the stirred solution alternately so that a pH 6-8 was maintained. During the addition care was taken to maintain the temperature between -35 and -45°. After addition of sodium borohydride solution was complete, the solution was stirred with cooling for an additional hour. A pH of 7 was maintained by occasional addition of hydrochloric acid. The contents were then poured into water (100 ml.) and made basic by addition of 40% sodium hydroxide solution. The layers were separated and the aqueous layer extracted with ether (3 x 75 ml.). The combined organic extracts were washed with saturated sodium chloride solution (100 ml.) and dried (K_2CO_3). The ether was removed under reduced pressure to give the crude tetrahydrooxazine (220).

The alkylated-tetrahydro-1,3-oxazines (220) from quinoline-2-aldehyde pyridine-3-aldehyde, pyridine-4-aldehyde and the alkylated oxazine (226) from 2-acetylpyridine were prepared by this method.

Attempted Hydrolytic Cleavage of 1-(2-Quinolyl)-2-(4,4,6-trimethyl-1,2,5,6-tetrahydro-1,3-oxazinyl-2)-ethanol (220, R = 2-quinolyl)

(a) The crude 2-quinolyloxazine (220, R = 2-quinolyl) (0.1 mole) was added dropwise to a solution of oxalic acid (20g.) in

water at its boiling point. The solution was boiled under reflux (1 hr.) and the cooled solution washed with chloroform (2 x 50 ml.). The aqueous solution was basified with solid sodium bicarbonate and the oily product extracted with chloroform. Evaporation of the dried (Na_2SO_4) extracts gave 2-quinolyloxazine (220, R = 2-quinolyl).

(b) A solution of crude 2-quinolyloxazine (0.1 mole) in concentrated hydrochloric acid (50 ml.) was boiled under reflux (1 hr.). The cooled solution was made basic with solid sodium bicarbonate and the product extracted with chloroform. Evaporation of the dried (Na_2SO_4) extracts gave 2-quinolyloxazine.

Attempted Hydrolytic Cleavage of 2-(2-Pyridyl)-1-(4,4,6-trimethyl-1,2,5,6-tetrahydro-1,3-oxazinyl-2)-propan-2-ol (226, R = 2-pyridyl)

A solution of crude 2-pyridyloxazine (226, R = 2-pyridyl) (1.0g.) in concentrated hydrobromic acid (30 ml.) was boiled under reflux (1 hr.). The cooled solution was diluted with water (30 ml.) neutralised with solid sodium carbonate and the product extracted with chloroform. The chloroform extracts were dried (Na_2SO_4) and evaporated to give 2-pyridyloxazine (226, R = 2-pyridyl).

Synthetic approaches to 3-(2-pyridyl)acraldehyde (222)

(a) Prepared by the method of Ohta and Isowa[101] from pyridine-2-aldehyde (221) and acetaldehyde in the presence of Amberlite resin IR4B in up to 10% yield.

(b) To potassium (3.9g.) under nitrogen was added a solution of 2,6-di-t-butylphenol (24.7g.) in anhydrous tetrahydrofuran (200 ml.) at room temperature over 30 minutes. After the initial vigorous reaction the solution was boiled (1 hr.), the magnetically stirred solution cooled to 0^{o} and freshly distilled acetaldehyde (4.4g.) in tetrahydrofuran (10 ml.) was added dropwise over 25 minutes. Freshly distilled pyridine-2-aldehyde (221) (10.7g.) in anhydrous tetrahydrofuran (10 ml.) was added over 25 minutes. The mixture was stirred and allowed to warm to room temperature. The residue from an evaporated sample (50 ml.) was dissolved in chloroform (50 ml.) and extracted with dilute hydrochloric acid (25 ml.) and the acidic extract basified with sodium bicarbonate. Extraction with chloroform followed by evaporation of the dried extracts gave a black oil which from its n.m.r. spectrum was found to be decomposition products of pyridine-2-aldehyde (221).

(c) Phosphorus oxychloride (16.9g.) was added to anhydrous dimethylformamide (8g.) cooled to 5^{o}, ethylene dichloride (25 ml.) was added and the mixture stirred under nitrogen with cooling until the temperature reached 5^{o}. A solution of freshly distilled 2-vinylpyridine (67) (10.5g.) in ethylene dichloride (25 ml.) was

added dropwise with stirring (1 hr.) and after addition the mixture was boiled for 15 minutes. The cooled solution was treated with a solution of sodium acetate (56g.) in water (120 ml.) with cooling and after addition the mixture was boiled for 15 minutes. The cooled solution was extracted with ether and the ether extracts dried (Na_2SO_4). Evaporation gave only unreacted 2-vinylpyridine.

3-(2-Pyridyl)acrylic acid

This was prepared from pyridine-2-aldehyde (221) and malonic acid by the method of Ried and Keller.[111]

Methyl 3-(2-Pyridyl)acrylate (224)

Concentrated sulphuric acid (10 ml.) was added dropwise to a solution of 3-(2-pyridyl)acrylic acid (9.6g.) in absolute methanol (30 ml.) and the resulting mixture heated (100°, 4 hr.). The cooled solution was poured onto a mixture of ice and concentrated ammonia solution (30 ml.) and the resulting mixture extracted with ether. Evaporation of the dried (Na_2SO_4) ether extracts gave methyl 3-(2-pyridyl)acrylate (224) which crystallised from petroleum-ether (b.p. 60-80°) as needles (6.5g., 61.8%). Hydrochloride m.p. 184-186° Lit.,[105] m.p. 185-186°.

Lithium Aluminium Monoethoxyhydride

This was prepared from lithium aluminium hydride and absolute ethanol in ether by the method of Davidson, Gunther, Waddington-Feather, and Lythgoe.[103]

Attempted Synthesis of 1-(2-Pyridyl)prop-1-en-3-ol (225)

(a) To a stirred solution of methyl 3-(2-pyridyl)acrylate (224) (2.0g., 0.13 mole) in anhydrous ether (25 ml.) was slowly added a solution of lithium aluminium monoethoxyhydride in ether (28 ml., 0.17 mole) under nitrogen. After addition was complete the mixture was stirred at room temperature (2 hr.). Excess hydride was decomposed by the addition of the minimum amount of water and the insoluble material filtered and triturated with hot chloroform (2 x 50 ml.). The combined organic layers were dried (Na_2SO_4) and evaporated to give an oil identified as 3-(2-pyridyl)propan-1-ol b.p. 148-155°/14 mm. (1.5g., 74%) Lit.,[106] b.p. 116-118°/4 mm.

(b) To a stirred solution of methyl 3-(2-pyridyl)acrylate (224) (2.0g., 0.13 mole), cooled to -35 to -45° in an acetone bath to which dry ice was added as needed, was added a solution of lithium aluminium monoethoxyhydride in ether (28 ml., 0.17 mole) under nitrogen. After addition was complete the mixture was stirred at -35 to -45° (1 hr.). Work up as above in (a) gave 3-(2-pyridyl)-propan-1-ol.

Methyl 3-(2-Pyridyl)propionate (227)

(a) A solution of 3-(2-pyridyl)acraldehyde (222) (1.66g.) in methanol (800 ml.) was irradiated (1 hr.). The solution was evaporated under reduced pressure and the black residue extracted with hot ether. Evaporation of the ether extracts gave an oil (1.39g.) which was purified by p.l.c. using chloroform (3 elutions). From one band an oil was obtained which was distilled to give methyl-3-(2-pyridyl)propionate (227) b.p. 80-85°/0.05 mm. (0.123g., 6%) Lit.,[108] b.p. 102-103°/2 mm.

$\delta(CDCl_3)$ 2.6-3.3 (4H, m, CH_2CH_2) 3.4 (3H, s, OCH_3) 6.85-7.7 (3H, m) 8.47 p.p.m. (1H, d).

$\nu_{max.}$ (film) 1740 $cm.^{-1}$

Mass spectrum $^m/e$ 165 (M^+), 134, 106, 92, 78.

(b) A solution of methyl 3-(2-pyridyl)acrylate (224) (1.07g.) in ethanol (20 ml.) was hydrogenated over palladium on charcoal (10%) catalyst (0.1g.) at ambient temperature and pressure. Absorption ceased when one molar equivalent of hydrogen was absorbed. Evaporation of the filtered solution gave the ester (227) as an oil, b.p. 90-95°/0.1 mm. (1.2g., 89.5%), identical in all spectral details with the ester (227) prepared in (a).

3-(3-Pyridyl)acraldehyde (228)

A solution of 1-(3-pyridyl)-2-(4,4,6-trimethyl-1,2,5,6-tetrahydro-1,3-oxazinyl-2)-ethanol (220, R = 3-pyridyl) (0.1 mole)

in water (250 ml.) containing oxalic acid (90g.) was boiled under reflux (18 hr.). The cooled mixture was filtered and the filtrate adjusted to pH 6 with solid sodium bicarbonate and the product extracted with chloroform. The dried (Na_2SO_4) chloroform extracts were evaporated to give 3-(3-pyridyl)-acraldehyde (228) (1.8g., 14.5%) b.p. 95-100°/0.3 mm. m.p. 66-67° Lit.,[109] m.p. 68-69°.

$\delta(CDCl_3)$ 6.75 (1H, q, CHCHO) 7.35 (1H, q) 7.52 (1H, d, CHCHCHO) 7.9 (1H, m) 8.6 (1H, q) 8.76 (1H, d) 9.7 p.p.m. (1H, d, CHO).

3-(4-Pyridyl)acraldehyde (229)

This was prepared from 1-(4-pyridyl)-2-(4,4,6-trimethyl-1,2,5,6-tetrahydro-1,3-oxazinyl-2)-ethanol (220, R = 4-pyridyl) using the same method used for the preparation of 3-(3-pyridyl)-acraldehyde (228). 3-(4-Pyridyl)acraldehyde (229) was obtained as an oil (2.9g., 23.3%) b.p. 137-140°/0.35 mm., m.p. 36-37°.

C_8H_7NO requires: C, 72.2; H, 5.15; N, 10.5%

Found: C, 71.7; H, 5.55; N, 10.4%

$\delta(CDCl_3)$ 6.8 (1H, q, CHCHO) 7.3-7.6 (3H, m) 8.7 (2H, d) 9.75 p.p.m. (1H, d, CHO).

$\nu_{max.}$ $(CHCl_3)$ 1680 $cm.^{-1}$

$\lambda_{max.}$ (EtOH) 263 nm. [log ε 3.22].

Photolysis of 3-(3-Pyridyl)acraldehyde (228)

A solution of 3-(3-pyridyl)acraldehyde (228) (1.0g.) in methanol was irradiated (1 hr.). Evaporation of a sample (100 ml.) at room temperature under reduced pressure gave an oil shown by its n.m.r. spectrum to be a mixture of cis- (22%) and trans-3-(3-pyridyl)acraldehydes. The sample was dissolved in methanol (100 ml.), returned to the reactor and the solution further irradiated (1 hr.). Evaporation of a sample (100 ml.) gave an oil shown by its n.m.r. spectrum to contain 35% of the cis-acraldehyde together with the trans-isomer (228) and some polymeric material. Attempts to separate the cis- from the trans-isomer were unsuccessful. Heating the mixture of isomers to 40° resulted in complete conversion to the trans-form (228). No ester was formed during the irradiation as shown by the absence of an ester carbonyl absorption in the i.r. spectrum of the oily product.

$\delta(CDCl_3)$ 6.26 (q, cis-CHCHO) 6.58 (q, trans-CHCHO) 7.2-8 (3H, m) 8.5-8.8 (2H, m) 9.69 (d, trans-CHO) 9.9 p.p.m. (d, cis-CHO).

Photolysis of 3-(4-Pyridyl)acraldehyde (229)

(a) A solution of 3-(4-pyridyl)acraldehyde (229) (1g.) in methanol (800 ml.) was irradiated (1 hr.). Evaporation of a sample (100 ml.) at room temperature under reduced pressure gave an oil. The n.m.r. spectrum of this oil showed the presence of

the cis-isomer. Further irradiation (2 hr.) and evaporation of the solvent under reduced pressure gave polymeric material with small amounts of cis- and trans-acraldehyde (229).

$\delta(CDCl_3)$ 6.26 (q, cis-CHCHO) 6.8 (q, trans-CHCHO) 7.2-8.0 (3H, m) 8.5-8.8 (2H, m) 9.69 (d, trans-CHO) 9.9 p.p.m. (d, cis-CHO).

(b) A solution of 3-(4-pyridyl)acraldehyde (229) (1g.) in methanol-triethylamine (1:1, 800 ml.) was irradiated (1 hr.). Evaporation of the solvent under reduced pressure at room temperature gave a residue of polymeric material.

Photolysis of Cinnamaldehyde (213)

A solution of cinnamaldehyde (213) (2g.) in methanol-triethylamine (1:1, 800 ml.) was irradiated (3 hr.). Evaporation of the solvent under reduced pressure gave a polymeric residue from which no identifiable products could be obtained.

2-(2-Pyridyl)-4-hydroxyoxetane (230)

A solution of 3-(2-pyridyl)acraldehyde (222) (0.4g.) in 1% sulphuric acid (25 ml.) was irradiated (1 hr.). The solution was adjusted to pH 7.5 with solid sodium bicarbonate and evaporated to dryness under reduced pressure. The residue was extracted with absolute ethanol and the solvent evaporated to leave a tar which

solidified on trituration with acetone (0.19g., 39%) m.p. 145-146°. Attempts to purify the material (222) by crystallisation or chromatography proved unsuccessful.

$\delta(CDCl_3)$	2.8-3.4 (3H, m, $CHCH_2$) 5.2-5.6 (1H, m, CHOH) 5.8 (1H, sbr, exchange with D_2O, OH) 6.9-7.8 (3H, m) 8.4 p.p.m. (1H, sbr).
$\nu_{max.}$ (Nujol)	3200 $cm.^{-1}$
Mass spectrum m/e	151.0628 (M^+, $C_8H_9NO_2^+$ requires 151.0633)
	122.0608 ($C_7H_8NO^+$ requires 122.0606)
	106.0655 ($C_7H_8N^+$ requires 106.0657)
	93.0577 ($C_6H_7N^+$ requires 93.0578)
	79.0420 ($C_5H_5N^+$ requires 79.0422).

3-(2-Pyridyl)propionic Acid

A solution of methyl 3-(2-pyridyl)propionate (227) (0.4g.) in ethanol (10 ml.) was treated with aqueous sodium hydroxide solution (10%, 10 ml.) and the mixture boiled under reflux (1 hr.). The ethanol was evaporated under reduced pressure and the aqueous solution adjusted to pH 6.7 with dilute hydrochloric acid. The resulting solution was saturated with sodium chloride and extracted several times with chloroform. The dried (Na_2SO_4) extracts were evaporated to give a residue (0.21g., 41.6%). Sublimation at 120°/0.01 mm. gave 3-(2-pyridyl)propionic acid, m.p. 138-140° Lit.,[110] m.p. 141°.

2-(3-Acrolyl)-1-methyl-pyridinium Perchlorate (231)

A solution of 3-(2-pyridyl)acraldehyde (222) (2.0g.) in anhydrous acetone (25 ml.) was treated with methyl iodide (15 ml.) and the solution boiled under reflux overnight. The solution was decanted and the residue dissolved in ethanol and percolated through Amberlite IRA 400 (ClO_4^-). Evaporation of the eluate gave the pyridinium perchlorate (231) which crystallised from water as prisms (1.7g., 45.1%) m.p. 134-135°.

$\delta(D_2O)$ 4.5 (3H, s, NCH_3) 7.2 (1H, q, CHCHO) 8.0-8.8 (4H, m) 8.9 (1H, d) 9.9 p.p.m. (1H, d, CHO).

$\nu_{max.}$ (Nujol) 1680 $cm.^{-1}$

Photolysis of 2-(3-Acrolyl)-1-methyl-pyridinium Perchlorate (231)

A solution of 2-(3-acrolyl)-1-methyl-pyridinium perchlorate (231) (0.1g.) in methanol (25 ml.) was irradiated (1 hr.). Evaporation of the solvent under reduced pressure gave a tar. The n.m.r. spectrum contained no absorptions due to a methyl ester and showed that decomposition had occurred to products which were not identified.

Methyl 3-(1-Methyl-v-triazolyl-4)-propionate (233)

A solution of 3-(1-methyl-v-triazolyl-4)-acraldehyde (125) (0.5g.) in methanol (25 ml.) was irradiated (1 hr.). Evaporation of

the solvent gave an oil which solidified on cooling (0.6g., 97.3%). Crystallisation from ether gave methyl 3-(1-methyl-v-triazolyl-4)-propionate (233) as prisms (0.53g., 92%), m.p. 65-66°.

$C_7H_{11}N_3O_2$ requires: C, 49.6; H, 6.5; N, 24.8%

Found: C, 49.7; H, 6.53; N, 24.7%

$\delta(CDCl_3)$ 2.5-3.2 (4H, m, CH_2CH_2) 3.65 (3H, s, OCH_3) 4.02 (3H, s, NCH_3) 7.4 p.p.m. (1H, s).

$\nu_{max.}$ $(CHCl_3)$ 1719 cm.$^{-1}$

$\lambda_{max.}$ (EtOH) 217, 275 nm. [log ε 2.73, 3.03].

Mass spectrum $^m/_e$ 169.0851 (M^+ requires 169.0851), 141.0791 ($C_7H_{11}NO_2^+$ requires 141.0790), 138.0669 ($C_6H_8N_3O^+$ requires 138.0667), 126.0558 ($C_6H_8NO_2^+$ requires 126.0555), 110.0716 ($C_5H_8N_3^+$ requires 110.0718), 98.0604 ($C_5H_8NO^+$ requires 98.0606), 82.0658 ($C_5H_8N^+$ requires 82.0657).

Photolysis of 3-(1-Methyl-v-triazolyl-4)-acraldehyde (125) (Pyrex)

(a) A solution of 3-(1-methyl-v-triazolyl-4)-acraldehyde (125) (0.3g.) in methanol (75 ml.) was irradiated through pyrex (1 hr.). Evaporation of the solution under reduced pressure at room temperature gave a solid which was shown by its n.m.r. spectrum to contain trans-3-(1-methyl-v-triazolyl-4)-acraldehyde (125) (21%)

cis-3-(1-methyl-v-triazolyl-4)-acraldehyde (232) (6%) and methyl 3-(1-methyl-v-triazolyl-4)-propionate (233) (79%).

$\delta(CDCl_3)$ 2.5-3.2 (m, CH_2CH_2) 3.65 (s, OCH_3) 4.0 (s, ester-NCH_3) 4.15 (s, aldehyde-NCH_3) 6.27 (q, cis-CHCHO) 6.75 (q, trans-CHCHO) 7.0-8.0 (m) 9.6 (d, trans-CHO) 10.6 p.p.m. (d, cis-CHO).

(b) A solution of acraldehyde (125) (0.1g.) in anhydrous tetrahydrofuran (25 ml.) was irradiated (1 hr.). Evaporation of the solvent gave an oil shown by its n.m.r. spectrum and t.l.c. to be a complex mixture of products which were not isolated.

(c) A solution of acraldehyde (125) (0.1g.) in anhydrous tetrahydrofuran (25 ml.) was irradiated through pyrex (1 hr.). Evaporation of the solvent again gave a complex mixture of products which were not identified.

(d) A solution of acraldehyde (125) (0.1g.) in anhydrous benzene (25 ml.) was irradiated through pyrex (1 hr.). Evaporation of the solvent gave a mixture of products which were not separated.

3-Amino-1-methylpyridinium Bromide (127)

This was prepared from 3-acetamido-1-methylpyridinium bromide by the method of König, Coenan, Bahr, May and Bassl.[49]

Attempted Synthesis of cis-3-(1-Methyl-v-triazolyl-4)-acraldehyde (232)

A stirred solution of 3-amino-1-methylpyridinium bromide (127) (1.0g.) in water (10 ml.) at 0° was treated with an excess of saturated aqueous sodium nitrite solution. One drop of dilute hydrochloric acid was added and the solution stirred at 0° for 30 minutes. The solution was saturated with sodium chloride and extracted with chloroform. Evaporation of the dried (Na_2SO_4) extracts gave trans-3-(1-methyl-v-triazolyl-4)-acraldehyde (125) (0.15g., 22%).

3-(1-Methyl-v-triazolyl-4)-propionic Acid (234)

(a) A solution of 3-(1-methyl-v-triazolyl-4)-acraldehyde (125) (0.5g.) in water (25 ml.) was irradiated (1 hr.). The solution was evaporated to dryness under reduced pressure and the residue extracted with hot benzene. Evaporation of the benzene extracts gave unreacted starting material (0.326g., 65%). The residue from the benzene extraction was crystallised from ethanol-benzene to give 3-(1-methyl-v-triazolyl-4)-propionic acid (234) (0.162g., 28.7%), m.p. 150-152°.

$C_6H_9N_3O_2$ requires: C, 46.5; H, 5.8; N, 27.7%

Found: C, 46.6; H, 5.85; N, 27.7%

$\delta(D_2O)$ 2.6-3.1 (4H, m) 4.05 (3H, s, NCH_3) 7.8 p.p.m. (1H, s).

$\delta(D_2SO_4)$ 3.4-3.7 (4H, m) 6.3 (3H, s, NCH_3)
8.85 p.p.m. (1H, s).

$\nu_{max.}$ $(CHCl_3)$ 1718 $cm.^{-1}$

$\lambda_{max.}$ (EtOH) 217 nm. [log ε 2.57].

(b) A solution of 3-(1-methyl-v-triazolyl-4)-acraldehyde (125) (0.3g.) in 20% sulphuric acid was irradiated (1 hr.). The solution was adjusted to pH 6.5 with solid sodium bicarbonate and evaporated to dryness. The residue was extracted with ethanol and evaporated to give a mixture. Extraction of this mixture with chloroform and evaporation of the extracts gave unreacted starting material (0.2g., 67%). The other component of the mixture was identified as the zwitter ion (235) of 3-(1-methyl-v-triazolyl-4)-propionic acid (54 mg., 15.9%).

$\delta(D_2O)$ 2.45-3.2 (4H, m) 4.1 (3H, s, NCH_3)
7.85 p.p.m. (1H, s).

$\delta(D_2SO_4)$ 3.4-3.7 (4H, m) 6.3 (3H, s, NCH_3)
8.85 p.p.m. (1H, s).

(c) Similar irradiation and neutralisation to pH 7.5 followed by extraction also gave the zwitter ion (235) of 3-(1-methyl-v-triazolyl-4)-propionic acid.

4-(3-Acrolyl)-1,3-dimethyltriazolium Iodide

(a) A solution of 3-(1-methyl-v-triazolyl-4)-acraldehyde (125) (2.7g.) in anhydrous acetone (50 ml.) was treated with methyl iodide

(6 ml.). The resulting solution was boiled under reflux for 20 hours. Evaporation of the solvent followed by extraction of the residue with hot benzene left the quaternary salt as a yellow solid which crystallised from acetone as yellow prisms (0.79g., 14.3%), m.p. 151-153°.

$C_7H_{10}IN_3O$ requires: C, 30.0; H, 3.58; N, 15.05%

Found: C, 30.1; H, 3.44; N, 15.2%

$\delta(D_2O)$ 4.44 (6H, s, $(NCH_3)_2$) 7.03 (1H, q, C<u>H</u>CHO) 7.85 (1H, d, C<u>H</u>CHCHO) 9.0 (1H, s) 9.83 p.p.m. (1H, d, CHO).

$\nu_{max.}$ (Nujol) 1678 $cm.^{-1}$

$\lambda_{max.}$ (EtOH) 221, 250sh nm. [log ε 3.27, 3.02].

(b) A solution of acraldehyde (125) (0.5g.) and methyl iodide (2 ml.) in sulpholane (30 ml.) was allowed to stand at 35° for 2 days. Precipitation of the product using ethyl acetate-anhydrous ether gave the iodide as an oil which solidified in acetone (0.331g., 32.5%).

4-(3-<u>Acrolyl</u>)-1,3-<u>dimethyltriazolium Perchlorate</u> (236)

A solution of 4-(3-acrolyl)-1,3-dimethyltriazolium iodide (0.25g.) in ethanol was percolated through Amberlite IRA 400 (ClO_4^-). Evaporation of the eluate gave the perchlorate (236) (0.21g., 93.3%).

Photolysis of 4-(3-Acrolyl)-1,3-dimethyltriazolium Perchlorate (236)

A solution of 4-(3-acrolyl)-1,3-dimethyltriazolium perchlorate (236) (0.1g.) in methanol (25 ml.) was irradiated (1 hr.). Evaporation of the solvent under reduced pressure gave a mixture shown by absorptions in the n.m.r. spectrum to be unreacted starting material and decomposition products which were not identified. No ester was produced as shown by the absence of an absorption in the i.r. spectrum of the mixture in the region 1700-1800 $cm.^{-1}$.

Methyl 3-Deutero-2-methyl-3-(3-v-triazolo[1,5-a]pyridyl)-propionate (238)

A solution of trans-1,3-dideutero-2-methyl-3-(3-v-triazolo[1,5-a]pyridyl)acraldehyde (115) (0.626g.) in methanol (800 ml.) was irradiated (1.5 hr.). Evaporation of the solvent under reduced pressure and distillation of the residue gave methyl 3-deutero-2-methyl-3-(3-v-triazolo[1,5-a]pyridyl)propionate (238), b.p. 145-155°/1.5 mm. (0.4g., 46%).

$\delta(CDCl_3)$ 1.25 (3H, d, CH_3) 2.9-3.5 (2H, m, CHCH) 3.6 (3H, s, OCH_3) 6.85-7.5 (2H, m) 7.8 (1H, d) 8.8 p.p.m. (1H, d).

Mass spectrum $^m/_e$ 220 (M^+), 192, 177, 161, 149, 133, 118, 106, 78.

Attempted Synthesis of 3-Amino-2,4,6-trideutero-1-methylpyridinium Bromide (239)

3-Amino-1-methylpyridinium bromide (127) (20 mg.) was dissolved in concentrated deuterosulphuric acid (0.1 ml.). The n.m.r. spectrum indicated exchange (D for H) had occurred at position 2. No further change was observed after heating (150°, 20 hr.).

$\delta(D_2SO_4)$ 4.6 (3H, s, NCH_3) 8.3 (1H, m, H5)
8.8 p.p.m. (2H, m, H4 + H6).

Methyl 2,3-Dideutero-3-(1-methyl-v-triazolyl-4)-propionate (240)

A solution of 3-(1-methyl-v-triazolyl-4)-acraldehyde (125) (0.2g.) in methanol-d_1 (25 ml.) was irradiated (1.5 hr.). Evaporation of the solvent gave methyl 2,3-dideutero-3-(1-methyl-v-triazolyl-4)-propionate (240) (0.24g., 96%).

$\delta(CDCl_3)$ 2.5-3.2 (2H, m, CHDCHD) 3.65 (3H, s, OCH_3)
4.02 (3H, s, NCH_3) 7.4 p.p.m. (1H, s).

Mass spectrum $^m/_e$ 171.0980 (M^+, $C_7H_9D_2N_3O_2$ requires 171.0977)
140, 128, 112, 100, 84, 69.

Methyl 2,3-Dideutero-3-(2-pyridyl)propionate

A solution of 3-(2-pyridyl)acraldehyde (222) (0.35g.) in methanol-d_1 (25 ml.) was irradiated (1 hr.). The solvent was evaporated under reduced pressure and the product purified by

p.l.c. using chloroform (3 elutions) to give methyl 2,3-dideutero-3-(2-pyridyl)propionate (43 mg., 8%).

$\delta(CDCl_3)$ 2.6-3.3 (2H, m, CHDCHD) 3.4 (3H, s, OCH_3) 6.85-7.7 (3H, m) 8.47 p.p.m. (1H, d).

Mass spectrum $^m/_e$ 167 (M^+), 136, 108, 93, 78.

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