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INSTITUTE OF TECHNOLOGY · DEPARTMENT OF CHEMISTRY
DIVISION OF ORGANIC CHEMISTRY · MINNEAPOLIS, MINNESOTA 55455

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SOME REACTIONS OF ALLOXAN WITH AMINES

A THESIS PRESENTED

FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

IN THE

UNIVERSITY OF ADELAIDE

BY

J. A. EDGAR, B.SC. (Hons.)

DEPARTMENT OF ORGANIC CHEMISTRY

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SUMMARY

The reactions of amines, (in particular o-dialkylaminoanilines and p-substituted anilines), with alloxan have been examined under a variety of conditions and the formation of unusual products is rationalised in terms of the electrophilic and oxidative properties of alloxan as well as its ability to ring-open.

Condensation of alloxan and o-dimethylaminoaniline yields 1,2,3,4-tetrahydroquinoxaline-2-spiro-5-(hexahydro-2,4,6-trioxopyrimidine) (41) formed by participation of one of the N-methyl groups of the o-dimethylamino substituent in a unique ring-closure[37]. Similar structures are assigned to compounds obtained from 6-methyl, 7-methyl, and 6,7-dimethyl-o-dimethylaminoanilines[36]. These compound were regarded as anils by Rudy and Cramer[36]. The closely related oxidation product of the spiran (41), previously[56] considered to be a carbinolamine (42), is now shown to be a dihydroquinoxalinium barbiturate (46; R=H) and similar betaine structures are also assigned to the 6,7-dimethyl[36] and 6,7-dichloro[37,58] analogues of the barbiturate (46; R=H). o-Diethylaminoaniline, unlike the o-dimethylaminoanilines, forms a benzimidazolium barbiturate (51; R=H) and a similar structure is proposed for the product obtained from 4,5-dimethyl-

2-dipropylaminoaniline[36].

Under acid conditions alloxan and p-substituted anilines gave dioxindole-carboxyureides (72), although these were previously[67] regarded as phenylaminodialuric acids (70), and alkaline hydrolysis of the dioxindole-carboxyureides (72) gave oxindole-oxazolidine-2,4-diones (76) previously[67] formulated as tartronimides (71). Interaction of p-substituted anilines and alloxan monohydrate in aqueous ethanol gave phenyluramils (83) and aniline salts of alloxanic acid and phenylaminodialuric acids (114), 5,5-diphenylamino barbituric acids (105) and alloxan-anils (116) have also been obtained.

With piperidine and benzimidazoles in acetic acid alloxan gave highly coloured, crystalline products which are presumably anhydro salts of 5-hydroxyhydantoin and 5-aminodialuric acids and with β-naphthylamine in acetic acid 5-(1-dibenzo-a,h-phenazinium) barbiturate (78) was obtained.

Several dihydrobenzimidazoles have been prepared and their n.m.r. and light absorption spectra recorded.

STATEMENT

The work described in this thesis incorporates no material previously submitted for a degree in any university, and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.

(John A. Edgar)

ACKNOWLEDGEMENTS

The author is deeply indebted to Professor J.W. Clark-Lewis for his guidance and encouragement, and for many helpful discussions.

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The author particularly desires to thank his wife for her assistance during preparation of this thesis.

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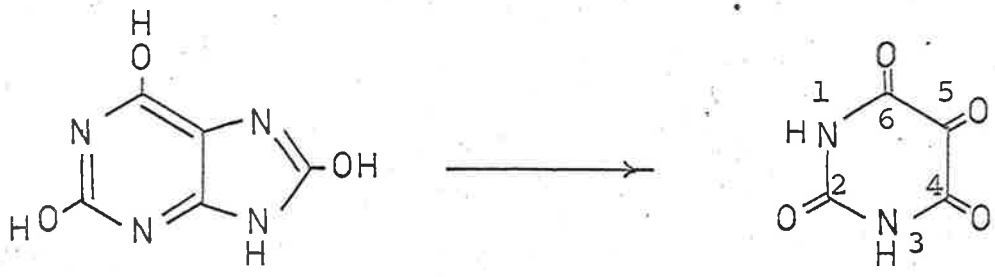
INTRODUCTION

Alloxan (1) was the first pyrimidine derivative isolated when it was obtained by Brugnatelli in 1818 from the oxidation of uric acid[1]. The original process was later modified by Wöhler and Liebig[2] and remains the basis of one



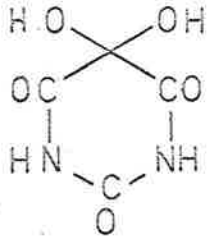
(1)

modern method of preparation[3,4]; others include oxidation of barbituric[5] acid and its 5-benzylidene derivative[6] with chromium trioxide.

The diabetogenic properties of alloxan were first described by Dunn et al.[7] in 1943 and since that time considerable interest has been shown in its effect on biological systems. The toxic effect of alloxan is believed to be due to the in activation of certain essential sulphydryl enzymes in

the β -cells of the islets of Langerhans in the pancreas[8]. Glutathione and cysteine were found to inactivate alloxan[9] by reducing it to dialuric acid[8] (8), a non-diabetogenic substance, and the selective sensitivity of the β -cells is believed to depend on their low protective glutathione content, due to a high consumption for the synthesis of insulin[8].

By comparison with the interest in the biological and biochemical properties of alloxan comparitively little recent work has been done on its complex chemical behaviour. Alloxan crystallizes from water as a tetrahydrate and can be readily dried to a stable, colourless monohydrate (2)[10]. The yellow



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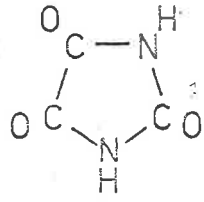
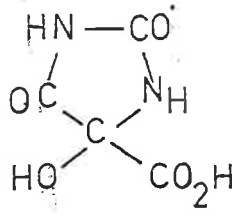


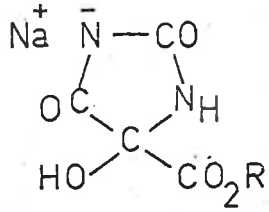
(3)

anhydrous material (1) is obtained by subliming the monohydrate at 150° in a high vacuum[11]. Oxidation with nitric acid results in the liberation of carbon dioxide and the

formation of parabanic acid (3)[12]; mild alkaline hydrolysis causes ring-contraction to salts of alloxanic acid (4)[12,13,14], and sodium alkoxides in alcohols yield the sodium salts of alloxanic acid esters (5)[15]. The base-catalysed ring-contraction of alloxan to alloxanic acid has been examined

(4)





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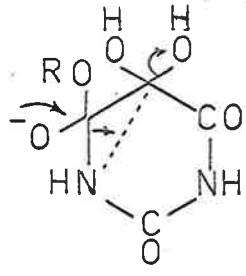
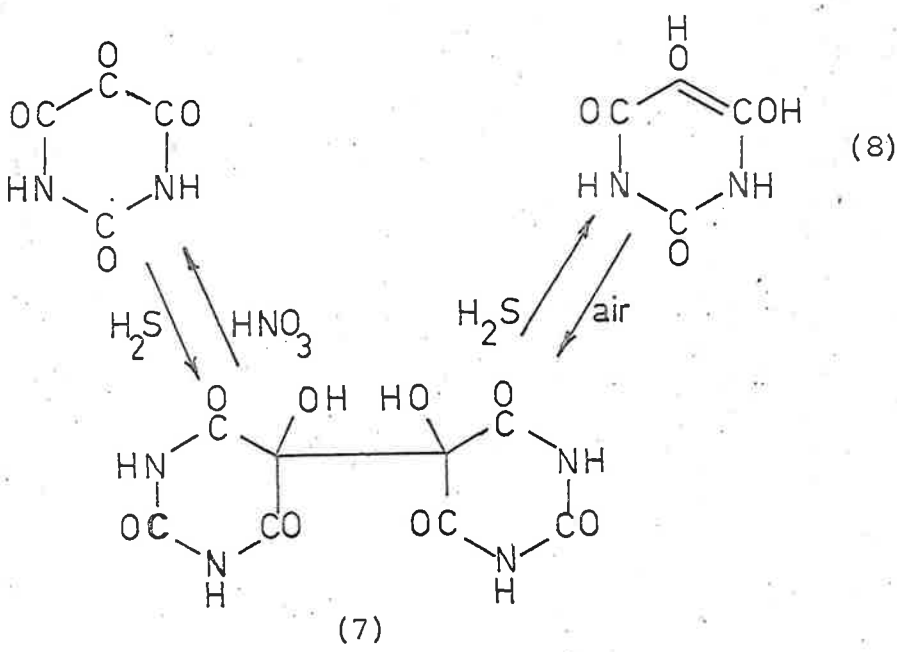


(6)

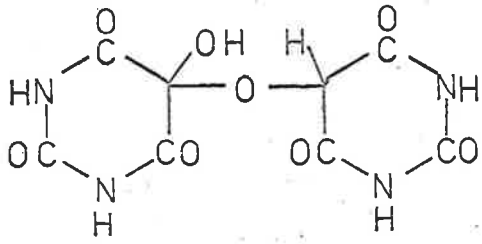
with C^{14} labelled alloxan[16] and the mechanism involves nucleophilic attack at C-4 followed by migration of nitrogen from C-4 to C-5 (6, arrows) and not the normal C ⟶ C migration found in rearrangements of the benzilic acid type. Partial reduction of alloxan with hydrogen sulphide gives alloxantin (7)[4] which on further reduction with more hydrogen sulphide [17] or with sodium amalgam[18] yields dialuric

acid (8). The process is readily reversed and aerial oxidation of dialuric acid gives alloxantin[19] which may be further oxidized to alloxan by continued aeration[20] or with



(7) (8)

nitric acid[3]. Alloxantin may also be prepared by mixing equimolar aqueous solutions of alloxan and dialuric acid (8)[17] when the less soluble alloxantin crystallizes, and it has been reported that aqueous solutions of alloxan gradually decompose especially on heating to alloxantin, parabanic acid and carbon dioxide[21]. Despite a considerable amount of work[22], the structure of alloxantin remained uncertain for some time. The two most likely structures were the pinacol form (7) and the hemiacetal form (9) and it is only comparatively recently that the pinacol structure has been accepted[23]. The earlier



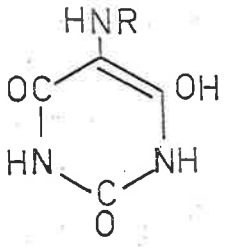
(9)

view that aqueous solutions of alloxantin were largely dissociated into the component alloxan and dialuric acid[24] is not supported by a recent polarographic study[20] which suggests that, at least in the pH range 3.5 to 5.6, little or no dissociation occurs. Alloxantin (7) forms an acetyl[25] and a benzoyl[25] derivative and many alkylated homologues are known[26]. It is decomposed by sulphuric acid at 120° into barbituric acid and parabanic acid (3)[27], and with ammonium salts[28] and aliphatic primary amines[29] it gives uramil (10; R=H) and its 7-alkyl derivatives (10; R=alkyl). With ammonia it forms murexide (28; p.12).

The products which have been obtained from reactions of alloxan with organic bases are remarkably diverse. The original structures assigned to a number of these products have

been questioned and there are others reported in the literature which lack unequivocal structural evidence. As a consequence an over-all picture of the reactions of alloxan with bases has not yet emerged.

Alloxan and diprimary and primary-secondary o-phenylenediamines under acid conditions form alloxazines (11) and isoalloxazines (12) respectively[31]. In aqueous-ethanol 1,2-dihydro-2-oxoquinoxaline-3-carboxyureides (13) are formed and these are readily converted to the isomeric spiro-hydantoins (14)[32]. Analogous 1,4,5- and 1,4,6-triazanaphthalenes (15 and 16) and spiro-hydantoins are obtained from 2,3- and 3,4-diaminopyridine respectively[33]. Hinsberg[34] had originally examined the reaction of alloxan with o-aminoanilines in aqueous-ethanol and he formulated the yellow products as quinoxaline-



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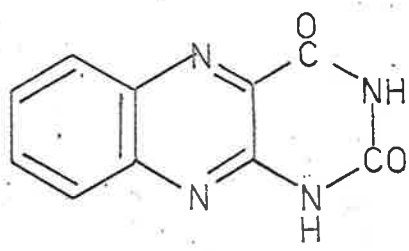

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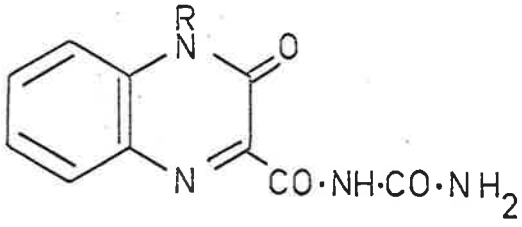

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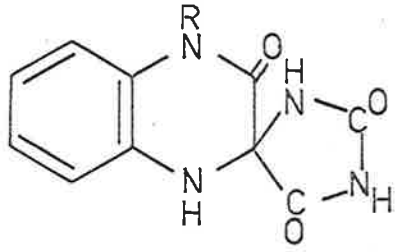

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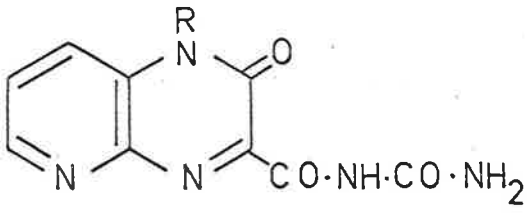

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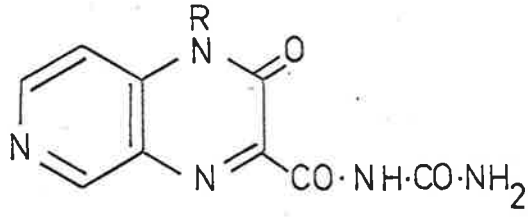
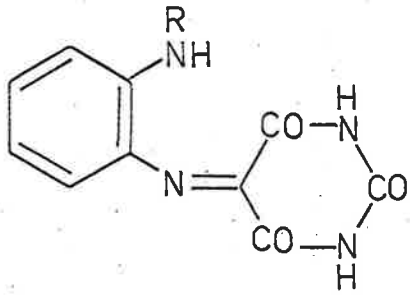


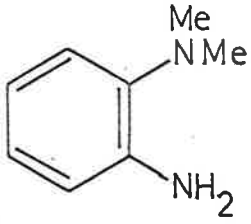
(16)

carboxyureides (13), but later workers[35] generally favoured alloxan-anil structures (17) for these compounds. Rudy and Cramer [36] attempted to differentiate between the alternative structures (13 and 17) by comparing the products formed from o-aminoaniline or o-methylaminoaniline with that obtained from o-dimethylaminoaniline (18) for which an anil structure alone seemed possible. They rejected Hinsberg's quinoxaline-carboxyureide structure (13), and based their conclusions on the supposed authentic anil obtained from o-dimethylaminoaniline



(17)

(18). King and Clark-Lewis[37] later showed that the supposed anil obtained by Rudy and Cramer from o-dimethylaminoaniline



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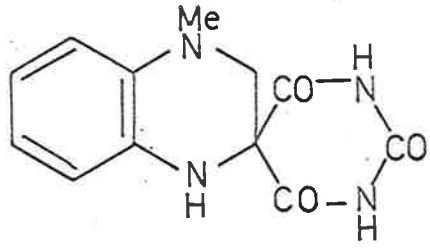
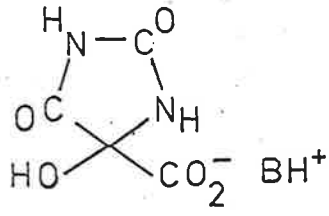


(19)

and alloxan was the spiran (19), and they further showed, by

methylation studies and by synthesis of degradation products, that Hinsberg's original structure was correct.

With alicyclic secondary amines (piperidine, morpholine, etc.) in aqueous-ethanol alloxan monohydrate gives amine salts of alloxanic acid (20)[38] and with anhydrous alloxan in anhydrous ethanol salts (21) of ethyl alloxanate are obtained[38]. The former had originally[15] been formulated as amide hydrates



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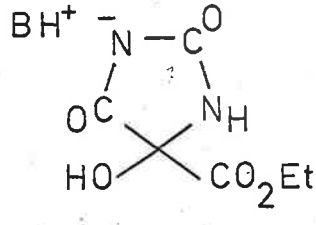
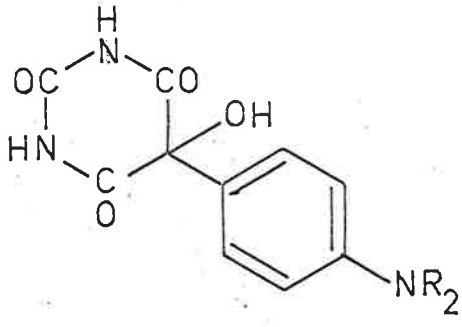


(21)

of alloxanic acid and the latter had been considered to be alcoholates of the amides[38].

Alloxan and aromatic secondary and tertiary amines yield 5-p-alkylamino- and 5-p-dialkylamino-aryldialuric acids (22)[39]. Aromatic primary amines usually yield 5-p-aminoaryl-

dialuric acids (22; R=H)[39] although intensely coloured all-oxan-anils (23) have been obtained in some cases where the para position is substituted[40,41]. Alkaline hydrolysis of



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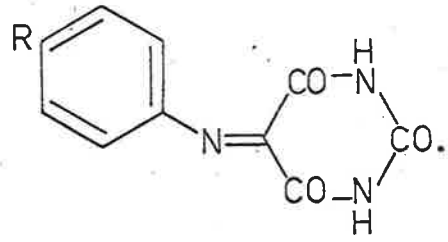
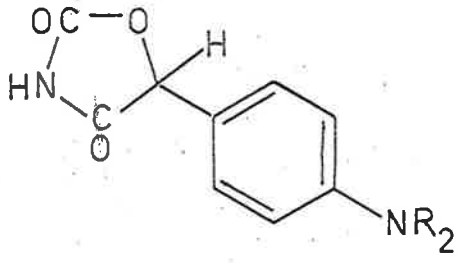


(23)

the dialuric acids (22) gives 2,4-oxazolidinediones (24)[42] although these were originally formulated as tartronimides (25)[39]. Phenols and aryl-ethers react in a similar manner to aromatic amines and form 5-aryldialuric acids[43] which are also converted into the corresponding oxazolidinediones (24) by alkaline hydrolysis. Under suitable conditions alloxan can be induced to react with un-activated aromatic compounds and with benzene in sulphuric acid it yields 5,5-diphenylbarbituric acid (26)[44], a compound which is difficult to obtain by other means[45]. With acetophenone and certain of its homologues



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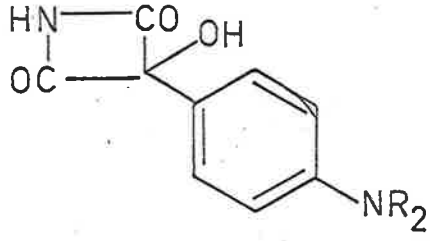

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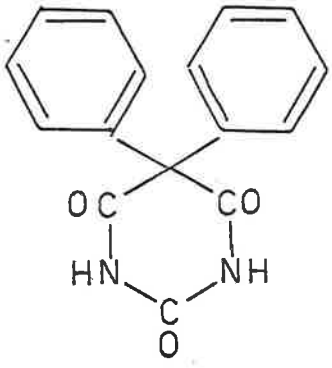
alloxan forms phenacyldialuric acids (e.g. 27)[46].



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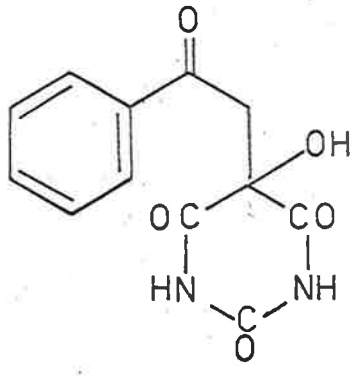
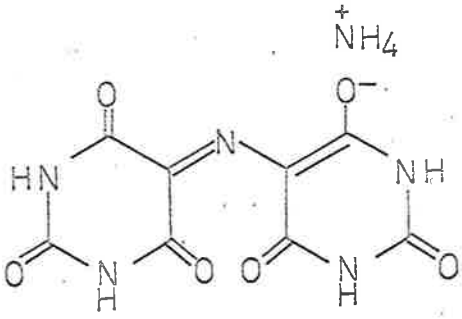


(27)

The reaction of alloxan with alcoholic-ammonia[47] yields an intensely coloured material, murexide (28), which is the

ammonium salt of an as yet unisolated acid, purpuric acid (29)[30,48,49]. Murexide can also be obtained by the direct condensation of alloxan with uramil (10; R=H) and by a variety of other procedures apparently involving the formation



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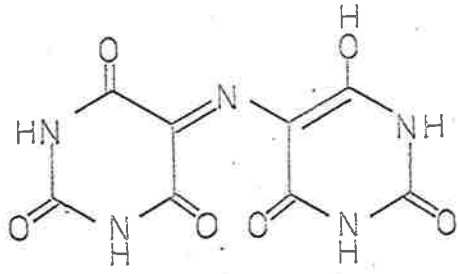
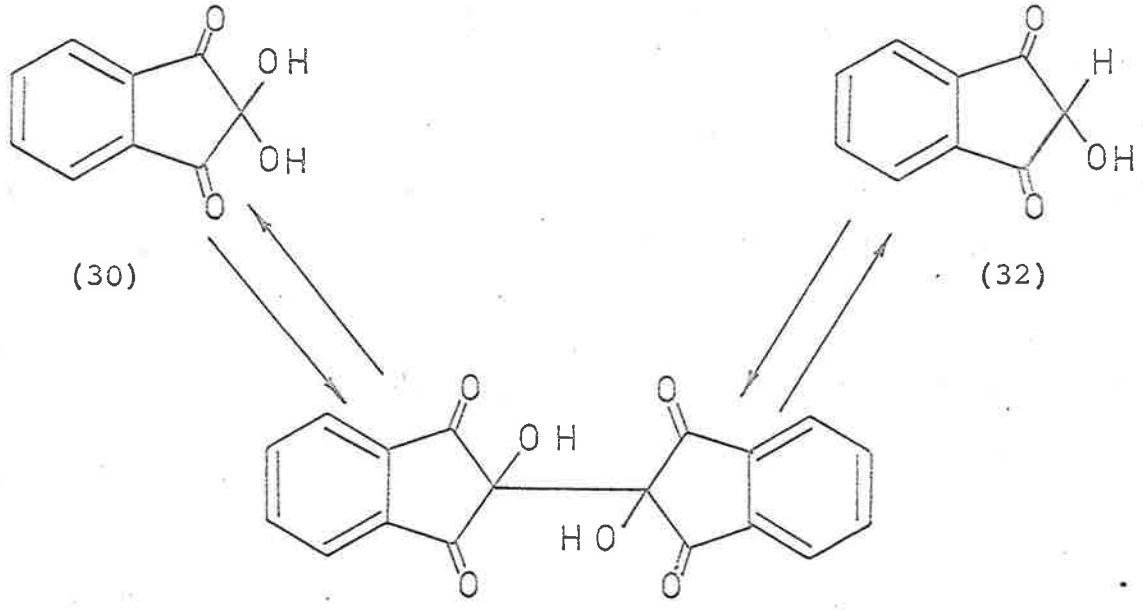


(29)

of alloxan, uramil and ammonia[49].

Alloxan, like ninhydrin (30)[50], degrades α-amino-acids to carbon dioxide and aldehydes containing one less carbon atom[50-52]. Murexide (28) and "Ruhemann's purple" are by-products in the respective degradations and the formation of these highly coloured materials has been used extensively in the detection and identification of aminoacids[53]. The similarity in the systems alloxan-alloxantin-dialuric acid and ninhydrin (30), hydrindantin (31), 2-hydroxyindandione (32)

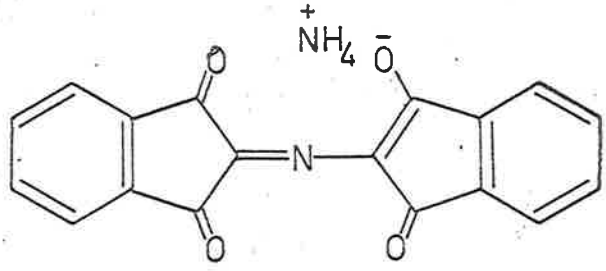
was first noted by Ruhemann[52] who was able to show that "Ruhemann's purple" (33) was an analogue of murexide. The



(30) (32)

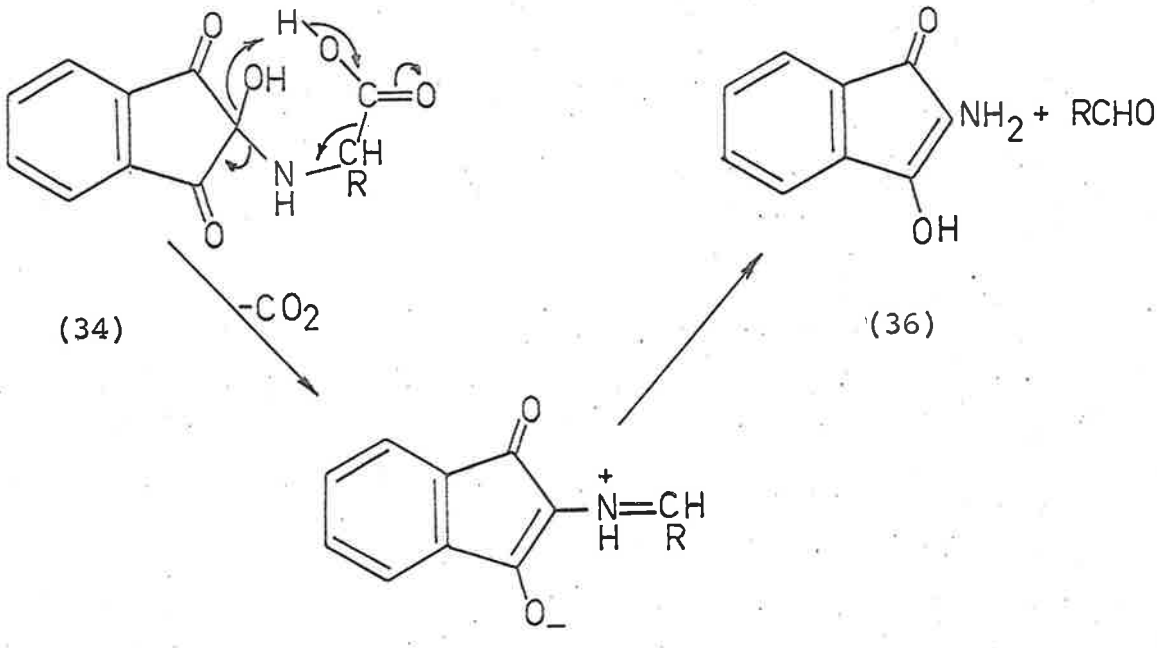
(31)

mechanism by which aminoacids are degraded is still a matter of controversy and a number of theories have been put forward[50]. This degradation is in fact a special case of the more general Strecker reaction[51,54] which refers to all degradations of α-amino acids by carbonyl compounds to give aldehydes and ketones containing one less carbon atom. McCaldin[50] has reviewed the evidence and the various mechanisms proposed for the degradation of aminoacids by ninhydrin. He suggested that degradation proceeds by a "concerted" decomposition of



(32)

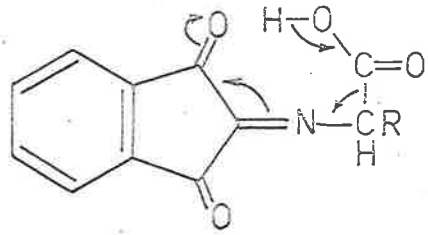
the intermediate 2-hydroxyindandione (34, arrows) to the



(34) (35) (36)

betaine (35) which is subsequently hydrolysed to the uramil

analogue (36) and a carbonyl compound. The intermediate (36) is then either hydrolysed further to 2-hydroxyindandione (32) and ammonia or condenses with more ninhydrin to give "Ruhemann's purple" (33). Although this mechanism explains all the accumulated facts of the ninhydrin reaction the electronic shifts indicated in formula 34 do not lead to structure 35. This transformation (34 to 35) is best portrayed as proceeding via the anil (37) and then to the betaine (35) by a concerted process involving decarboxylation. The analogous

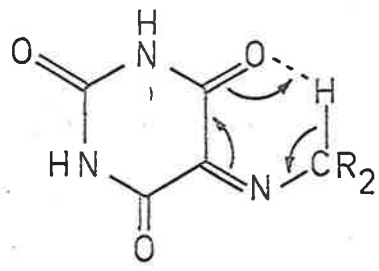


(37)

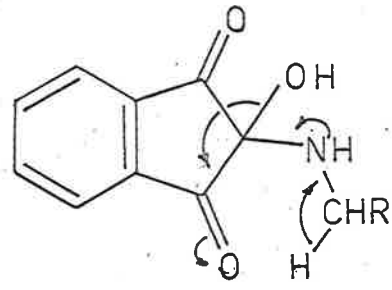
reaction with alloxan presumably proceeds by a similar mechanism.

The carboxyl group of the α-aminoacids is not essential for degradation as many aliphatic primary amines have been

degraded to carbonyl compounds and murexide[55]. The degradation of primary amines may be considered as a special case of the reaction with aminoacids, and in this case tautomerism of the anil (38) to an intermediate of type (35) is aided by the six-membered transition state shown. McCaldin[50] suggests



(38)



(39)

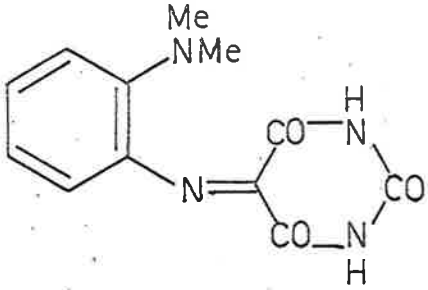
that the reaction proceeds by the electronic changes shown in formula 39.

Very little work has been done on the reactions of alloxan with p-substituted anilines and, in view of the unusual behaviour of alloxan with o-dialkylaminoanilines [37] (p.8) the reactions with aromatic amines were investigated in more detail. The results obtained are discussed in the following section.

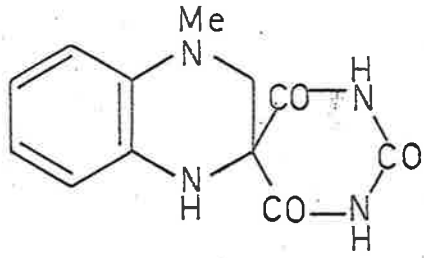
DISCUSSION

(In the discussion of nuclear magnetic resonance spectra the chemical shifts will be given as τ values).

The compound originally obtained by Rudy and Cramer[36] by condensation of o-aminodimethylaniline and alloxan in aqueous ethanol, and assigned an anil structure (40), was later shown to be the spiran (41) [37].

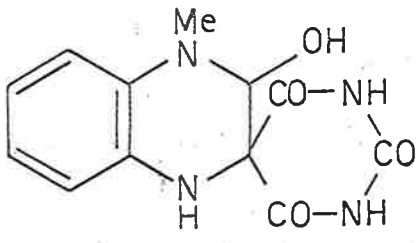


(40)

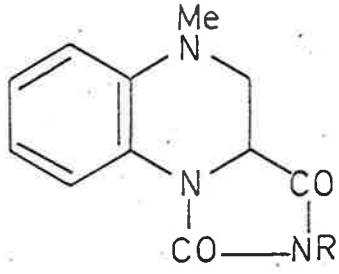


(41)

The spiran is formed by an apparently unique ring-closure involving participation of one of the N-methyl groups, and is accompanied by a second product which has a molecular formula differing by one oxygen atom from that of the spiran. The second product was formulated as a carbinolamine (42) by King and Clark-Lewis[56].



(42)



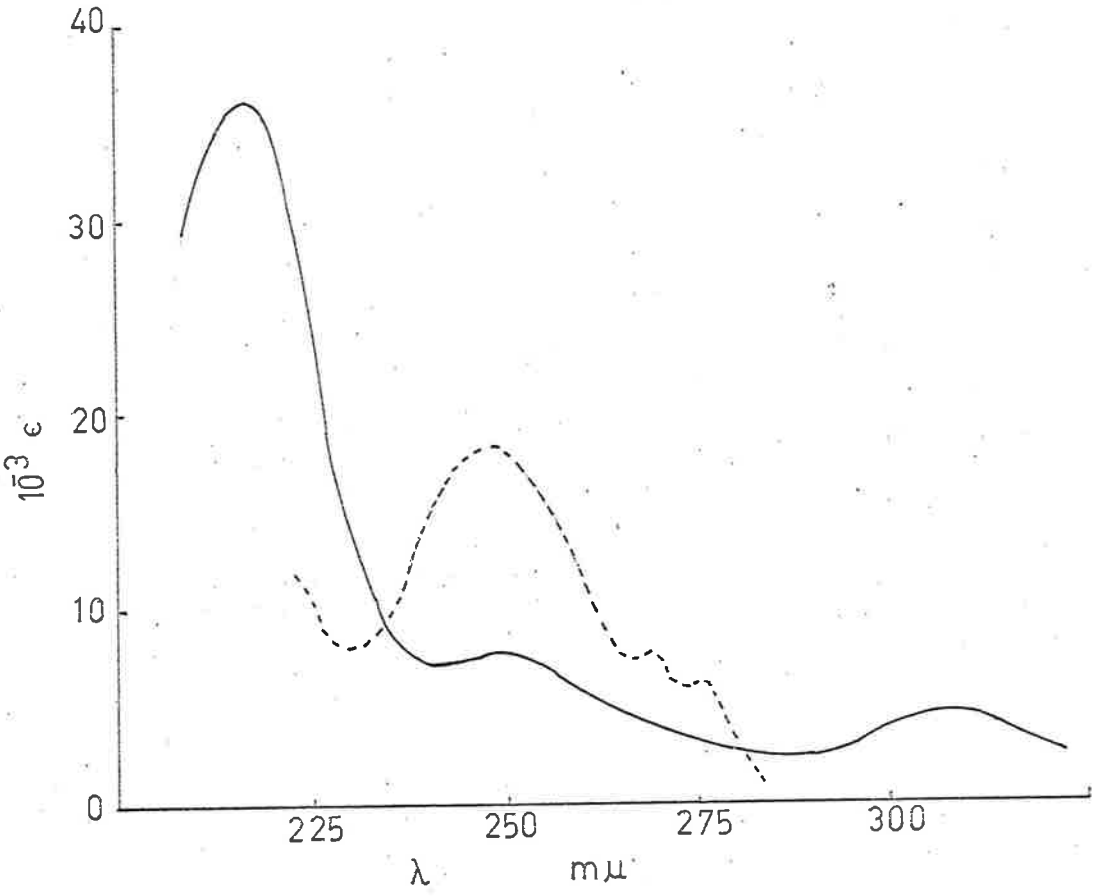
(43)

The ultraviolet light absorption (fig. 1) of the "carbinolamine" however differs considerably from that of the closely related spiran (fig. 1) and it was this difference and the apparent lack of carbinolamine properties which prompted a re-examination of the carbinolamine structure.

Since mild oxidation[56] readily converts the spiran to the "carbinolamine" the two compounds are presumably in close structural relationship. In view of this a thorough investigation of the spiran was considered necessary because an unambiguous synthesis had not been achieved[57] although evidence for its structure seemed conclusive.

The evidence which led to the proposal of the spiran structure[37] includes : (a) degradation of the spiran with 30% aqueous sodium hydroxide to the hydantoin (43 ; R=H),

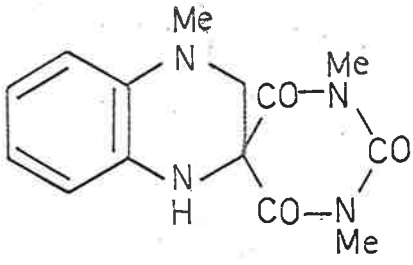
Fig.1



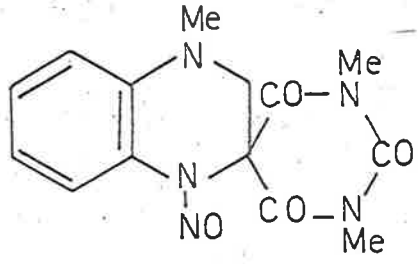
——— 1,2,3,4-Tetrahydro-4-methylquinoxaline-2-spiro-5'-(hexahydro-2',4',6'-trioxophrimidine) (41) in 95% ethanol.

------- 1,2-Dihydro-4-methylquinoxalinium-2-spiro-5'-barbiturate (46; R=H) in 95% ethanol.

the structure of which was confirmed by synthesis; (b) the stability of the spiran to acid, which indicates that the pyrimidine ring is intact; (c) N-methyl determination (Herzig-Meyer) showed the presence of only one N-methyl group, and (d) methylation of the spiran gave a dimethyl derivative (44) which contained three N-methyl groups and one active hydrogen (Zerewitinoff). The dimethylspiran



(44)



(45)

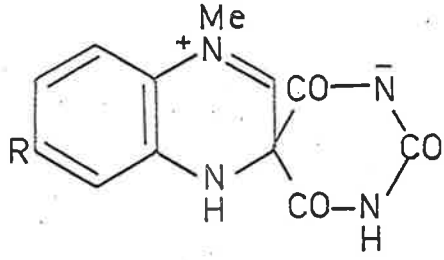
(44) formed an acetyl derivative with acetic anhydride.

The present work provides further evidence confirming the spiran structure. The nuclear magnetic resonance spectrum of the dimethylspiran (44) in deuterochloroform showed four aromatic protons which absorbed as a single peak at 3.23, the N(4)Me group appeared as a three-proton peak at 7.11, and a six-proton peak at 6.68 was assigned to the N(1')Me and N(3')Me groups. The methylene group

absorbed as a single two-proton peak at 6.75. The position of the carbonyl absorption in the infrared spectrum of the dimethylspiran confirmed that the pyrimidine ring was intact and an N-H stretching vibration present in this spectrum was found to be absent from that of the N-nitroso derivative (45). The active hydrogen in the dimethylspiran was positively located on N(1) by mild alkaline hydrolysis when the hydantoin (43 ; R=Me) was obtained and found to be identical with that prepared by methylation of the hydantoin (43 ; R=H) with diazomethane[37] . Nuclear magnetic resonance confirmed the structure of the methylhydantoin (43 ; R=Me). The spectrum showed two three-proton peaks at 7.05 and 6.98 which have been assigned to the N-methyl groups, and three quartets centred at 6.98, 6.37 and 5.78 due to the $-CH_2-$ CH= system.

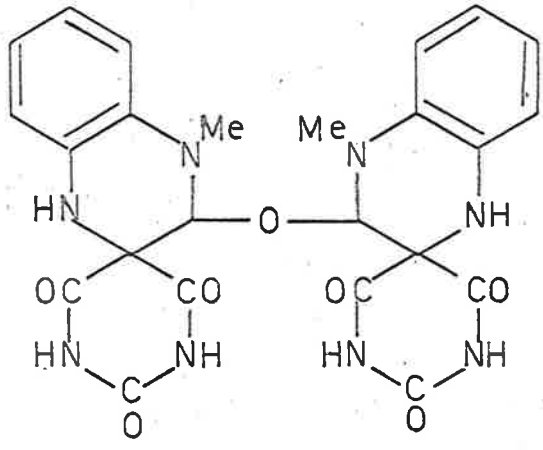
The spiran structure is firmly established by the above-mentioned evidence and the 6-methyl,7-methyl, and 6,7 -dimethyl compounds obtained by Rudy and Cramer[36] presumably have analogous structures.

The second product previously[56] considered to be a carbinolamine (42) has now been shown to exist as the betaine (46 ; R=H) hydrate. This structure overcomes the problems associated with the carbinolamine formulation and is supported by new experimental evidence. The change in ultraviolet light absorption in going from the spiran to the



(46)

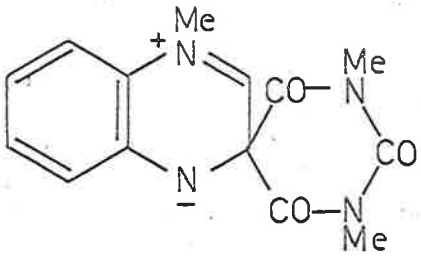
betaine is now understandable. The ultraviolet spectrum of the betaine resembles that of benzimidazolium salts (e.g. 50) which possess a similar chromophore. The betaine (46; R=H) crystallized from water as a dihydrate ($C_{12}H_{10}N_4O_3.2H_2O$) and could be dried to a hemihydrate ($C_{12}H_{10}N_4O_3.\frac{1}{2}H_2O$ or $C_{24}H_{22}N_8O_7$).



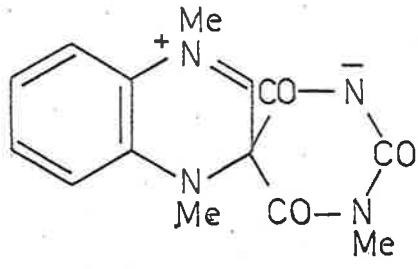
(47)

The retention of one molecule of water for every two molecules of betaine was one factor which had previously hindered elucidation of the structure. On the carbinolamine structure two molecules must lose three molecules of water to give the dimeric anhydride (47). The betaine structure offers a more reasonable explanation.

Although oxidation of the spiran to the betaine had been observed, attempted catalytic hydrogenation of the betaine to the spiran had failed[56] . It has now been found that the betaine is reduced quantitatively to the spiran by sodium borohydride. This reduction confirms the belief that the oxidation product and the spiran are very closely related and also suggests that no rearrangement of the structural skeleton has occurred. The 1',3'-dimethyl derivative (48) of the betaine was obtained by methylation of the betaine

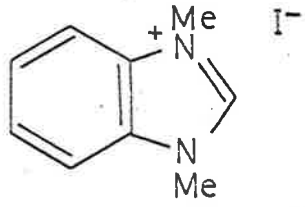


(48)



(49)

with diazomethane and found to be identical with the product previously[56] obtained by oxidation of the dimethylspiran (44). Reduction of the 1',3'-dimethylbetaine (48) with sodium borohydride gave the dimethylspiran (44) once more. These interconversions establish that the structure of the dimethylbetaine (48) is as shown and not the isomeric compound (49). The nuclear magnetic resonance spectrum of the dimethylbetaine (48) showed the 3-proton at very low field (0.37) close to the absorption of the 2-proton (0.30) in1,3-dimethylbenzimidazolium iodide (50).

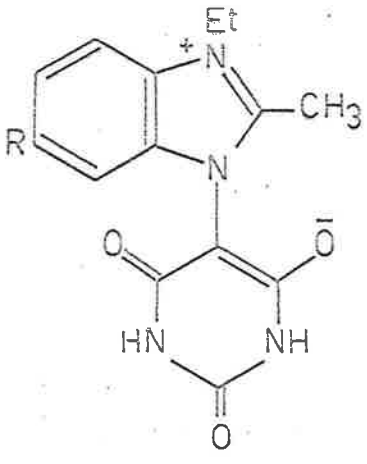


(50)

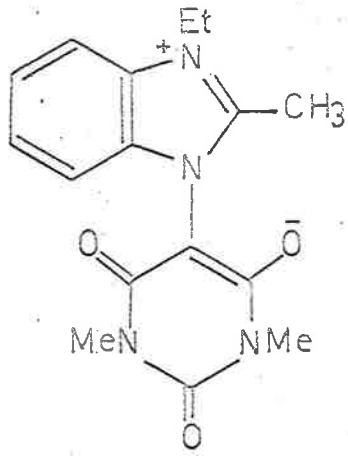
Rudy and Cramer [36] obtained the 6,7-dimethyl analogue of the betaine (46) and the 6,7-dichlorocompound is also known[56, 58]. The 7-bromo derivative (46; R=Br) has been prepared and dehalogenation of the bromo and dichloro com-

pounds with W-7 Raney nickel confirmed their relationship to the parent betaine. The 7-Bromo compound (46; R=Br) was prepared from 2-amino-4-bromodimethylaniline and alloxan in order to confirm its structure by x-ray diffraction studies but it has not been used for this purpose as it was found to be less suitable than an apparently analogous but structurally different compound (51; R=Br) discussed below. The 6,7-dichloro betaine was reduced with sodium borohydride to the previously unknown dichloro analogue of the spiran (41). Its structure was confirmed by elemental analysis and ultraviolet light absorption.

The interaction of o-aminodiethylaniline with alloxan was investigated[59] in order to determine the scope of these unusual cyclisations and a compound was obtained which was



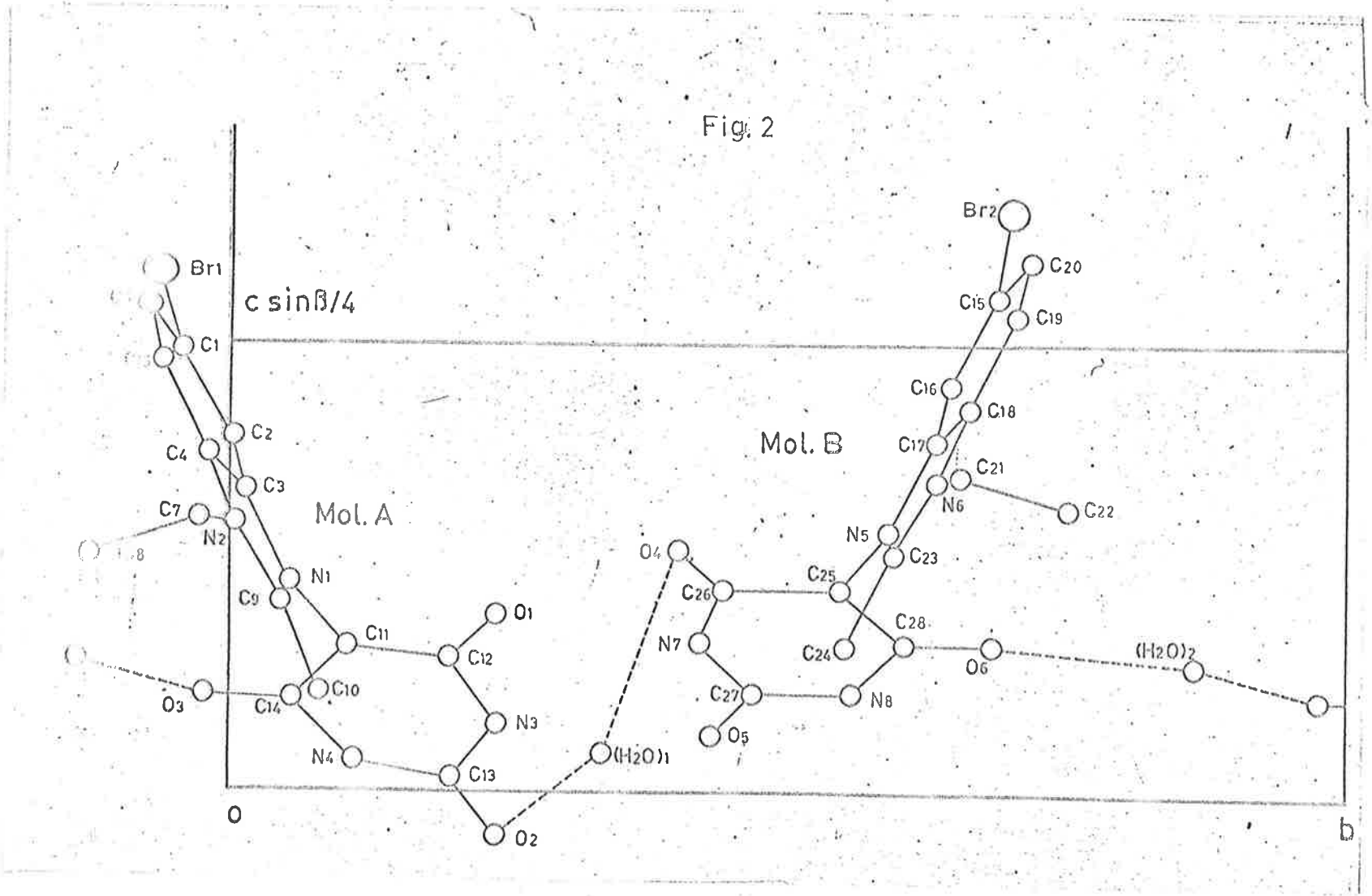
(51)



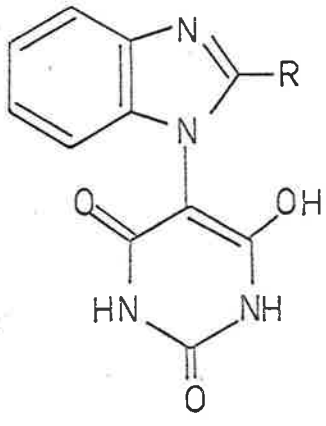
(52)

apparently an analogue of the betaine (46 ; R=H); no material analogous to the spiran (41) was isolated. The product has now been shown to be a benzimidazolium barbiturate (51 ; R=H). The 6'-bromo derivative (51 ; R=Br) of the benzimidazolium barbiturate was prepared from 4-bromo-2-aminodiethylaniline and alloxan and its structure was determined by x-ray diffraction[60] (fig. 2). Debromination to the parent compound (51 ; R=H) was achieved with W-7 Raney nickel, so that its structure was also defined by the x-ray work. The nuclear magnetic resonance spectrum of the benzimidazolium barbiturate (51 ; R=H) in trifluoroacetic acid showed the triplet and quartet of the N-ethyl group at 8.29 and 5.44 and the 2'-methyl group appeared as a singlet at 7.12. The 1,3-dimethyl derivative (52), obtained by methylation of the barbiturate (51 ; R=H) with diazomethane, showed n.m.r. absorption in deuterochloroform at 8.45 and 5.67 (Triplet and quarter due to the N-ethyl group); 7.29 (singlet due to the 2'-methyl group); and 6.64 a six proton peak due to the 1,3-dimethyl groups). The ultraviolet light absorption of the benzimidazolium barbiturate (fig. 3) remained unchanged in water and in sulphuric acid concentrations up to 50%. The spectrum corresponded to the superposition of the absorption of the barbiturate anion on that of simple benzimidazolium salts[61] .

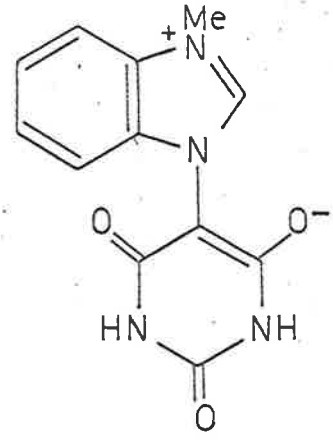
Fig. 2


Br1
c sinβ/4
C1
C2
C4
C3
C7
N2
Mol. A
N1
C9
C11
O1
C12
C10
O3
C14
N3
N4
C13
O2
O
(H2O)1
O4
C26
N7
C27
O5
C25
C24
C28
N8
O6
(H2O)2
Mol. B
Br2
C20
C15
C19
C16
C18
C17
C21
N6
C22
N5
C23
b

The physical properties of the betaine (46 ; R=H) and the benzimidazolium barbiturate (51 ; R=H) are extremely similar. They exhibit high melting points and crystallise from water in which they are sparingly soluble. They are less soluble in methanol and ethanol and insoluble in aprotic solvents. The most notable similarity is their ultraviolet absorption spectra (fig. 3) which show an intense peak at about 248 mμ and two subsidiary maxima near 270 and 275 mμ . Benzimidazole barbituric acids (53 ; R=H or Me) prepared for comparison (see below) possessed similar absorption except that the maxima at 248 mμ were less intense.



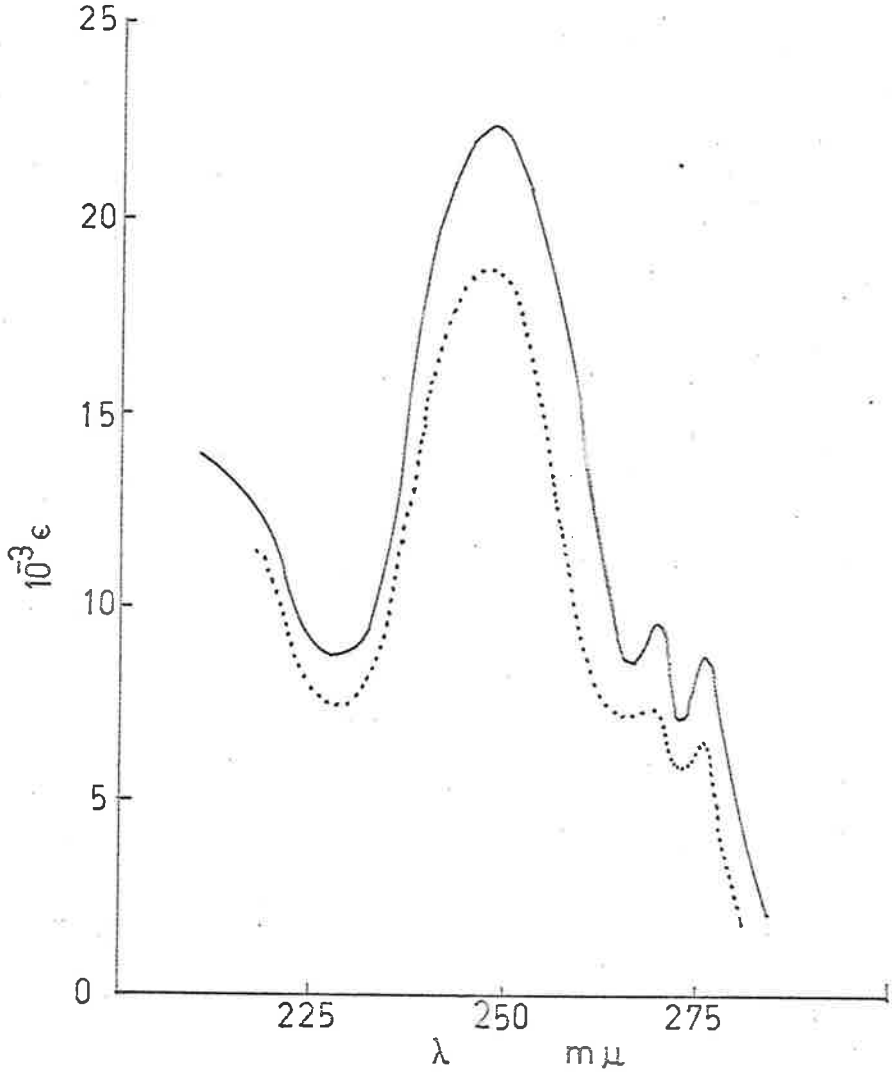
(53)



(54)

Introduction of bromine into the 7-position of the betaine (46 ; R=Br) and into the 6'-position of the benzimidazolium

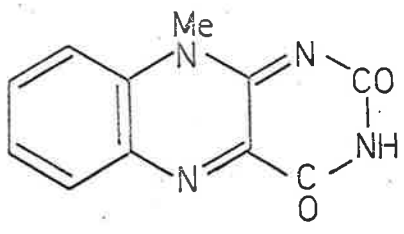
Fig. 3



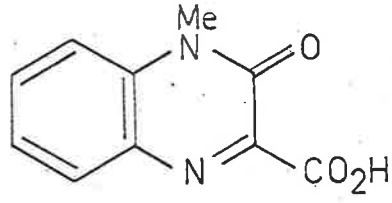
——— 5-(3'-Ethyl-2'-methylbenzimidazolium)barbiturate (51; R=H) in water.

····· 1,2-Dihydro-4-methylquinoxalinium-2-spiro-5'-barbiturate (46; R=H) in 95% ethanol.

barbiturate (51; R=Br) cause a similar bathochromic shift in the position of the two subsidiary maxima (fig. 4). This similarity in physical properties made it necessary to consider a benzimidazolium structure (54) for the dihydroquinoxalinium barbiturate (46; R=H). The alternative structure appears to be eliminated by a comparison of the chemical properties of the authentic benzimidazolium barbiturate (51; R=H) with those of the dihydroquinoxalinium barbiturate (46; R=H). The benzimidazolium barbiturate is remarkably stable to alkali[59] and was recovered quantitatively from a 30% aqueous potassium hydroxide solution after three days at room temperature. It was also recovered from 5N sodium hydroxide after being boiled for several hours. The extraordinary stability of the barbiturate (51; R=H)

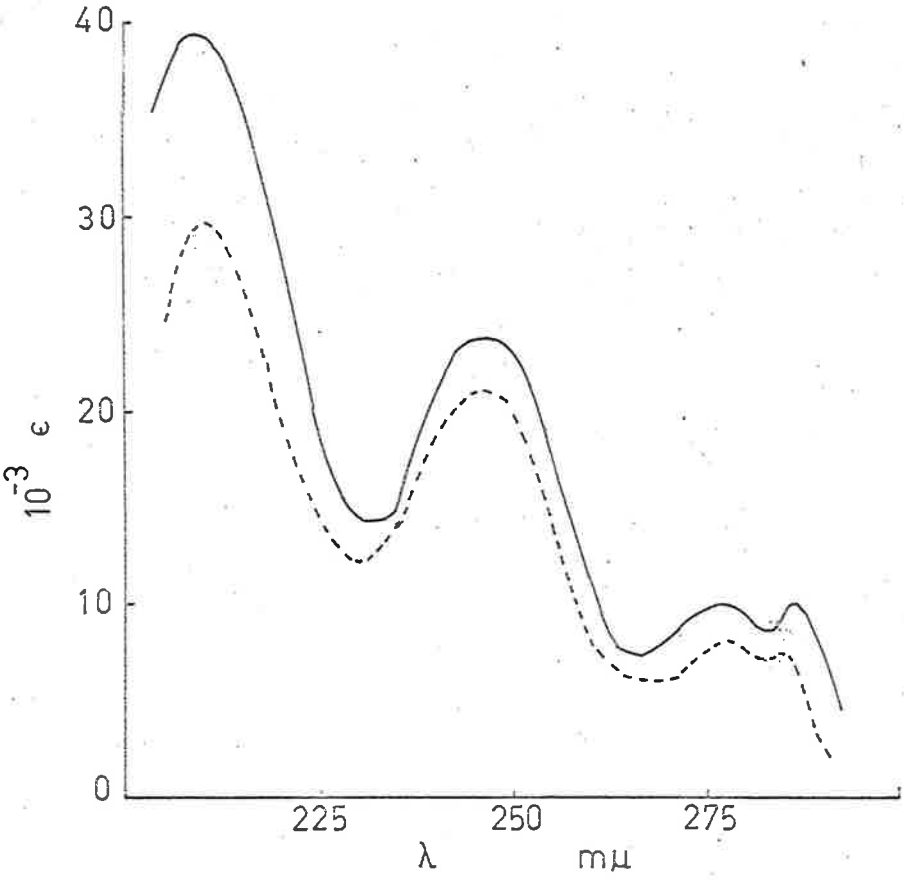


(56)



(55)

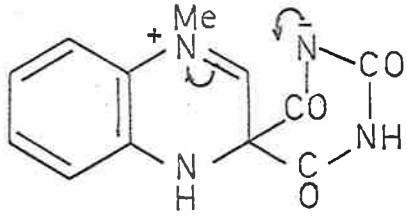
Fig.4



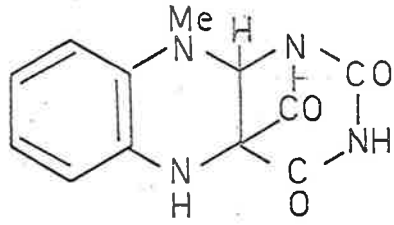
——— 5-(6'-Bromo-3'-ethyl-2'-methylbenzimidazolium) barbiturate (51; R=Br) in 95% ethanol.

------- 7-Bromo-1,2-dihydro-4-methylquinoxalinium-2-spiro-5'-barbiturate (46; R=Br) in 95% ethanol.

towards alkali contrasts with the lability of the dihydroquinoxalinium barbiturate (46 ; R=H) which undergoes mild alkaline hydrolysis to 3,4-dihydro-4-methyl-3-oxoquinoxaline-2-carboxylic acid (55) and formic acid[56] . The two compounds behave differently when fused with a mixture of sodium and potassium hydroxides. The betaine (46 ; R=H) was converted to 9-methyliso alloxazine (56) in good yield[59]



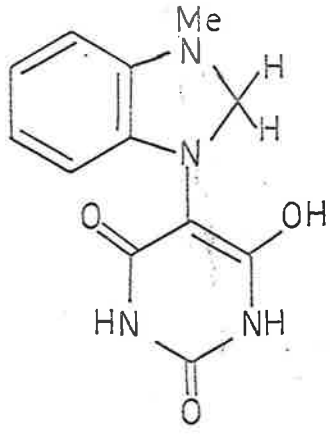
(57)



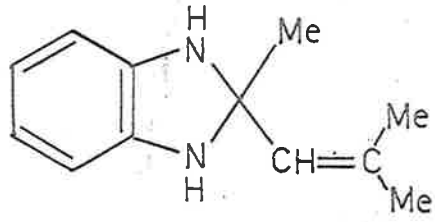
(58)

while the benzimidazolium barbiturate gave 1-ethyl-2-methylbenzimidazole as the major product. The reaction pathway involved in the formation of the isoalloxazine (56) may be portrayed as an attack by the electrons on N(1') of the pyrimidine ring on the electron deficient C(3) position (57 arrows) to give an intermediate (58) which then undergoes oxidative decarbonylation. A similar transform-

ation occurs with the 6,7-dichlorobetaine under less vigorous conditions[56]. The quantitative reduction of the



(59)

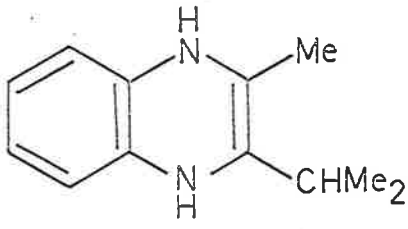


(60)

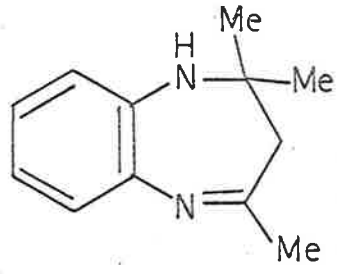
betaine (46; R=H) to the spiran (41) is best explained by the dihydroquinoxalinium structure. A benzimidazolium structure would need to undergo a ring expansion and although this is not inconceivable it seems improbable particularly in view of the behaviour of the authentic benzimidazolium barbiturate (51; R=H). The barbiturate was reduced slowly by sodium borohydride, and the reduction could be followed by observing the change in the ultraviolet light absorption of the reaction mixture. After some time the ultraviolet spectrum resembled that of dihydrobenzimidazoles but acidification yielded only recovered benzimidazolium barbiturate. This behaviour is characteristic of dihydrobenzimidazoles (see below) which

were found to revert readily to benzimidazolium salts under acid conditions.

The suggestion that the betaine (46 ; R=H) might be a benzimidazolium barbiturate (54) made it necessary to consider a benzimidazoline structure (59) for the spiran (41). Model compounds were required to test this possibility. Very few simple benzimidazolines are known. Bohlmann[62]



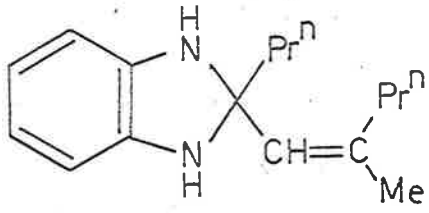
(61)



(62)

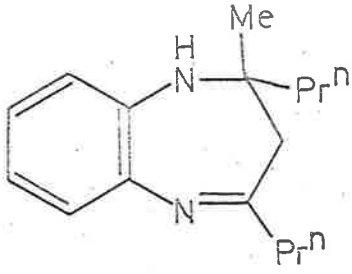
reduced benzimidazole with lithium aluminium hydride under vigorous conditions and obtained the parent dihydrobenzimidazole as an unstable oil. Elderfield and McCarthy[63] prepared several other benzimidazolines from ketones and o-phenylenediamine. Most of these were also unstable oils which decomposed into hydrocarbons and benzimidazoles when pyrol-

ysed. A solid, and relatively stable compound, supposedly the benzimidazoline (60) was obtained from o-phenylene-diamine and acetone or mesityl oxide[63] . This compound had previously been obtained by Ekely and Wells[64] and formulated as a dihydroquinoxaline (61). The nuclear magnetic resonance spectrum of the compound is incompatable with both structures but supports a benzodiazepine structure (62).



(63)

This benzodiazepine was prepared by Reid and Stahlhofen [65] but without reference to Elderfield and McCarthy [63] . Another supposed dihydrobenzimidazole (63) obtained by Elderfield and McCarthy from pentan-2-one and o-phenylenediamine is presumably also a benzodiazepine (64). It has an untraviolet spectrum almost identical with that of the trimethyl-benzodiazepine (62) and differs considerably from the spectra of



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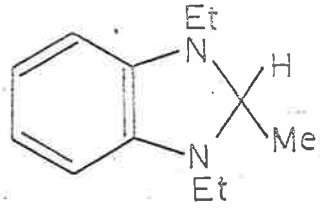

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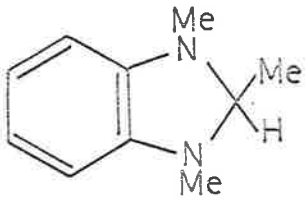
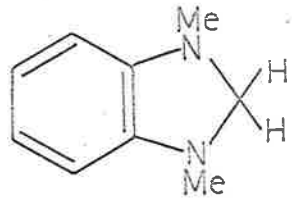


(66)



(67)

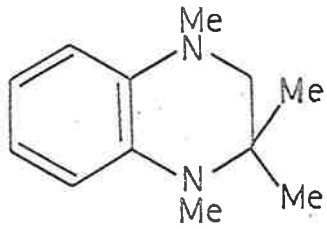
authentic benzimidazolines.

A number of 1,3-disubstituted (e.g. 65 - 67) benzimidazolines have now been prepared by reduction of the corresponding benzimidazolium iodides with sodium borohydride. The reductions proceeded rapidly at room temperature and

gave good yields of product. The benzimidazolines prepared in this manner were found to be unstable oils which could be purified by distillation under reduced pressure but which decomposed on exposure to air. A chloroform solution of 1, 3-dimethylbenzimidazoline deposited 1,3-dimethylbenzimidazolium chloride on standing. Attempts to form picrates and hydrochlorides from benzimidazolines resulted in the formation of the corresponding benzimidazolium picrates and chlorides. It therefore seems likely that the picrate obtained by Bohlmann[62] from benzimidazoline is benzimidazole picrate[66] which has the same m.p. and for which Bohlmann's analytical figures are in good agreement.

The instability of the model benzimidazolines, particularly in acid solution, appears to exclude the possibility of a benzimidazoline structure (59) for the spiran (41). The behaviour of the benzimidazoline apparently formed on reduction of the benzimidazolium barbiturate (51; R=H) is, however, in agreement with the behaviour expected from a study of the model compounds. The structures of 1,2,3-trimethylbenzimidazoline (66) and 1,3-dimethylbenzimidazoline (67) were confirmed by their nuclear magnetic resonance spectra. The spectrum of the trimethyl-benzimidazoline showed the four aromatic protons as a multiplet, a quartet at 6.0 due to the 2-proton, a six-proton peak at 7.38 which

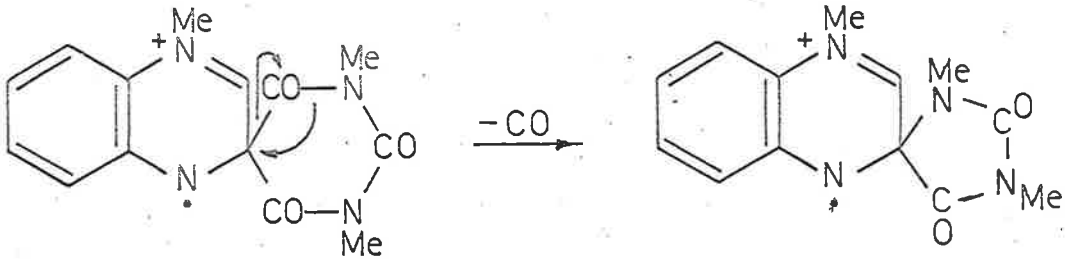
was assigned to the two N-methyl groups, and a three-proton doublet at 8.54 due to the 2-methyl group. The spectrum obtained from the dimethyl compound showed the two N-methyl groups at 7.34, and the 2-methylene group absorbed as a singlet at 5.77. The position of the 2-methylene group absorption decisively excludes a benzimidazoline structure (59) for the spiran (41) which showed methylene group absorption at much higher field (6.75) close to the methylene group absorption (7.12) of a reference tetrahydroquinoxaline (68).



(68)

It was thought that the mass spectra of the barbiturates might provide positive evidence for the proposed structures. These spectra were determined by Dr. J.S. Shannon and the discussion of the mass spectra that follows is based largely on his interpretation of the results.

The barbiturates gave good mass spectra but the spectrum of the benzimidazolium barbiturate (51 ; R=H) was somewhat similar to that of the dihydroquinoxalinium barbiturate (46 ; R=H) and no distinctive features indicative of different structures were observed. The main evidence provided by the mass spectra was the fact that the dimethyl derivative (48) exhibited an M-28 peak attributed to the loss of carbon monoxide. Carbon monoxide however was not lost from the dimethyl derivative (52). A molecule with the structure (54) should not lose carbon monoxide because its analogue (52) does not. The loss of carbon monoxide from a molecule with the betaine structure (48) is readily explained as follows :



The benzimidazolium barbiturate (51 ; R=H) showed

main peaks at m/e 286, 258, 172, 159, 141, and 131. The m/e 159 peak was the most intense with the exception of the molecular peak. Metastable peaks indicated the following transitions:

$$286^{+} \longrightarrow 158^{+} + 28$$

$$258^{+} \longrightarrow 172^{+} + 86$$

$$172^{+} \longrightarrow 144^{+} + 28$$

$$159^{+} \longrightarrow 131^{+} + 28$$

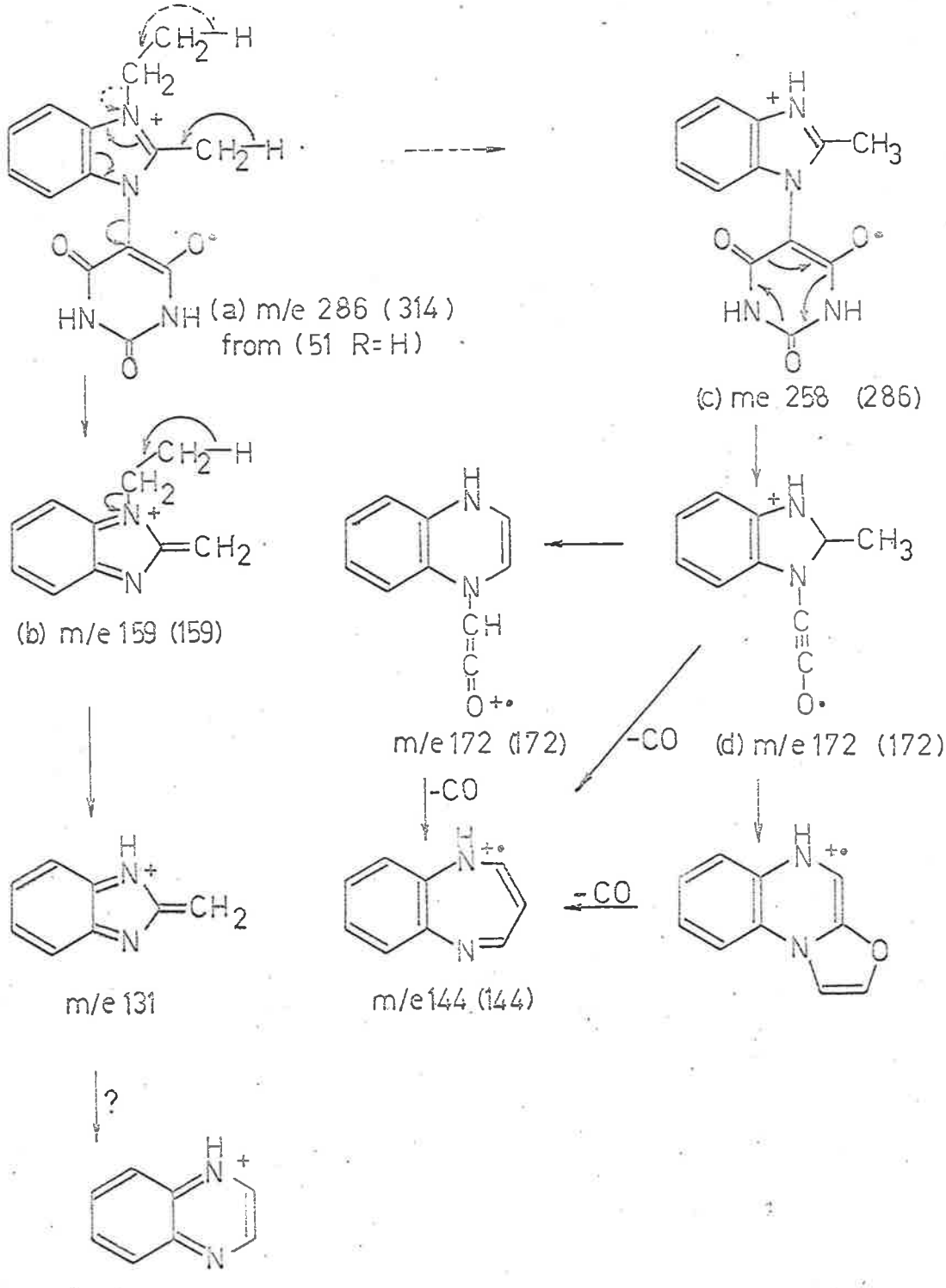
Crystallization of the barbiturate (51 : R=H) from deuterium oxide resulted in the exchange of five hydrogen atoms. The hydrogens which exchanged were the N(1)H and N(3)H atoms and those of the 2'-methyl group. The mass spectral data obtained from the undeuterated molecule combined with the results from the deuterated compound can be explained by the ion reactions shown in figure 5. The results obtained for the dimethyl derivative (52) are given in parentheses. The ion b for the deuterated molecule had lose 2-3 deuterium atoms, while ion c had retained all the deuterium and ions d and e had both lost two atoms.

The spectrum of the betaine (46 ; R=H) showed an intense peak at m/e 241 as well as peaks at m/e 258, 198, and 172. Metastable peaks confirmed the following transitions:

$$258^{+} \longrightarrow 241^{+} + 17$$

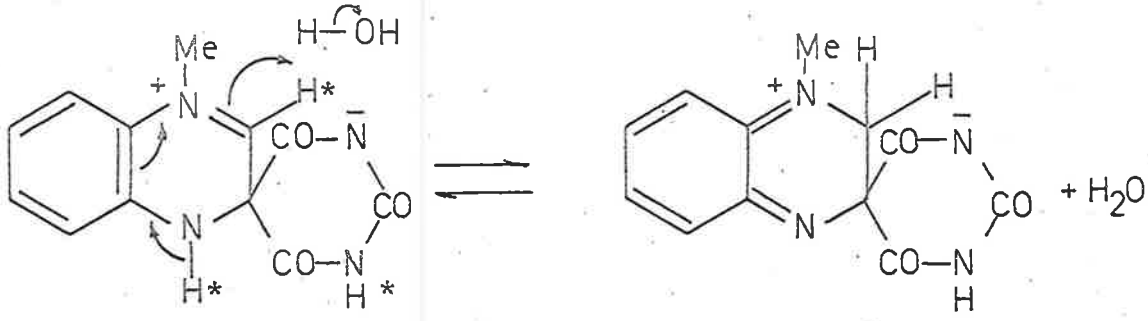
$$241^{+} \longrightarrow 198^{+} + 43$$

Fig. 5


(a) m/e 286 (314)
from (51 R=H)
(b) m/e 159 (159)
(c) me 258 (286)
m/e 172 (172)
(d) m/e 172 (172)
-CO
-CO
-CO
m/e 131
m/e 144 (144)
?

The spectrum of the deuterated betaine showed that the M-17 peak was due to OH and not NH_3 and the m/e 198 and 172 peaks were shifted by one mass unit. These results can be explained by ion reactions shown in figure 6. The m/e values in parentheses refer to the dimethyl derivative (48). The ion m/e 172 may be formed by an alternative route as shown in figure 7.

It was found that three hydrogen atoms in the betaine (46 ; R=H) can be replaced by deuterium and this gives further support to the dihydroquinoxalinium barbiturate structure (46 ; R=H). The two N-hydrogen atoms would exchange in both structures (46 and 54) but the exchange of the third hydrogen atom is more easily understood on the quinoxalinium structure.



H*, exchangeable hydrogen atom

Fig.6

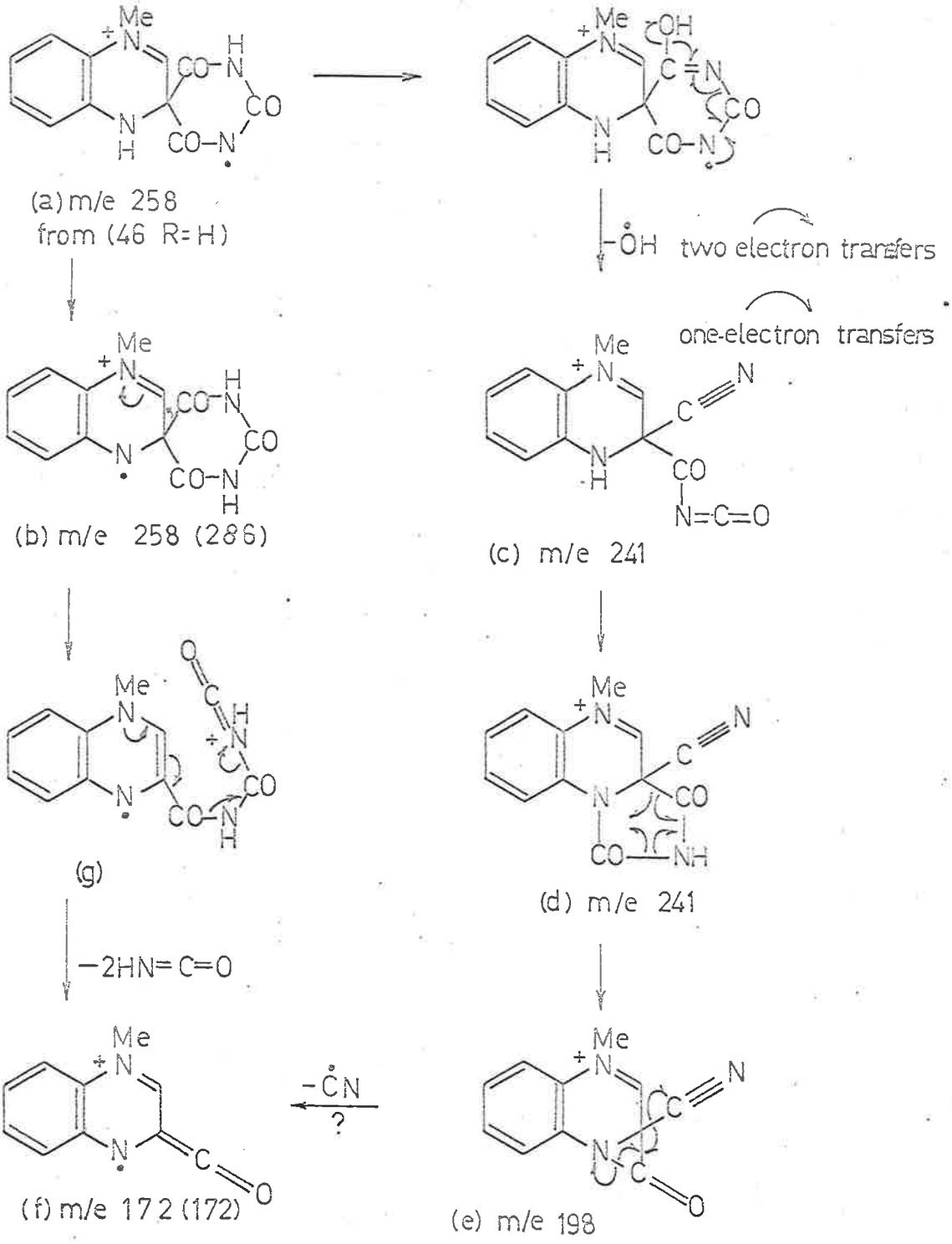
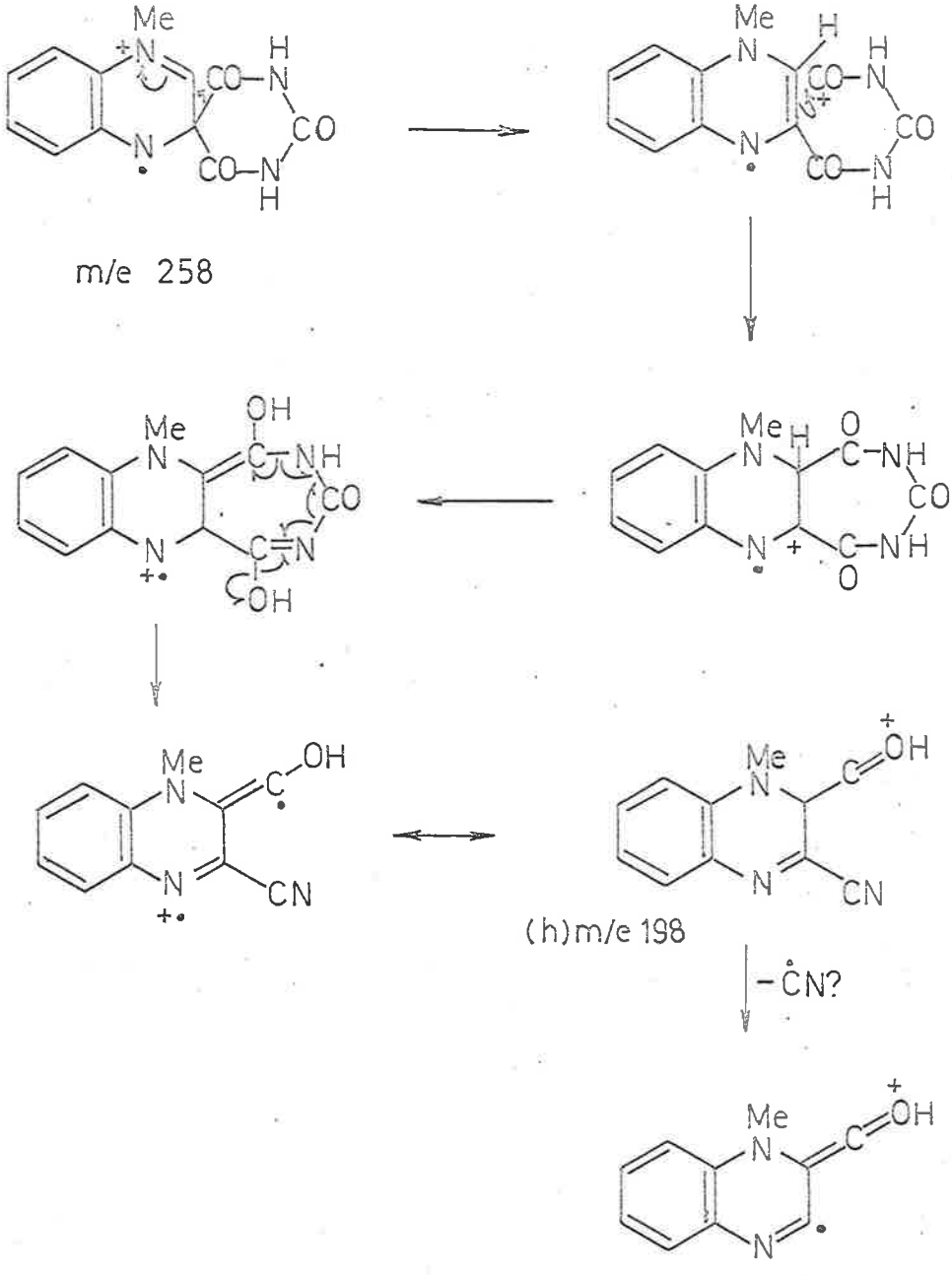

(a) m/e 258
from (46 R=H)
(b) m/e 258 (286)
(c) m/e 241
(d) m/e 241
(e) m/e 198
(f) m/e 172 (172)
(g)
-OH
two electron transfers
one-electron transfers
-2HN=C=O
-ĊN
?

Fig.7



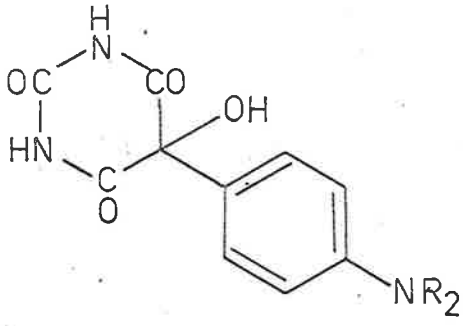
The anionic charge on the isomeric barbiturates (46; R=H) and (54) should be neutralized at different pH, but the strengths of the conjugate acids of the compounds (46; R=H) and (51; R=H) could not be determined because they proved too insoluble for electrometric titration.

During preparation of 4-bromo-2-nitrodiethylaniline by bromination of o-nitrodiethylaniline it was observed that the reaction was accompanied by de-ethylation which resulted in the formation of 4-bromo-2-nitro-N-ethylaniline as well as the required product. Chromatography on alumina or silica gel separated the two compounds and the mono-ethyl compound was reduced to the corresponding o-phenylenediamine and condensed with alloxan in aqueous-ethanol. The quinoxaline-carboxyureide formed resembled the unbrominated ureide in light absorption and other properties.

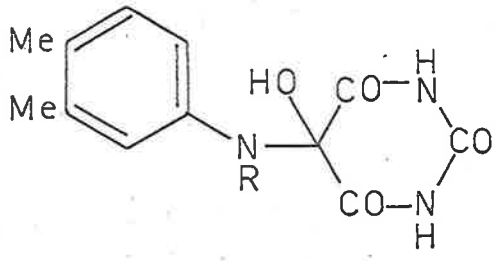
The structures of the dihydroquinoxalinium barbiturate (46; R=H) and the benzimidazolium barbiturate (51; R=H) are established by the above evidence and possible mechanisms to explain the formation of these compounds are discussed in part 4.

Part 2.

It has been known for sometime that anilines which are unsubstituted in the para position react with alloxan to give 5-aryldialuric acids (69) [39] . There are however



(69)

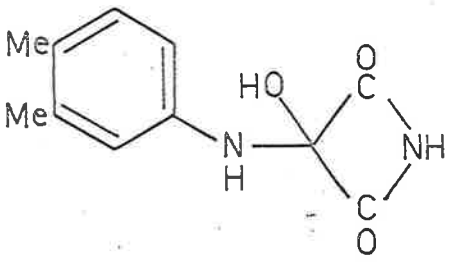


(70)

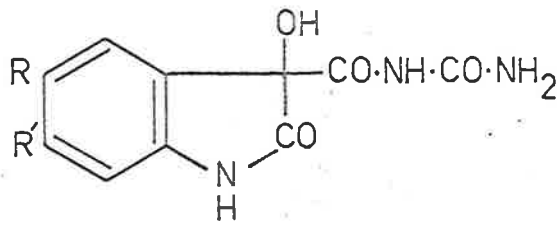
no authentic cases recorded in the literature where alloxan has attacked the aromatic nucleus ortho to the amino group, although there appears to be no reason for excluding ortho substitution.

In order to investigate the formation of alloxan anils Berezovskii, Rodionova and Gurko [67] attempted to prevent attack by the alloxan molecule on the aromatic nucleus by blocking the para position. They treated alloxan with 3,4-dimethyl-aniline and 3,4-dimethylphenyl-D-ribitylamine and

obtained compounds which they formulated as arylaminodialuric acids (70). Analyses and absence of primary amino-group properties were quoted as evidence for the proposed structures. The ultraviolet light absorption was put forward as evidence excluding an anil structure, using as a reference compound the incorrectly formulated anil obtained from 2-dimethylamino-4,5-dimethylaniline and alloxan discussed earlier (p.23). The compound obtained by mild alkaline hydrolysis of the supposed arylaminodialuric acid (70; R=H) was formulated as a malonimide (71) by analogy with supposed malonimides[36] now known



(71)

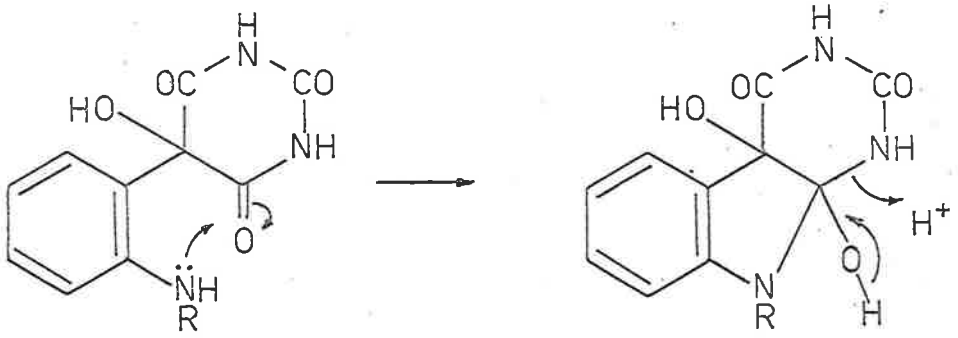


(72)

to be hydantoins[37].

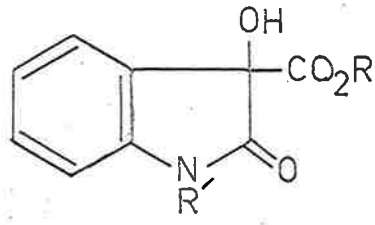
On re-investigation, the supposed arylaminodialuric acids were shown to be dioxindoles (72) formed by the previously

unknown substitution of alloxan ortho to the amino group. The formation of the dioxindoles can be portrayed as an acid-catalysed cyclisation of the phenyldialuric acid (73, arrows). An analogous reaction occurs with oxomalonic esters which yield dioxindole carboxylic esters (74).



(73)

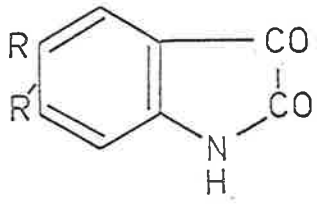
The 5-methyl and 5,6-dimethyldioxindole-3-carboxyureides have now been prepared from p-toluidine and 3,4-dimethoxyaniline respectively. The ease of formation of the dioxindoles was found to be very dependant on the activation of the ortho position. 3,4-Dimethoxyaniline formed the dioxindole very rapidly and in high yield; 3,4-dimethylaniline reacted less readily and gave a lower yield, and p-toluidine was the least reactive of the three anilines examined.



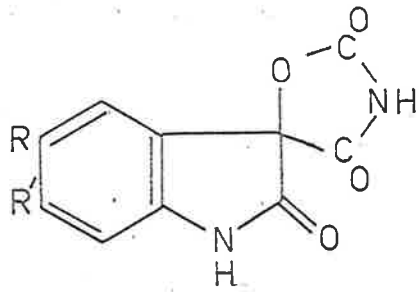
(74)

The reaction appears to be fairly general for p-substituted anilines under acid conditions, and electron donating groups in the 3-position clearly facilitate dioxindole formation.

The structure of the dioxindoles was established by a study of their chemical properties, infrared spectra, and degradation products. The dioxindoles were readily hydrolysed by dilute mineral acids which suggests the presence of a ureide side-chain in the molecule. Aeration of the basified hydrolysis mixture and reacidification gave the corresponding isatins (75). The infrared spectra of the dioxindoles (72) were similar, particularly in the -NH, -OH and carbonyl regions. The dioxindole carbonyl appeared at 5.75 μ [69] while a broad absorption band at 5.9 to 5.95 μ is attributed to the ureide carbonyls. Treatment of the dioxindoles with 50%



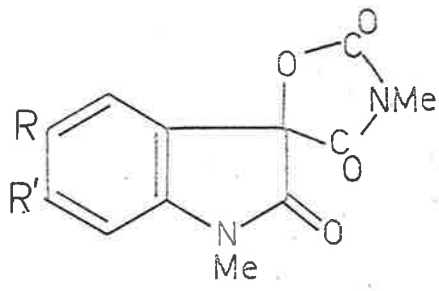
(75)



(76)

aqueous potassium hydroxide, under the conditions described by Berezovski et al.,[67] liberated ammonia and gave crystalline potassium salts. Acidification of the latter gave the oxazolidine-2,4-diones (76). The product ($C_{11}H_{12}N_2O_3$) obtained by the Russian workers[67] from the 5,6-dimethyldioxindole (72; R=R'=Me) and formulated as a tartronimide (71) was not isolated. The structure of the oxazolidinediones was established by analyses, infrared absorption, nuclear magnetic resonance, and methylation studies. The infrared spectra all showed an -NH band at 3.1 μ and three carbonyl peaks at 5.5, 5.7 and 5.8 μ . The absorption at 5.5 and 5.7 μ is characteristic of oxazolidine-2,4-diones[70] and the bands are due to urethane and amide carbonyls respectively. The 5.8 μ absorption is assigned to the oxindole carbonyl. The nuclear magnetic

resonance spectrum of the dipotassium salt of the 5,6-dimethoxy-oxindole (76 ; R=R'=OMe) in deuterium oxide showed two unsplit one-proton peaks at 3.03 and 3.21 due to the C-4 and C-7 aromatic protons and the 5,6-dimethoxy groups appeared as two three-proton peaks at 6.07 and 6.17. Methylation of the oxazolidinediones with methyliodide and potassium carbonate in acetone gave the 1,3'-dimethyl derivatives (77). The same compounds were obtained by methlation of the dioxindole-ureides (72) under the same conditions. The dimethyl derivatives (77) possessed infrared absorption almost identical with the unmethylated compounds except that the -NH

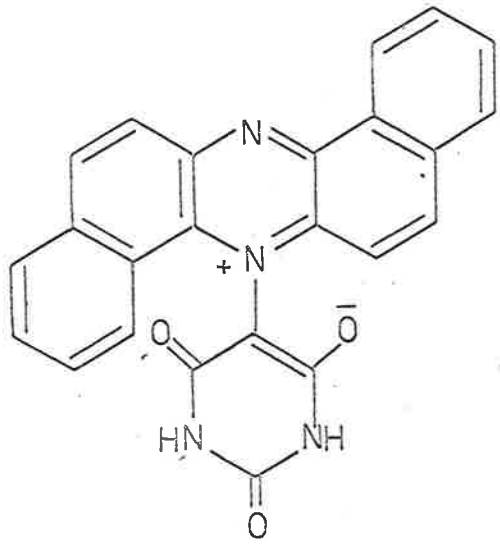


(77)

absorption was absent.

The reaction of β-naphthylamine with alloxan in

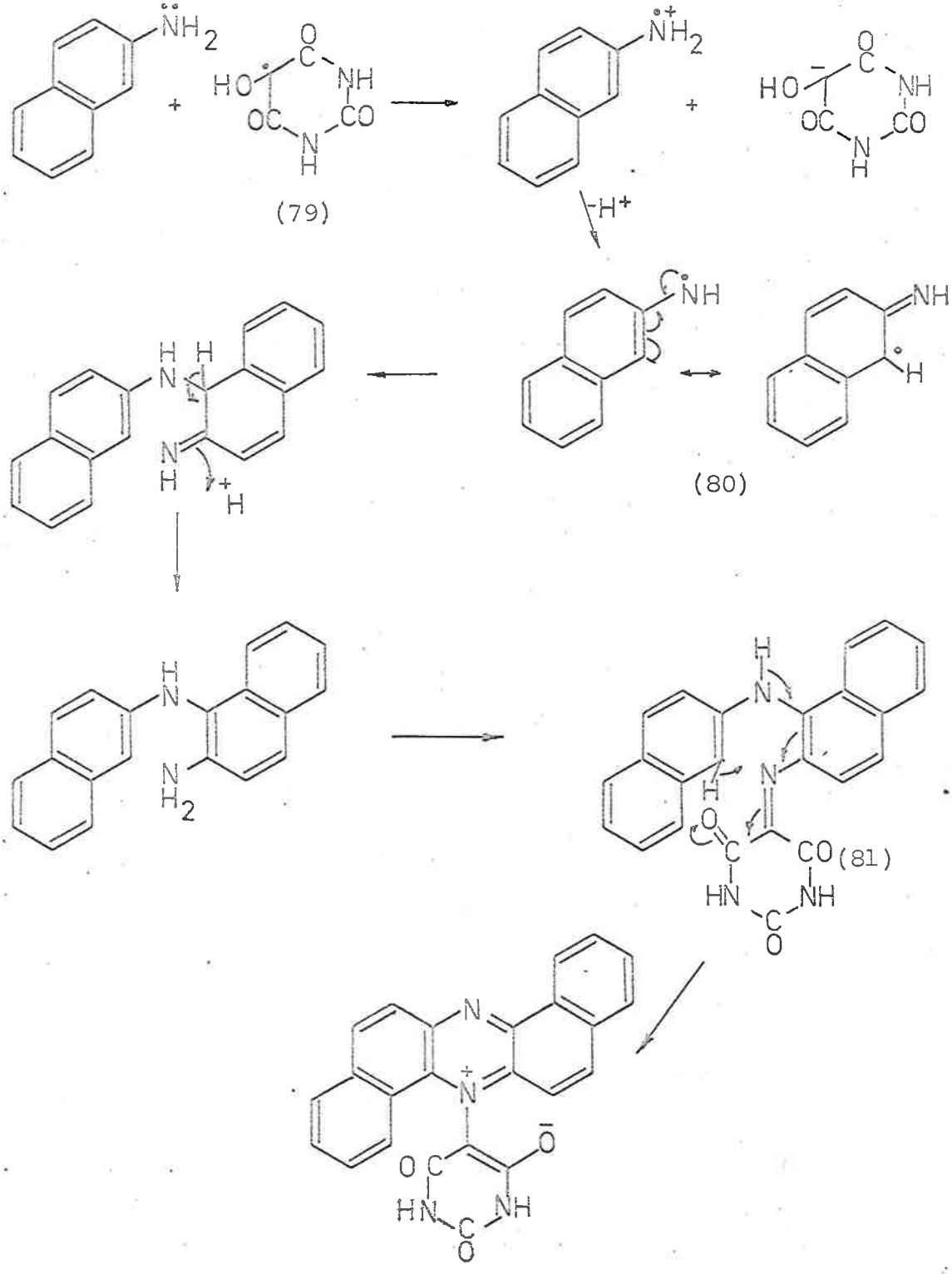
acetic acid is unusual and results in the formation of dibenzo-a,h-phenazinium barbiturate (78) which crystallizes from the hot reaction mixture as the dihydrate in brown prisms with a green metallic lustre. The colour and properties of the phenazinium barbiturate were similar to those



(78)

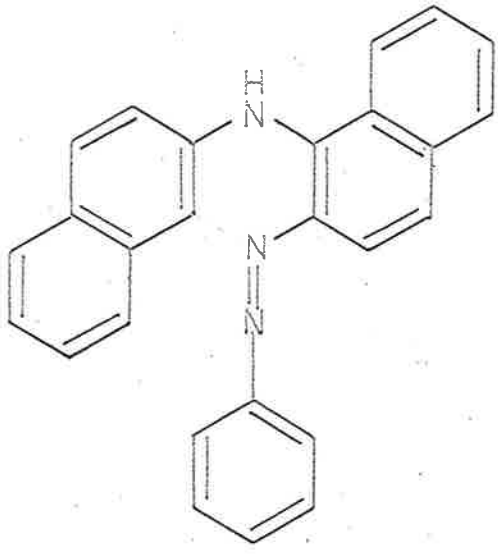
reported for dibenzo-a,h-phenazine methiodide [71] and like the methiode it exhibited a brilliant cornflower blue colour on treatment with concentrated sulphuric acid. The phenazinium barbiturate was converted into dibenzo-a,h-phenazine by pyrolysis or by treatment with aqueous alkali. The ultraviolet light absorption of the barbiturate (78) and dibenzo-a,h-phenazine were similar. The spectrum of the barbiturate

Fig. 8



exhibited a bathochromic shift of about 10 mμ and showed less fine-structure.

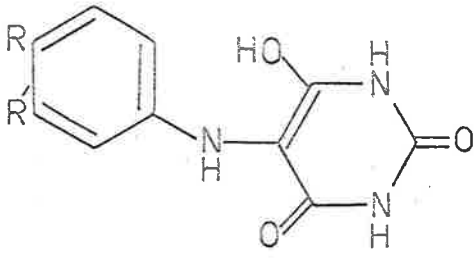
The oxidative dimerisation of β-naphthylamine to dibenzo-a,h-phenazine is well known and has been induced by a variety of oxidising agents [72]. In view of this the formation of the dibenzophenazine (78) in this reaction is not unexpected and a possible mechanism for its formation is shown in figure 8. Orr [73] and Lagercrantz and Yhland [74] have recently reported the existance of the alloxan free radical (79) which may be involved in the initial oxidation of β-naphthylamine to the radical (80). The intermediate anil (81) is analogous to azo-compounds (e.g. 82) which are known to undergo ring-closure to phenazines under acid conditions [75].



(82)

The major products isolated from the interaction of alloxan and p-substituted anilines in acetic acid were the dioxindoles (72) already discussed. The course of the reaction changed entirely when aqueous-ethanol was used as the solvent. In this case, substituted 7-phenyluramils (83) and aniline salts of alloxanic acid (84) were obtained.

The compound previously[41] isolated from the reaction of p-toluidine with alloxan in aqueous-ethanol and given the structure (85) has now been shown to be the p-toluidine salt of 7-p-tolyluramil (86; R=Me, R'=H). Analogous uramil salts were isolated from the reaction of p-anisidine and 3,4-dimethylaniline. The uramil salts were all extremely insoluble and precipitated from the boiling reaction mixture. Their decomposition points were indistinct and appeared to vary considerably according to the rate of heating. They were difficult to purify as they tended to decompose in boiling solvents, but a satisfactory analysis was obtained for the p-toluidine compound (86; R=Me, R'=H). Treatment of the salts with aqueous sodium hydroxide immediately precipitated the anilines and acidification of the basic solution yielded the 7-phenyluramils (83). The 7-phenyluramils were also obtained directly by treatment of the salts with hydrochloric acid. They too were very insoluble but could be purified by repeated precipitation from alkaline solution



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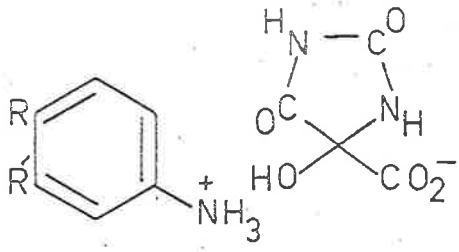
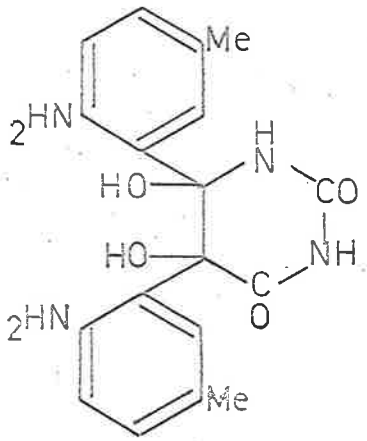
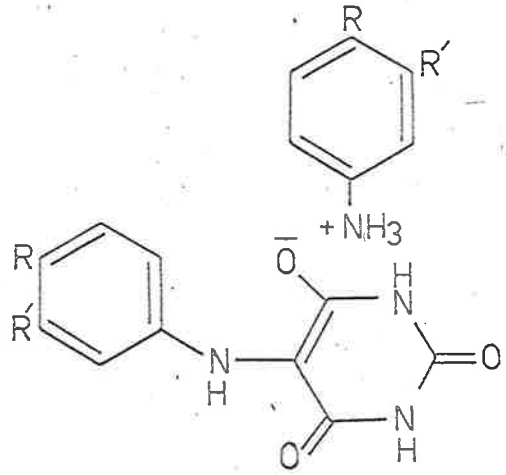


(84)



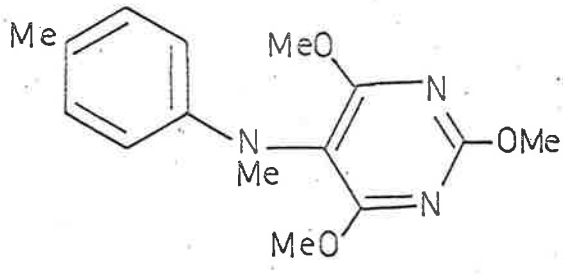
(85)



(86)

with acid, or by precipitation from dimethylformamide or dimethylsulphoxide with water. They were soluble in concentrated hydrochloric acid but were precipitated on dilution of the acid solution with water. Methylation of 7-p-tolyluramil (83 ; R=Me, R'=H) gave a tetramethyl derivative (87) and its structure was confirmed by nuclear magnetic resonance. The nuclear magnetic resonance spectrum in carbon

tetrachloride showed the four aromatic protons as two doublets at 3.83, 3.68 and 3.24, 3.10; the aromatic methyl group absorbed at 7.08 and the N-methyl group at 6.99. The 2-methoxy group



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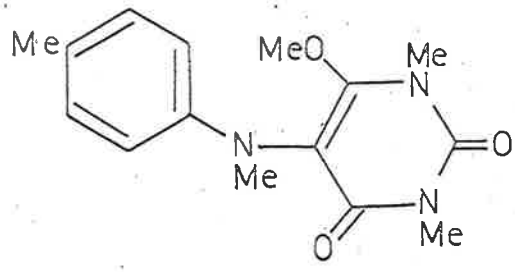
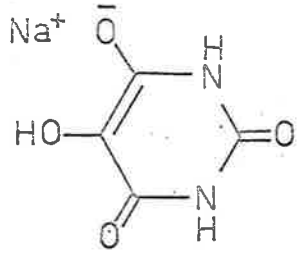


(88)

absorbed at 6.09 close to the absorption of the 4- and 6-methoxy groups which appeared as a single six-proton peak at 6.14. Methylation on the pyrimidine nitrogens to give the lactam (88) is excluded by the position of the absorption of the methoxy groups (N-Me groups in model compounds e.g. 44, p.19 absorbed near 6.7). The infrared spectrum (Nujol) provided further support for the lactim structure (87); the carbonyl region, 5.5 to 6.3 μ, was devoid of absorption except for a very weak band at 6.0 μ. The infrared spectra (Nujol) of the unmethylated uramils (83) however each showed absorption at 6.0 and 6.2 μ, identical with the carbonyl absorption

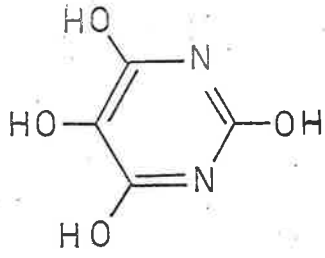
of sodium dialurate (89),[20] and an absorption band at 287 mμ



(89)

present in the ultraviolet light absorption of the tetramethyl derivative (87) was absent from the spectrum of the unmethylated compound (83; R=Me, R'=H). In view of this it would appear that the lactam form (83) is the predominant tautomer present in the case of the unmethylated phenyluramils (83), although no definite conclusions can be drawn without reference to a compound permanently fixed in the lactam form (e.g. 88). The absorption band at 6.0 μ , observed in the infrared spectra of the phenyluramils (83), is attributed to the -NH.CO.NH- carbonyl while the more intense absorption at 6.2 μ is assigned to the α , β -unsaturated ketone present in these compounds. Tipson and Crether[76] have proposed that the structure (90) represents crystalline dialuric acid. They based

their conclusions on the absence of infrared absorption (Nujol) in the region 5.6 to 5.8 and they suggested that the observed multiplicity of bands in the region 5.88 to 6.25 μ was due to C=N and C=C stretching vibrations. In view of the lack of absorption in this region (5.88 to 6.25μ) in the spectrum of the tetramethyl compound (87). Tipson and



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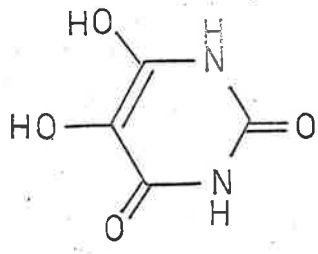
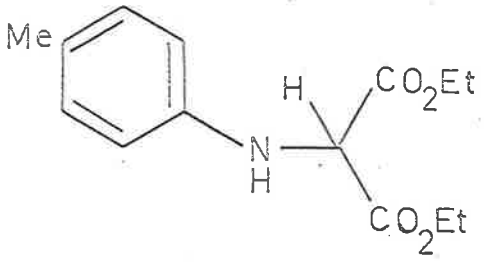


(91)

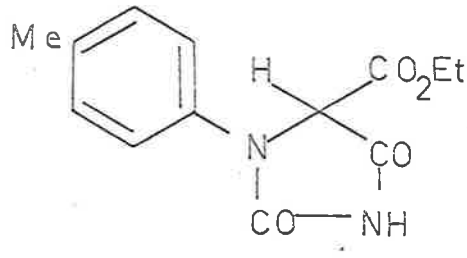
Cretchers argument is no longer valid and it would appear that the lactam form (91) is present to some extent at least.

The 7-p-tolyluramil (83; R=Me, R'=H) was synthesised by sodium borohydride reduction of p-toluidine-alloxan anil (116, p.63) and also by condensation of diethyl-p-tolyl-aminomalonate (92) and urea in methanol containing sodium methoxide[77]. In the latter synthesis an alternative cyc-

lisation to give the hydantoin (93) was possible however



(92)



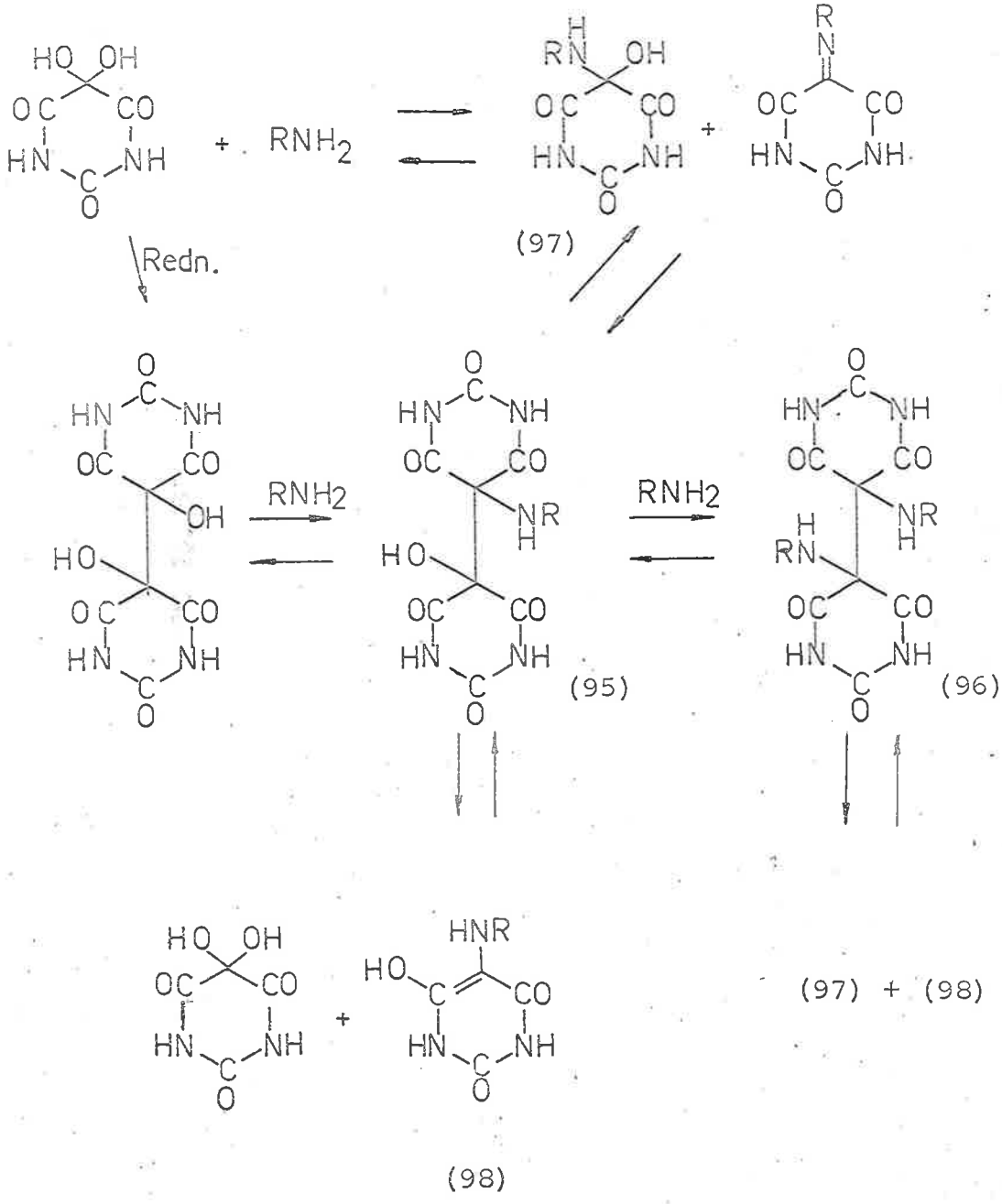
(93)

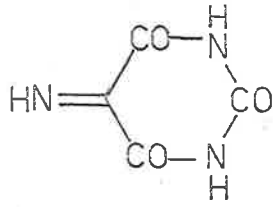
no material of this nature was isolated from the reaction mixture. The phenyluramil (83 ; R=Me, R'=H) was further synthesised from p-toluidine and dialuric acid in the presence of a catalytic amount of alloxan.

The formation of N-substituted uramils from amines and alloxantin is well known[29] and it seemed possible that alloxantin was involved in the formation of the 7-phenyluramils. It was found that when a solution of alloxan in aqueous-ethanol was heated under reflux for several hours reduction to alloxantin occurred. Biltz and Damm[78] considered the mechanism of formation of uramils from alloxantin and amines to involve dissociation of the alloxantin into dialuric acid and alloxan and condensation of the resulting

dialuric acid with the amine. The participation of dialuric acid in the formation of the uramils (83) was excluded when it was found that the reaction of dialuric acid with anilines gave only the aniline salts of dialuric acid. Biltz, Marwitsky and Heyn [79] have also reported the formation of dialuric acid salts during attempts to prepare uramils from dialuric acid and amines. Once salt formation occurs the dialurate anion presumably repels any further attack of the nucleophile. It was found that addition of a small quantity of alloxan to the reactions involving dialuric acid resulted in good yields of the phenyluramils. Davidson and Soloway [80] have reported the catalytic effect of alloxan in the formation of uramil from dialuric acid and ammonium salts, and they suggested that the reaction proceeds by formation of alloxanimine (94) and reduction of this intermediate by dialuric acid gives uramil and regenerates alloxan. A mechanism incorporating alloxantin is shown in figure 9. The oxidation-reduct ion step was not defined in the mechanism proposed by Davidson and Soloway. The present mechanism envisages this step as a disproportionation involving alloxantin type intermediates (95 and 96) and the equilibrium reaction is made irreversible by the insoluble nature of the phenyluramils formed on hydrolysis of these intermediates.

Fig. 9



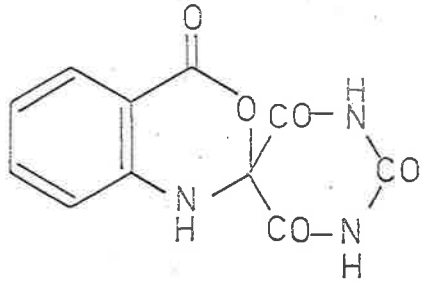


(94)

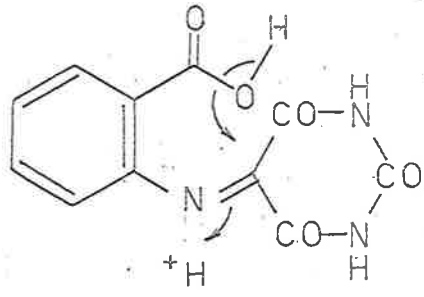
Aniline salts of alloxanic acid (84) were isolated from the mother liquors of the reactions carried out in aqueous ethanol. They were readily identified by their infrared spectra which showed characteristic carbonyl absorption[38]. The assignment of structure was further supported by the observation that they decarboxylated at their melting points, which is characteristic of alloxanic acid salts[38], and confirmation was achieved by synthesis from alloxanic acid and the anilines. The base-catalysed ring-contraction of alloxan to alloxanic acid salts is well known[38] and in view of this the formation of aniline salts in these reactions is not surprising.

The benzoxazone (99) was obtained from the reaction of anhydrous alloxan with anthranilic acid in acetic acid.

Its formation may be portrayed as an acid-catalysed cyclisation of the intermediate anil (100 , arrows). Similar acid



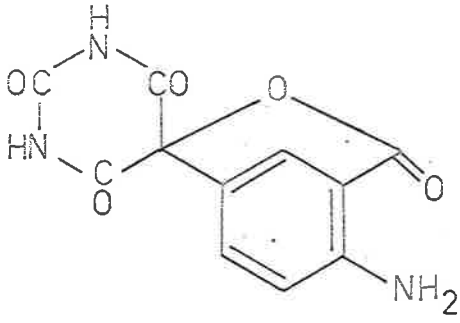
(99)



(100)

catalysed cyclisations of anthranilic acid anils are well known [81] . The infrared spectrum of the benzoxazone showed a band at 5.6 μ which has been assigned to the 4-carbonyl group by analogy with the position of the carbonyl absorption in isocoumarin derivatives [82] .

Anthranilic acid and alloxan in aqueous ethanol are reported[41] to give (101). This compound has now been shown to be the o-carboxyphenyluramil (102). The analytical figures are in better agreement with the new structure which is also supported by its infrared spectrum and by its synthesis by reduction of the benzoxazone (99) with sodium borohydride (103, arrows)



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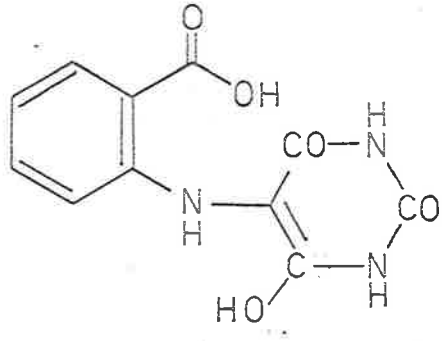
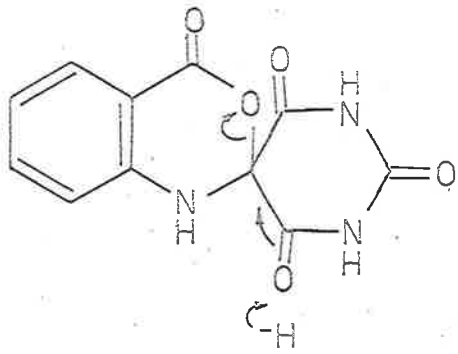


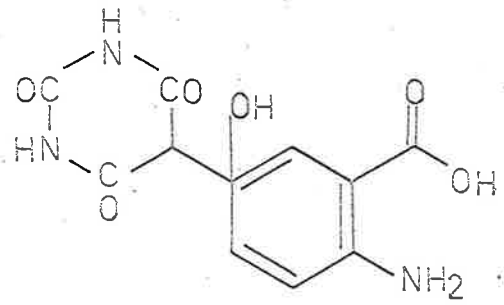
(102)

The filtrate from the reaction of anthranilic acid and alloxan monohydrate in aqueous ethanol contained a compound $C_{11}H_9O_6N_3$ presumed to be the dialuric acid (104).

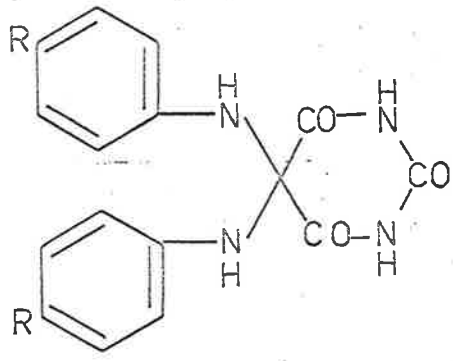
Prolonged reactions of alloxan monohydrate with p-substituted anilines in boiling aqueous ethanol gave phenyluramils (83) and salts of alloxanic acid (84) but these were not the initial products of the reactions. When the reactions were carried out at room temperature, and the solutions diluted with water 5,5-di(phenylamino) barbituric acids (105) were obtained and these were readily converted into the uramils and alloxanic acid salts by boiling with aqueous ethanol, whereas treatment with 5% aqueous sodiumhydroxide gave the corresponding anilines and sodium alloxanate. Similarly



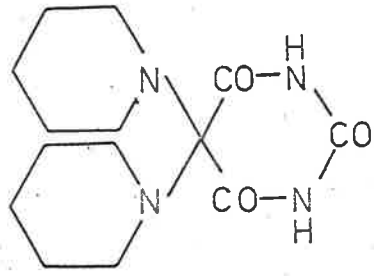
(103)



(104)



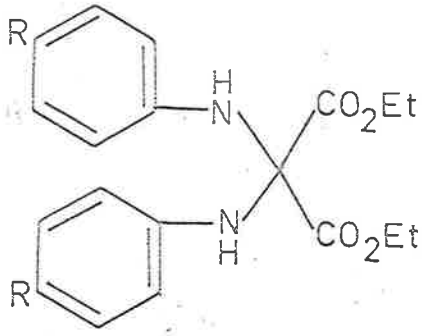
(105)



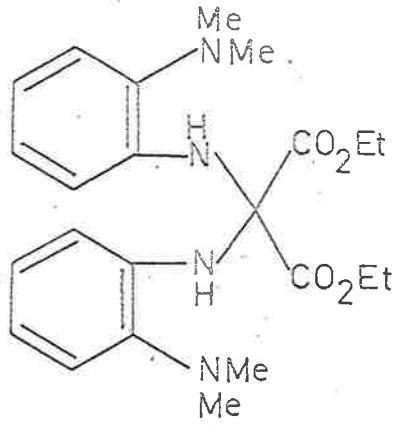
(106)

5,5-di(piperidino)barbituric acid (106) was obtained from piperidine and anhydrous alloxan in diglyme or tetrahydrofuran and it was hydrolysed to piperidine and sodium alloxanate by dilute alkali or converted into the piperidine salt of alloxanic acid by boiling aqueous-ethanol.

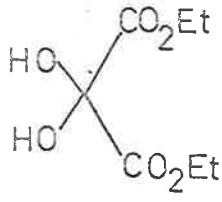
The compounds (107; R=Me), and (108), analogous to the products (105) and (106) were obtained from the reaction of p-toluidine and o-dimethylamino-aniline with the hydrate (109) of ethyl oxomalonate in aqueous-ethanol. In the latter reaction cyclisation to the tetrahydroquinoxaline (110), analogous to the spiran (41 p.17), did not occur nor did cyclisation occur with ninhydrin and o-dimethylamino-aniline. In this case a dark blue compound was obtained



(107)

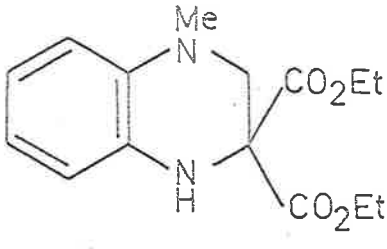


(108)



(109)

and the absence of -NH absorption in the infrared spectrum and the ease of hydrolysis by dilute mineral acids suggested that it was an anil (111). The nuclear magnetic resonance



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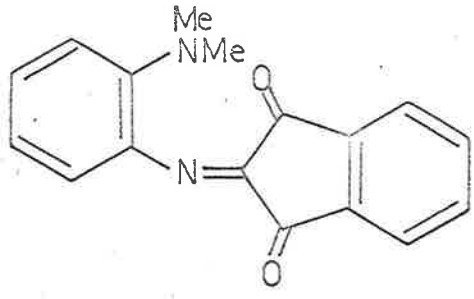
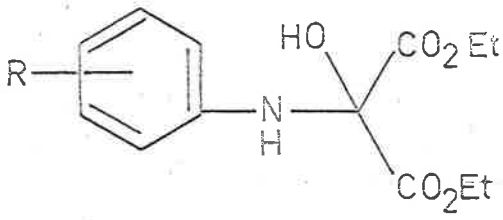


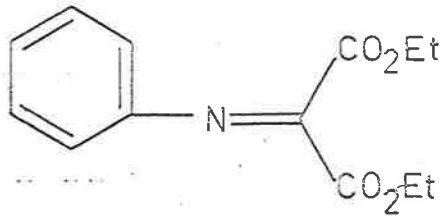
(111)

spectrum of the o-dimethylaminoanilino-malonate (108) in deuterochloroform/10% carbontetrachloride showed the four equivalent N methyl groups as a 12-proton peak at 7.29; the triplet and quartet of the two ethyl groups appeared at 9.01 and 5.93 , and the aromatic and -NH protons occurred as a 10-proton multiplet centred at 3.09.

Curtiss et al. 83 examined the reactions of anhydrous oxomalonic esters with primary aromatic amines in dry ether and obtained phenylaminotartronic esters (112). Dehydration of ethyl anilinotartronate (112; R=H) to the anil (113) was achieved only under vigorous conditions and the C=N bond formed was found to be extremely reactive and reminiscent of that found in phenylisocyanate. It reacted vigorously with alcohols, dry ammonia, dry hydrogen chloride, amines and acids with loss of colour and formation of sub-



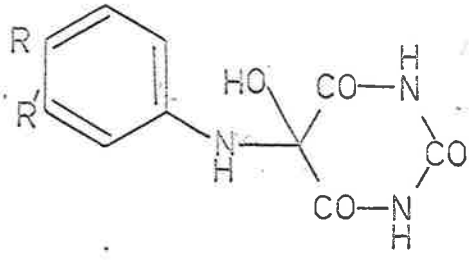
(112)



(113)

stituted phenylaminomalonates. Treatment of ethyl anilinotartronate (112; R=H) or the anil (113) with water gave a mixture of ethyl dianilinomalonate (107; R=H) and ethyl oxomalonate hydrate (109) and the apparent stability of diphenylaminomalonic esters (107) under aqueous conditions is therefore in agreement with the isolation in the present work of the compounds (105), (107; R=Me or OMe) and (108).

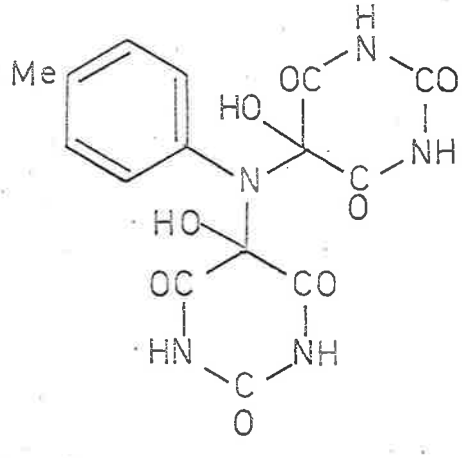
It was of interest to prepare 5-arylaminodialuric acids (114) since one such compound (114; R=R'=Me) had supposedly been obtained[67] from 3,4-dimethylaniline and alloxan monohydrate although the product has now been shown to have a different structure (see p.40). The authentic 5-arylaminodialuric acid (114; R=R'=Me) was obtained from the reaction of anhydrous alloxan with 3,4-dimethylaniline in cold, dry



(114)

diglyme, and it was identified by elemental analysis and degradation. It was difficult to recrystallize and turned red even in slightly warm solutions (presumably due to dehydration to the anil), but an analytical sample was obtained directly from the reaction mixture after taking suitable precautions. It was hydrolysed by dilute sodium hydroxide to 3,4-dimethylaniline and sodium alloxanate; in boiling aqueous-ethanol it turned a deep red initially and was eventually converted into the 3,4-dimethylaniline salt of alloxanic acid (84; R=R'=Me) and the salt of the uramil (86; R=R'=Me).

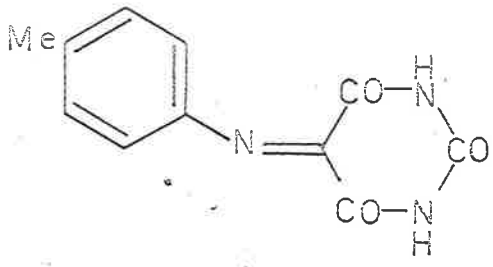
An attempt to obtain the p-toluidine analogue (114; R=Me, R'=H) yielded a highly crystalline compound presumed



(115)

to have the structure (115). This compound also was difficult to purify and analytical data on a sample taken directly from the reaction mixture and dried at room temperature and 0.1 mm were unsatisfactory and indicated that the sample was contaminated with diglyme. When dried at 120° and 0.2 mm for 3 hours the compound (115) turned a reddish-purple colour and gave analytical figures in good agreement with an equimolar mixture of alloxan monohydrate and p-toluidine-alloxan anil (116). Reduction of the mixture with sodium borohydride gave 7-p-tolyluramil (83; R=Me, R'=H) and sodium dialurate and the infrared and ultraviolet light absorption spectra of the mixture were identical with the spectra of an artificial mixture of the two components. The compound (115) was readily hydrolysed to p-toluidine and sodium alloxanate by dilute sodium hydroxide and when heated under reflux in aqueous-ethanol it was converted into the p-toluidine salt of alloxanic acid (84; R=Me,R'=H) and the salt of the uramil (86; R=Me, R'=H).

The deep red p-toluidine-alloxan anil (116) was obtained from p-toluidine and anhydrous alloxan in acetic acid. It was very soluble in water and was readily decolourized by warming the solution. When kept in acetic acid it was slowly converted into 5-methyldioxindole-3-carboxyureide (72; R=Me, R'=H) and when reduced with sodium boro-

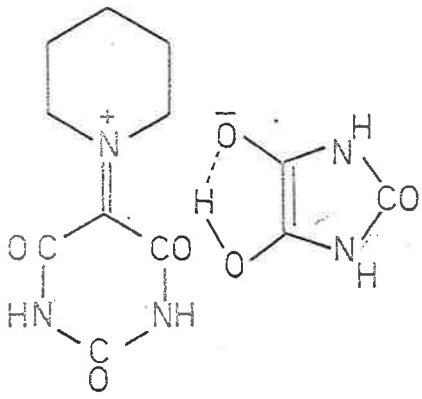


(116)

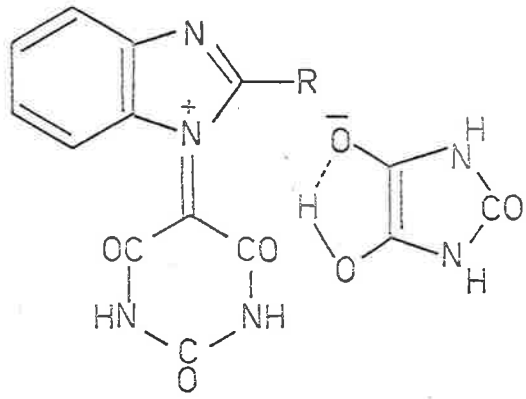
hydride it gave 7-p-tolyluramil (83; R=Me, R'=H).

Part 3.

Piperidine reacts with alloxan monohydrate in aqueous ethanol to give the piperidine salt of alloxanic acid[38], but with anhydrous alloxan in diglyme or tetrahydrofuran 5,5-dipiperidinobarbituric acid (106) was obtained. The reaction has now been carried out in acetic acid with anhydrous alloxan and the product is thought to be the salt (117) on the basis of analytical data, physical and chemical properties, and hydrolysis products. The vigorous exothermic



(117)



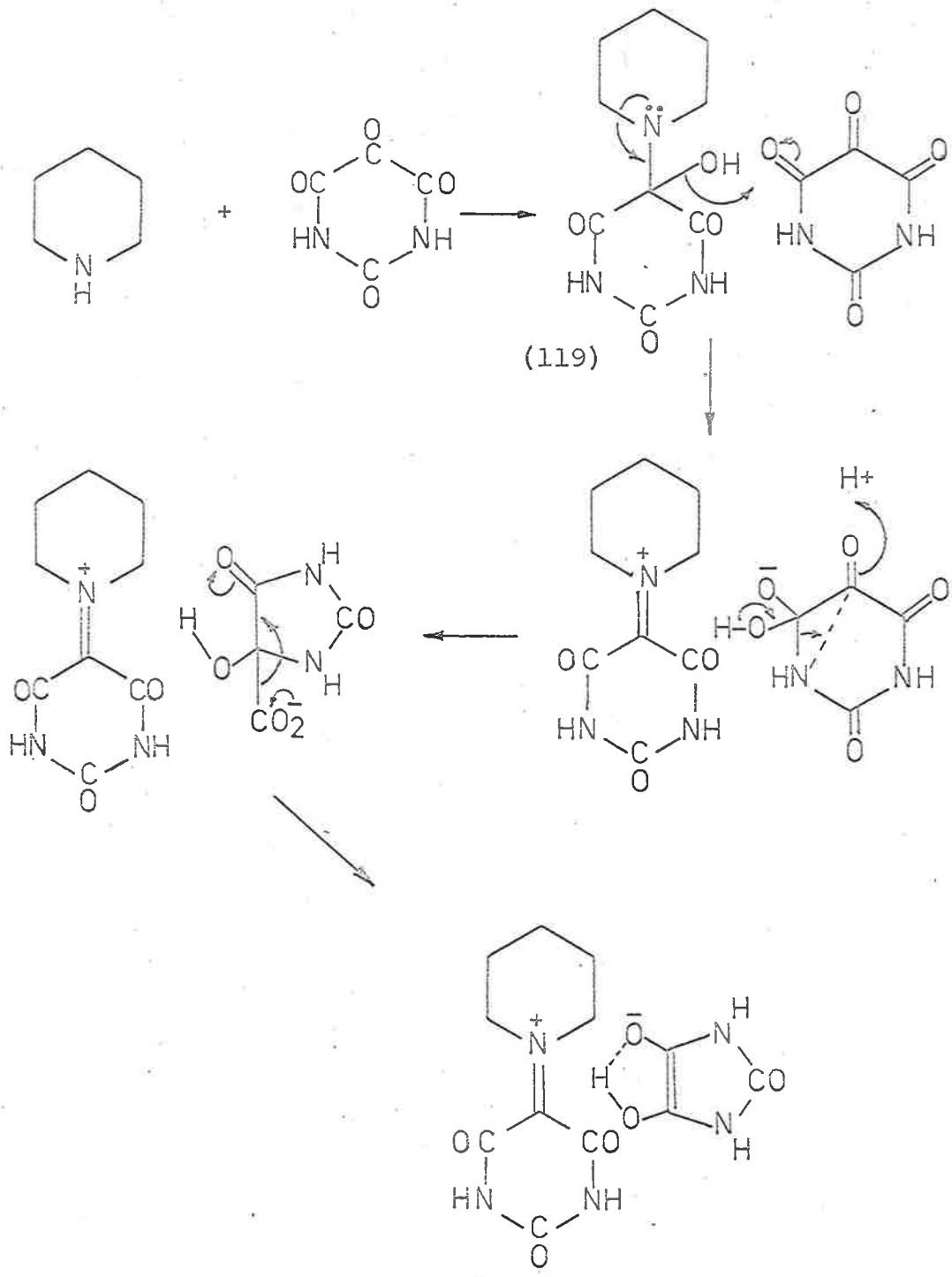
(118)

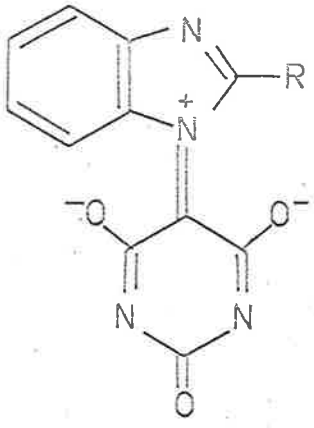
reaction was accompanied by the evolution of carbon dioxide and after 5 to 10 minutes the highly crystalline product was precipitated in reddish-brown plates with a green lustre. It was slightly soluble in water and alcohol but completely insoluble in a wide variety of other organic solvents. Benzimidazole and 2-methylbenzimidazole behaved similarly to

piperidine and the analogous products (118; R=Me or H) were obtained. A possible route to these compounds is illustrated for piperidine in figure 10. The initial step is envisaged as formation of the 5-(1'-piperidino) dialuric acid (119) which causes ring-contraction of a second alloxan molecule by the concerted process shown and subsequent decarboxylation of the alloxanate anion formed yields the final product. The proposed mechanism involves known reactions of alloxan and the final decarboxylation is not unexpected since decarboxylation of alloxanic acid to 5-hydroxyhydantoin occurs readily under mild conditions[84].

Alkaline hydrolysis of the salts (117) and (118) resulted in an initial deep blue colour which disappeared when the solution was boiled and eventually gave a yellow solution. The final products of the hydrolyses were the amines (benzimidazole, 2-methylbenzimidazole, or piperidine) and the transient blue colour was thought to be associated with paraquinonoid structures (e.g. 120). Alkaline hydrolysis might be expected to proceed by attack of hydroxyl ions on the cation (121, arrows) to give the dialuric acid intermediate (122) which would then be hydrolysed to the amine and alloxan. Acid hydrolysis of the salts (117) and (118) occurred readily and alloxantin was obtained from the hydrolysis mixture while basification of the acid solutions gave

Fig. 10





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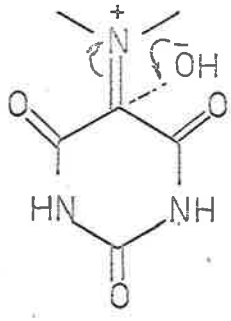
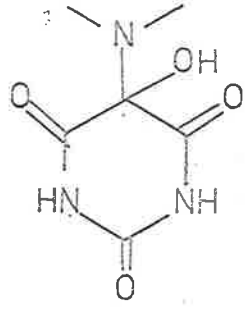
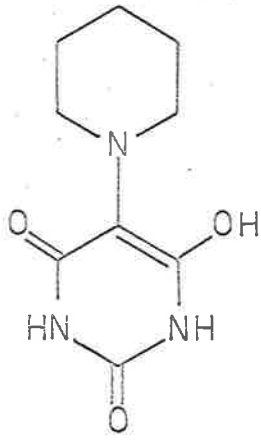


(121)



(122)

the amines (piperidine, benzimidazole, or 2-methylbenzimidazole). The compounds (117) and (118) were slowly decolourized by hot water and gave 5-piperidinobarbituric acid (123) and benzimidazolylbarbituric acids (124; R=H or Me) respectively as well as extremely insoluble, colourless compounds



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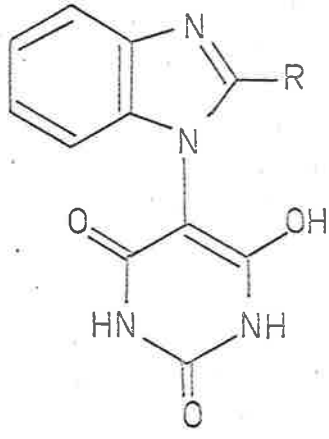
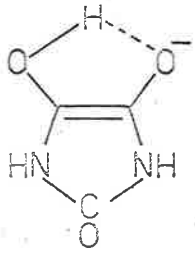


(124)

which have not been identified. The structures of the barbituric acids (123 and 124) were established by analyses, nuclear magnetic resonance, and ultraviolet light spectra. The nuclear magnetic resonance spectrum of 5(1'-benzimidazolyl) barbituric acid (124; R=H) in deuterium oxide containing sodium deuteroxide showed the 2'-proton as a single 1-proton peak at 2.28 while the aromatic protons absorbed as two 2-proton multiplets centred at 2.65 and 3.18. The spectrum of 5-piperidinobarbituric acid (123) in deuterium oxide containing sodium deuteroxide showed a 4-proton multiplet at 7.30 and a 6-proton multiplet at 8.81 due to the 2',6' and to the 3', 4', 5' protons of piperidine respectively.

Aqueous and acidic solutions of the salts (117) and (118) exhibited reducing properties indicated by the isolation of the barbituric acids (123 and 124), and alloxantin from the respective solutions. The reducing character of these compounds (117 and 118) is presumably associated with the 5-hydroxyhydantoin anion (125), which is analogous to known reducing agents, e.g. reductic acid (126) and reductones[85] (e.g. 127).



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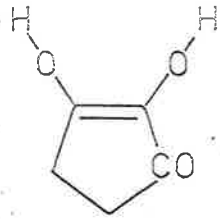
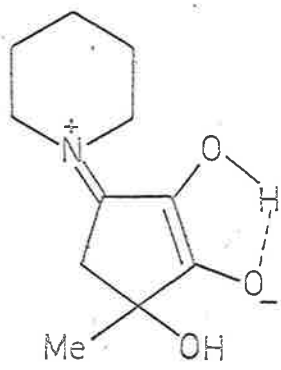


(126)



(127)

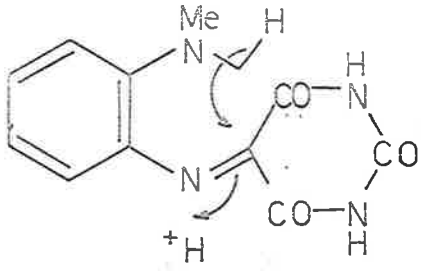
Part 4.

Although a number of reactions involving alloxan are readily explained by its electrophilic character there are others which undoubtably involve free radicals. The electrophilic character of alloxan is associated with the 5-carbon atom which because of its situation between two electron-withdrawing amide functions, is deficient in electrons and it is here that alloxan undergoes reaction with nucleophiles, e.g. with water to form a stable monohydrate. With anilines the initial products are 5-phenylaminodialuric acids (114), 5,5-diphenylaminobarbituric acids (105), and alloxan-anils (e.g. 116), but these compounds are easily hydrolysed in aqueous solutions and are only isolated under suitable conditions. Compounds formed by irreversible processes are those normally obtained, e.g. dioxindole - carboxyureides (72) and 5-phenyldialuric acids (83) which are formed by electrophilic attack by alloxan on the aromatic ring either ortho or para to the amino group. In suitable cases further reaction of the initial anils (or 5-phenylaminodialuric acids) may occur, as in the formation of the benzoxazone (99) from anthranilic acid. The reaction of di-primary and primary-secondary o-phenylenediamines presumably involves initial formation of the alloxan anil, followed by nucleophilic attack of the o-amino group on the 4-carbonyl of the alloxan ring, and subsequent ring-opening or

dehydration gives either the quinoxaline-carboxyureides (13) or the alloxazines (11) and isoalloxazines (12). Alloxanic acid salts (84) are also obtained by the irreversible base-catalysed ring-contraction of alloxan.

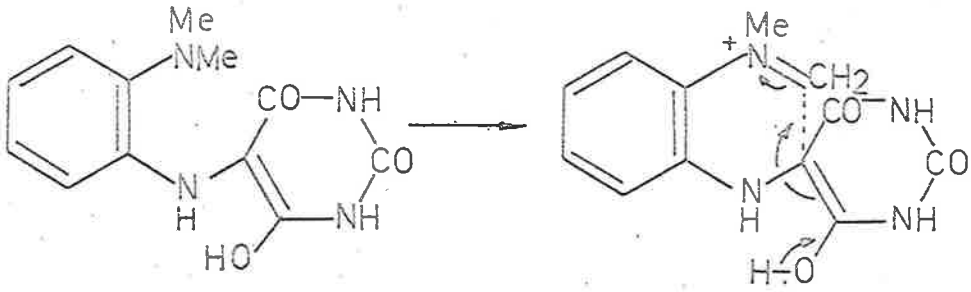
During the course of this investigation it became apparent that oxidation and reduction reactions were occurring and the recently reported[73,74] existance of an alloxan free radical provided evidence for the suspected participation of one-electron processes. The presence of alloxantin in these reactions was indicated by the isolation of 7-phenyluramils (83), and the formation of alloxantin presumably involves dimerisation of alloxan radicals formed from alloxan by oxidation of the anilines or solvent ethanol.

The reaction of alloxan with o-dimethylaminoaniline to give the spiran (41) and the formation of the benzimidazolium barbiturates (e.g. 51) from other o-dialkylaminoanilines are unusual and the mechanisms involved in the two alternative cyclisations have not yet been clarified. The acid-catalysed cyclisation of the anil (128, arrows) appears to be unlikely and moreover, it does not provide an explanation for the observed difference in the reaction of o-dimethylamino- and other o-dialkylaminoanilines. The participation of free radicals in this reaction has gained support



(128)

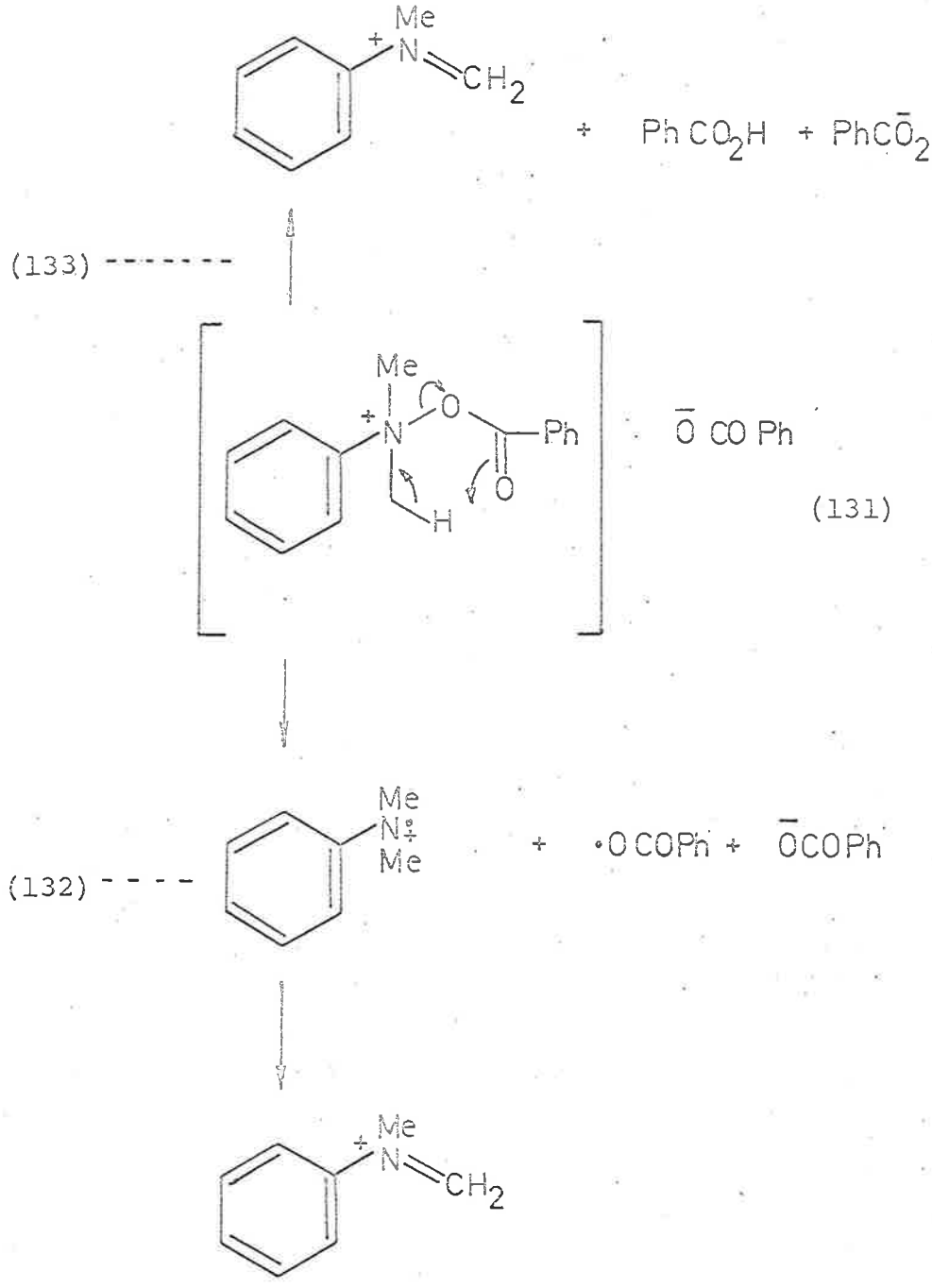
from the demonstration by e.s.r.[86] that free radicals are present in the reaction mixture. A mechanism with some experimental support involves cyclisation of an intermediate (130, arrows) formed by oxidation of the phenyluramil (129)



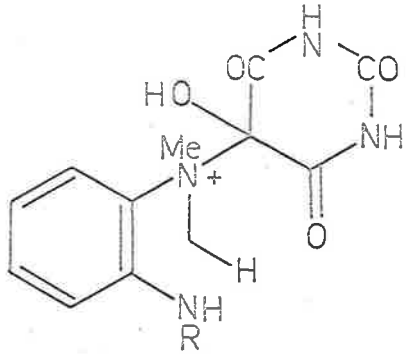
(129) (130)

(a similar ring-closure has recently been reported for alkaloid biosynthesis[87]). The formation of the uramil (129) would not be unexpected because analogous 7-phenyluramils have been isolated from similar reactions (see p.47), and the oxidation (129 to 130) is analogous to the known oxidation of the spiran (41) to the betaine (46). The oxidation of dihydrobenzimidazoles (e.g. 67) to benzimidazolium salts is also somewhat similar. The oxidation of dialkylanilines by benzoyl peroxide has been studied extensively by Horner et al[88]., and Walling[89] but this reaction is not fully understood. Free radicals are involved and these appear to arise from the breakdown of an initial unstable polar addition product (131). There is extensive evidence for the formation of (131) but subsequent steps are not so well substantiated. Walling[89] suggested that the reaction may proceed by hydrogen abstraction from the aminium radical (132) or by loss of a proton from the quarternary hydroxylamine (133) (the latter reaction may be aided by the six-membered transition state shown). Walling[89] gives as evidence supporting a non-radical path (133) the low efficiency of the system as a polymerisation initiator.

By analogy with the above oxidation alloxan may well be involved in the oxidation of the uramil (129) to the intermediate (130) via the quarternary uramil (134). Breakdown


Me
N
CH2
+ PhCO2H + PhCO2
(133)
Me
N
O
Ph
O
H
O CO Ph
(131)
Me
N
Me
(132)
+ ·O COPh + OCOPh

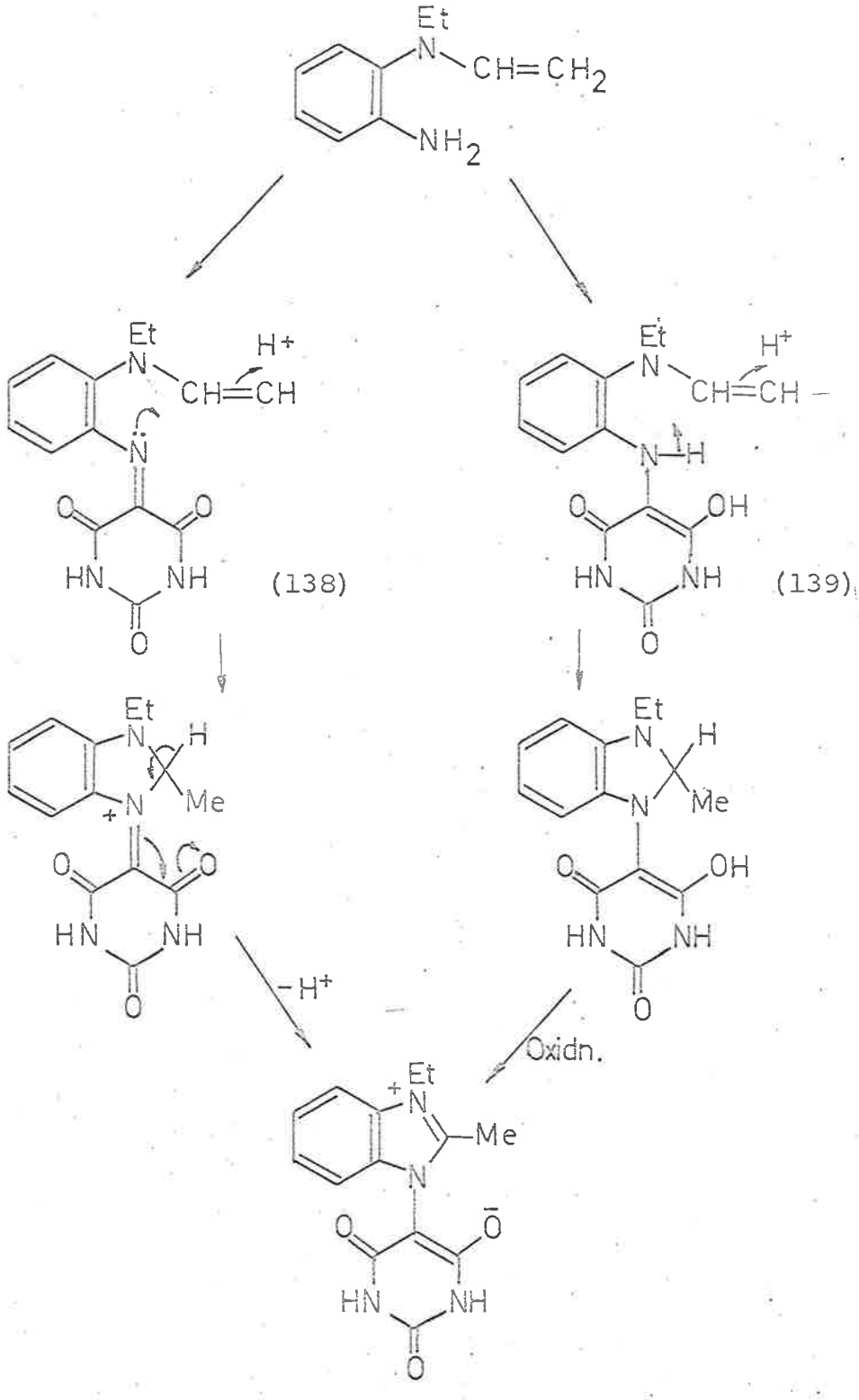
of this product (134) by a process analogous to reactions 132 or 133 would give the intermediate (130) and either dialuric acid or alloxan radicals. The difference in the



(134)

(135) (136)

behaviour of o-dimethylaminoaniline and o-diethylaminoaniline results from the ability of the intermediate (135), formed from the latter compound, to lose a proton. The intermediate (135) is in fact the conjugate acid of the corresponding enamine (136). Walling and Indictor[99] isolated the unstable enamine (137) from the reaction of triethylamine with benzoyl peroxide. Cyclisation of (138) and (139), obtained from the

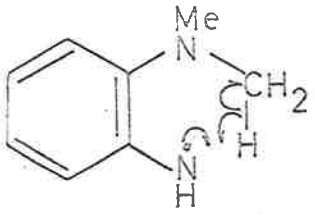

Et
N
CH=CH2
NH2
H+
CH=CH
(138)
(139)
OH
HN
NH
O
Me
H
-H+
Oxidn.

$$(C_2H_5)_3N \longrightarrow (C_2H_5)_2\overset{+}{N}{=}CHCH_3 \longrightarrow (C_2H_5)_2{:}N{-}CH{=}CH_2$$

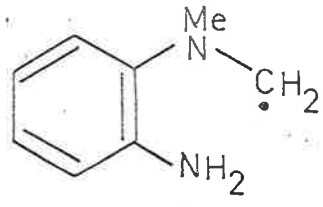
(137)

enamine (136), would yield the benzimidazolium barbiturate.

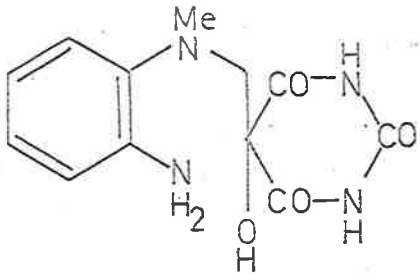
An alternative mechanism for the formation of the spiran (41) involves abstraction of a hydrogen atom from the primary amino group of the o-dimethylaminoaniline to give the radical (140) followed by intramolecular abstraction of a hydrogen atom from the suitably placed N-methyl group to give a radical (141). Combination of this with an alloxan radical would give the dialuric acid (142) which could then cyclise to the spiran. The intermediate radical (143), obtained from o-diethylaminoaniline, may undergo hydrogen abstraction or disproportion ation to give the enamine (136) which may cyclise to the benzimidazolium barbiturate via intermediates (138) and (139(as before.



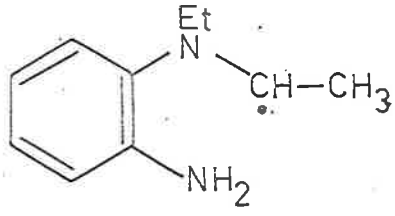
(140)



(141)



(142)



(143)

The diverse products obtained from reactions involving alloxan result from the variety of reactions in which it can participate. The apparent ease with which the initial products react further also accounts for the complexity of products isolated from these reactions.

EXPERIMENTAL

Nuclear magnetic resonance spectra were determined with a Varian DP60 spectrometer and calibrated with side bands generated by a Muirhead-Wigan decade oscillator (D890A) from the signal of tetramethylsilane used as an internal standard. Chemical shifts are given in τ values Infrared spectra were recorded with an Infracord, and ultra violet light absorption measurements were made with Optica and Unicam SP700 recording spectrophotometers and with a Hilger Uvispek. Melting points are uncorrected.

1,2,3,4-Tetrahydro-4-methylquinoxaline-2-spiro-5'-(hexadro-2',4',6'-trioxopyrimidine) (41) and its 1',3'-Dimethyl Derivative (44)

(a) The spiran was prepared (19%) according to King and Clark-Lewis [37] and was crystallized from aqueous pyridine in small yellow plates, m.p.250° (decomp.). The infrared spectrum showed carbonyl absorption near 5.72, 5.80, and 5.95 μ and N-H stretching absorption near 3.06 and 3.11 μ (Nujol). The 1',3'-dimethyl derivative was prepared by methylation of the spiran (suspended in methanol), with diazomethane. It crystallized from ethanol in pale yellow prisms, m.p.194° and its infrared spectrum showed carbonyl absorption near 5.95 μ (with a weak band at 5.75 μ), and

N-H stretching absorption near 2.95 μ ($CHCl_3$). The n.m.r. showed four sharp peaks at 3.23 (four aromatic protons), 6.68 (six protons of 1',3'-dimethyl groups), 6.75 (two protons of the 3 methylene group) and 7.11 (three protons of the 4-methyl group).

(b) 1,2-Dihydro-4-methylquinoxalinium-2-spiro-5'-barbiturate (1g) in water (20ml) was treated with an excess of sodium borohydride (0.5g), in small portions, over a period of 30 min. During this time the quinoxalinium barbiturate dissolved and acidification with acetic acid precipitated the spiran (0.87g, 98%) in small yellow plates m.p. 250° (decomp.) alone and when mixed with that described under (a). Reduction of 1,2-dihydro-4-methylquinoxaline-2-spiro-5'-(hexahydro-1',3',-dimethyl-2',4',6' trioxo pyrimidine) Betaine (0.1g) during a period of 2 hours with sodium borohydride gave the dimethyl spiran. It crystallized from ethanol in pale yellow prisms (0.05g, 53%), m.p. 194° undepressed by admixture with a sample prepared as described under (a).

1,2,3,4-Tetrahydro-4-methyl-1-nitroso quinoxaline-2-spiro-5'-(hexahydro-2',4',6'-trioxopyrimidine) (45).

The nitroso-derivative was prepared by adding sodium nitrite (0.17g) in water (2ml) dropwise to the dimethyl

spiran (0.65g) dissolved in acetic acid (6ml). The product crystallized in golden yellow needles (0.6g, 85%) from the deep yellow solution after chilling. 1,2,3,4-Tetrahydro-4-methyl-1-nitroso-2-spiro-5'-(hexahydro-2',4',6'-trioxo-1',3'-dimethyl pyrimidine) crystallized from ethanol in needles, m.p. 176° (Found : C, 53.4; H,5.1; N, 22.3%. $C_{14}H_{15}N_5O_4$ requires C,53.0; H, 4.8; N, 22.1%). Carbonyl absorption occurred near 5.95 μ (with a weak band at 5.75 μ) and the spectrum was devoid of absorption in the region 2.5-3.1 μ ($CHCl_3$).

1,2,3,4,2',4'-Hexahydro-2',4'-dioxo-4,3'-dimethyl glyoxalino (1'5':1,2) quinoxaline (43).

Methylamine was evolved and potassium carbonate precipitated when 1,2,3,4-tetrahydro-4-methylquinoxaline-2-spiro-5'-(hexahydro-1',3'-dimethyl-2',4',6'-trioxo pyrimidine (1g) was boiled with 5% alcoholic - potassium hydroxide (20 ml). The solution was acidified with dilute hydrochloric acid after 3-5 mins., and extracted with chloroform. 1,2,3,4,2',4'-Hexahydro-2',4'-dioxo-4,3'-dimethylglyoxalino (1',5':1,2) quinoxaline (0.5g, 62%) was obtained on evaporation of the extract. It crystallized from ethanol in prisms, m.p. 154° alone and when mixed with a synthetic sample.[37] The identical infrared spectra (Nujol) of the two samples showed

carbonyl absorption near 5.70 and 5.88 μ . The n.m.r. spectrum (CCl_4 with c. 10% $CDCl_3$) revealed the 8 proton as a doublet with secondary splitting at very low field (centre 2.11) due to deshielding by the 2'-carbonyl group. The remaining three aromatic protons formed a multiplet which was not analysed; the 2H-quartet was centred at 5.78, one of the quartet due to the 3-methylene protons at 6.37, and only the outside peaks of the remaining quartet (centre 6.97) were visible owing to overlap with absorptions by the two N-methyl groups (6.98 and 7.05).

1,2-Dihydro-4-methylquinoxalinium-2-spiro-5'-barbiturate (46)

(a) This was obtained from 0-dimethylamino aniline and alloxan, or from 1,2,3,4-tetrahydro-4-methylquinoxaline-2-spiro-5'-(hexahydro-2',4',6'-trioxopyrimidine) by the method described by King and Clark-Lewis [56] for 1,2,3,4-tetrahydro-3-hydroxy-4-methylquinoxaline-2-spiro-5'-(hexahydro-2',4',6'-trioxopyrimidine). It crystallized from water as colourless prisms m.p. 370-375° (decomp.). Light absorption in ethanol (95%): max. 248 (ε 18,700), 268 (ε 7,400), and 275 mμ (ε 5,900); min. 228 (ε 7,300), 266 (ε 7,200), and 272 mμ (ε 5,800).

(b) The 7-Bromo-1,2-dihydro-4-methylquinoxalinium-2-spiro-5'-barbiturate (see below) (0.1g) was warmed for

2 hours with an aqueous suspension of W7 Raney nickel. The solution was then filtered, acidified with acetic acid, evaporated, and the residue crystallized from water. The debrominated barbiturate (0.05g, 60%) crystallized in prisms m.p. 370-375° (decomp.) and was found to be identical (mixed m.p. and ultra violet light absorption) with that described under (a).

(c) 6,7-Dichloro-1,2-dihydro-4-methylquinoxalinium -2-spiro-5'-barbiturate (0.4g) was warmed with a suspension of W7 Raney nickel in water (20 ml) for 3-4 hours. Filtration of the solution, evaporation of the filtrate and crystallization of the residue from water gave the dechlorinated barbiturate (0.12g, 35%) identical with that described under (a).

6,7-Dichloro-1,2,3,4-tetrahydro-4-methylquinoxaline-2-spiro-5'-(hexahydro-2',4',6'-trioxopyrimidine).

6,7-Dichloro-1,2-dihydro-4-methylquinoxalinium-2-spiro-5'-barbiturate (previously described[56] as a 6,7-dichloro-3-hydroxyquinoxaline) (0.3g) in water (20 ml) was treated with an excess of sodium borohydride. The starting material dissolved during a period of 3 hours and after acidification of the solution with acetic acid it was stored at 4° overnight. The precipitated 6,7-Dichloro-1,2,3,4-tetra-

hydro-4-methylquinoxaline-2-spiro-5'-(hexahydro-2',4',6'-trioxopyrimidine) (0.28g, 98%) was collected by filtration and washed with ethanol. Recrystallization from aqueous pyridine gave small, pale yellow plates, m.p. 238° (Found: C, 44.4; H, 3.3; Cl, 20.9; N, 17.1%. $C_{12}H_{10}Cl_2N_4O_3$ requires C, 43.8; H, 3.1; Cl, 21.5; N, 17.0%). Ultra violet light absorption in 95% ethanol: max. 230 (ϵ 21,600) and 312 (ϵ 4,200), and a shoulder at 260 mμ (ϵ 5,500); min. 295mμ (ϵ 1,900).

1,2-Dihydro-4-methylquinoxaline-2-spiro-5'-(hexahydro-1',3'-dimethyl-2',4',6'-trioxopyrimidine) Betaine (48)

A suspension of 1,2-Dihydro-4-methylquinoxalinium-2-spiro-5'-barbiturate (1g) in methanol (100 ml) at 0° was treated with a large excess of diazomethane. After storage at 0° overnight the unreacted starting material (0.7g) was filtered off and the filtrate evaporated. Crystallization of the residue from methanol gave 1,2-dihydro-4-methylquinoxaline-2-spiro-5'-(hexahydro-1',3'-dimethyl-2',4',6'-trioxopyrimidine) Betaine (0.1g) in needles, m.p. 331-333° undepressed when mixed with a sample previously prepared [56] by oxidation of 1,2,3,4-tetrahydro-4-methylquinoxaline-2-spiro-5'-(hexahydro-1',3'-dimethyl-2',4',6'-trioxopyrimidine) (Found: C, 55.2; H, 5.4; N, 18.5%. $C_{14}H_{14}N_4O_3.H_2O$ requires

C, 55.2; H, 5.3; N, 18.4%). The infrared spectrum (nujol) showed carbonyl absorption at 6.0 μ and in the n.m.r. (dimethylsulphoxide) the 2-proton absorbed at 0.37.

7-Bromo-1,2-dihydro-4-methylquinoxalinium-2-spiro-5'-barbiturate Hydrate (46)

4-Bromo-2-nitrodimethylaniline, m.p. 68°, was obtained by bromination of 2-nitrodimethylaniline in acetic acid[100]. It was reduced by tin and hydrochloric acid to 2-amino-4-bromodimethylaniline, b.p. c.170°/25m.m., acetyl derivative, m.p. 111° (lit.[101] b.p. 165°/23mm., deriv. m.p. 111°). The diamine (5g) in ethanol (25 ml) was added to alloxan monohydrate (5g) dissolved in water (10 ml) containing concentrated hydrochloric acid (3 drops). The solution deposited solid after 15 hours at room temperature and the product (4g) was collected after 3 days. It was extracted with boiling water and with pyridine. Crystallization of the water soluble pyridine insoluble fractions from water (charcoal) gave 7-Bromo-1,2-dihydro-4-methylquinoxalinium-2-spiro-5'-barbiturate Hydrate (1.4g, 19%), in long needles, m.p. 360-365° (decomp.), d 1.752 (Found: C, 40.7; H, 3.2; N, 15.2; O, 18.4%. $C_{12}H_9BrN_4O_3.H_2O$ requires C, 40.6; H, 3.1; N, 15.8; O, 18.0%). Light absorption in 95% ethanol: max. at 210 (ε 29,100), 247 (ε 21,000), 278 (ε 8,000), and 286 mμ (ε 7,100);

min. at 231 (ϵ 12,000), 267 (ϵ 6,000), and 282 mμ (ϵ 7,000). The dimensions of the unit cell of the triclinic crystals were found[60] to be a 7.23; b 9.08; c 12.07 Å; α 63.5°; β 106°; γ 99.5°. The molecular distribution was possibly non-centric.

5-(3'-Ethyl-2'-methylbenzimidazolium) barbiturate Trihydrate (51)[59]

o-Nitrodiethylaniline[102] was obtained as a red oil, b.p. 114-116°/1m.m. (bath temp. 150°) without decomposition, and gave a picrate, m.p. 122° (lit.[102] m.p. 122-123°). The diamine (17.0g, 81 %) b.p. 130-131°/30m.m. (bath temp. 170°) (lit.[102] b.p. 127/25m.m.) was obtained by hydrogenation over Raney nickel. o-Aminodiethylaniline (10g) in ethanol (70ml) containing hydrochloric acid (10 drops) was mixed with alloxan monohydrate (15g) in water (40ml). The product precipitated over a period of 4 days at room temperature and was collected by filtration and washed with ethanol. Crystallization from water gave the barbiturate trihydrate (5.2g, 25%) in large prisms, m.p. c.396° (decomp.) (Found: C, 49.2; H, 5.9; N, 16.5; O, 28.9%. $C_{14}H_{14}N_4O_3.3H_2O$ requires C, 49.4; H, 5.9; N, 16.5; O, 28.2%). Light absorption in water: max. at 247 (ϵ 22,100), 270 (ϵ 9,500), and 276 mμ (ϵ 8,900); min. at 228 (ϵ 8.700), 266 (ϵ 8,500), and 273 (ϵ 6,700). When

dried over phosphoric oxide it gave a hemihydrate, m.p. c. 396° (decomp.) (Found: C, 56.6; H, 5.1; N, 19.0; O, 19.0%. $C_{14}H_{14}N_4O_3.\frac{1}{2}H_2O$ required C, 56.9; H, 5.1; N, 19.0; O, 18.9%). The n.m.r. spectrum of the betaine in trifluoroacetic acid showed four aromatic protons as a multiplet centred at 2.28, the methylene and methyl protons of the ethyl group at 5.44 and 8.29, and a single peak at 7.12 due to the 2' methyl group. The barbiturate was recovered (65%) after being boiled with 20% aqueous sodium hydroxide for 3½ hours, and it was recovered quantitatively from a solution in 30% aqueous sodium hydroxide which had been stored at room temperature for 3 days. It was also recovered after being heated in concentrated sulphuric acid. Reduction of the betaine with sodium borohydride occurred slowly and after 12 hours the ultra violet light absorption of the solution corresponded to that of a benzimidazoline, but acidification yielded the original benzimidazolium barbiturate.

Alkali fusion of 5-(3'-Ethy)-2'-methylbenzimidazolium) barbiturate.

The betaine (2g) was fused with a 1:1 mixture of potassium and sodium hydroxides (2g) for several minutes. The residue was dissolved in water (25 ml) and extracted several times with ether. Evaporation of the dried (Na_2SO_4) extract

and distillation of the residue under reduced pressure gave a pale yellow viscous oil (0.2g, 21%) with light absorption typical of benzimidazoles. The hydrochloride crystallized from methanol-ether in prisms, m.p. 191° not depressed by admixture with the hydrochloride (m.p. 193-194°) prepared from authentic 1-ethyl-2-methylbenzimidazole (see below).

5-(3'-Ethyl-2'-methylbenzimidazolium)-1,3-dimethylbarbiturate (52).

5-(3'ethyl-2'-methylbenzimidazolium) barbiturate (0.9g) was suspended in methanol (100 ml) at 0° and treated with a large excess of ethereal diazomethane. After 15 hours the unreacted material (0.6g) was removed by filtration and evaporation of the filtrate afforded the dimethylbarbiturate (0.2g, 23%) which crystallized from acetone in large prisms, m.p. 285-286° (Found: C, 60.8; H, 6.2%. $C_{16}H_{18}N_4O_3.H_2O$ required C, 60.7; H, 6.4%). The n.m.r. spectrum in $CDCl_3$ showed a single peak at 2.5 due to four aromatic protons, the N-ethyl quartet at 5.67 and triplet at 8.45, a six proton peak at 6.64 (1,3-dimethyl groups) and a three proton peak at 7.29 (2'-methyl group).

4-Bromo-2-nitro-diethylaniline and 4-Bromo-2-nitro-N-ethylaniline

Bromine (5.2g) in acetic acid (10 ml) was added to o-nitrodiethylaniline (6g) in acetic acid (20 ml) during 45 min., and the mixture was stirred at 60° for 12 hours. Thin-film chromatography on silica gel plates developed with benzene-hexane (1:9) mixture indicated the presence of two products. The mixture was separated by chromatography on an alumina column with hexane as eluent 4-Bromo-2-nitro-N-ethylaniline[103] (1.9g, 25%) crystallized from ethanol or hexane in orange-red prisms m.p. 91° (Found: C, 39.4; H, 4.0; Br, 31.1%. $C_8H_9BrN_2O_2$ requires C, 39.2; H, 3.7; Br, 32.6%). 4-Bromo-2-nitro diethylaniline (4.1g, 49%) was obtained as an orange red oil b.p. 129.130°/0.7 mm, n_D^{25} 1.5943 (Found: C, 44.1; H, 4.8; Br, 29.1%. $C_{10}H_{13}BrN_2O_2$ requires C, 44.0; H, 4.8; Br, 29.3%). Reduction of 4-Bromo-2-nitrodiethylaniline with tin and hydrochloric acid gave 2-amino-4-bromodiethylaniline (82%) as a colouless oil, b.p. 150°/2.5mm, n_D^{26} 1.5810 (Found: C, 49.2; H, 6.0; Br. 33.0%. $C_{10}H_{15}BrN_2$ requires C, 49.4; H, 6.2; Br, 32.9%).

5-(6'-Bromo-3'-ethyl-2'-methylbenzimidazolium) barbiturate (51; R=Br)

Alloxan hydrate (12g) in water (40 ml) was added to a mixture of 2-amino-4-bromodiethylaniline (10g), ethanol (70 ml), and hydrochloric acid (5 drops). After standing for three days at room temperature the precipitated 5-(6'-bromo-3'-ethyl-2'-methylbenzimidazolium) barbiturate (1.2g, 8.0%) was collected and crystallized from water (charcoal) in large prisms, m.p. c. 400° (decomp.), d 1.652 (Found: C, 44.0; H, 3.8; Br, 21.4; N, 14.1; O, 17.2%. $C_{14}H_{13}BrN_4O_3.H_2O$ requires C, 43.9; H, 3.9; Br, 20.9; N, 14.6;), 16.7%). Light absorption in 95% ethanol: max. at 209 (ϵ 40,300), 247 (ϵ 23,700), 279 (ϵ 10,000), and 287 mμ (ϵ 9,200); min. at 233 (ϵ 13,300), 266 (ϵ 6,600), and 284 mμ (ϵ 8,100). The unit cell of the monoclinic prisms (space group $P2_1/n$) was found [60] to contain eight molecules and to have dimensions a 8.687 $\pm$ 0.004, b 14.995 $\pm$ 0.003, c 23.730 $\pm$ 0.004 A, and β95° 5.3 $\pm$ 1.5'. The bromo-compound (0.05g) was warmed for 1½ hours with an aqueous suspension of W7 Raney nickel. The catalyst was filtered off and the filtrate acidified with acetic acid and stored at 2-3°. 5-(3'-Ethyl-2'-methylbenzimidazolium) barbiturate (0.02g, 45%) crystallized in prisms, m.p. c.396° (decomp.) identical (m.p., infrared

and ultraviolet spectra) with the material already described.

5,7,7-Trimethyl-2,3-benzo-1,4-diazepine (62)

This compound was prepared according to Elderfield and McCarthy[63] (compare ref.[64] and it crystallized from light petroleum, b.p. 40-60, in large prisms, m.p. 125° (lit.[63, 65] m.p. 125°). The benzodiazepine structure was confirmed by the n.m.r. spectrum ($CDCl_3$) which showed four aromatic protons in a multiplet, a single proton peak at 7.08 (NH), a three proton peak at 7.63 (5 methyl group), and a six proton peak at 8.66 (7,7-dimethyl group).

1,2,3-Trimethylbenzimidazoline (66)

1,2,3-Trimethylbenzimidazolium iodide[104] crystallized from ethanol in plates, m.p. 256° . An aqueous solution (25 ml) of the iodide (2g) was treated during 45 min. with excess sodium borohydride. The reaction mixture was extracted within ether, and evaporation of the dried ($MgSO_4$) extract left a residue which on distillation gave 1,2,3-trimethylbenzimidazoline (1.6g, 90%) as an oil, b.p. 110°/3mm, n_D^{27} 1.5710, unstable on exposure to air (Found: C, 74.0; H, 8.8%. $C_{10}H_{14}N_2$ requires C, 74.0; H, 8.7%). Light absorption in 95% ethanol: max 218 (ϵ 33,100), 266 (ϵ 5,700),

and 310 (ϵ 5,700); min. 243 (ϵ 4,200) and 286 mμ (ϵ 3,100). The n.m.r. spectrum of the compound (in CCl_4) showed a four proton multiplet (aromatic protons), a quartet at 6.0 due to the 2-H, a six proton peak at 7.38 (N-methyl groups), and a three proton doublet (5 c/s splitting) at 8.54 (C-methyl group). Addition of dry hydrogen chloride to an ethereal solution of the benzimidazoline gave 1,2,3-trimethylbenzimidazolium chloride, which crystallized from ethanol-ether as a dihydrate in prisms m.p. 227° (lit.[105] m.p. 225-230°) (Found: C, 51.7; H, 7.9; N, 11.8%. Calc. for $C_{10}H_{13}ClN_2 \cdot 2H_2O$: C, 51.6, H, 7.4; N, 12.0%).

1,3-Diethyl-2-methylbenzimidazoline (65)

1-Ethyl-2-methylbenzimidazole hydrochloride, m.p. 193-194°, was converted into 1,3-diethyl-2-methylbenzimidazolium iodide[106] which crystallized from ethanol in prisms m.p. 200°, and reduction of this compound with sodium borohydride as described for the trimethylanalogue gave 1,3-diethyl-2-methylbenzimidazoline as a colourless oil, b.p. 74-75°/0.5 mm, n_D^{26} 1.6376 (Found: C, 75.9; H, 9.4%. $C_{12}H_{18}N_2$ requires C, 75.7; H, 9.5%). Light absorption in 95% ethanol: max. at 220 (ϵ 26,400), 268 (ϵ 5,000), and 315 mμ (ϵ 4,600); min, at 242 (ϵ 3,700), and 292 mμ (ϵ 2,800).

1,3-Dimethylbenzimidazoline (67)

1,3-Dimethylbenzimidazolium iodide was prepared according to Fischer and Fussenegger[107] and crystallization from methanol yielded colourless prisms, m.p. 200-201° (lit.[108] m.p. 200-201°). The 2-proton absorbed as a singlet at 0.30 (dimethyl sulphoxide solution). Reduction with sodium borohydride gave 1,3-dimethylbenzimidazoline (81%) as a colourless oil, b.p. 86°/1.5 mm, n_D^{27} 1.5850 (Found: C, 72.7; H, 8.0%. $C_9H_{12}N_2$ requires C, 72.9; H, 8.2%). The n.m.r. spectrum (CCl_4) showed four aromatic protons in a multiplet, a two-proton peak (5.77) due to the methylene group and a six-proton peak (7.34) due to the N-methyl groups. Light absorption in 95% ethanol: max. 217 (ϵ 36,900), 265 (ϵ 5,700), and 310 mμ (5,700); min. at 241 (ϵ 3,400) and 286 mμ (ϵ 3,100). On treatment with ethanolic picric acid the benzimidazoline yielded 1,3-dimethylbenzimidazolium picrate, which crystallized from ethanol in needles, m.p. 195-196° alone and when mixed with an authentic specimen. The light absorption of the picrate in 95% ethanol showed the sharp maxima at 270 and 278 mμ typical of benzimidazolium salts.

1-Methyl-3-(2-oxopropyl) benzimidazolium Iodide and 1-Methyl-3-(2-hydroxypropyl) benzimidazoline

A mixture of benzimidazole (3g), chloroacetone (5ml),

anhydrous potassium carbonate (5g), and acetone (250 ml) was stirred under reflux for 19 hr. and then filtered. Evaporation of the filtrate left an oil, which solidified (2g, 45%), and recrystallization from ethylacetate gave 1-(2-oxopropyl) benzimidazole in needles m.p. 131° (Found: C, 69.1; H, 5.8; N, 15.8%. $C_{10}H_{12}N_2O$ requires C, 69.0; H, 5.8; N, 16.1%). The methiodide crystallized from ethanol in plates, m.p. 196° (Found: C, 42.4, H, 4.5; N, 8.4%). $C_{11}H_{13}IN_2O$ requires C, 41.8; H, 4.1; N, 8.9%). Reduction of the methiodide (0.5g) with sodium borohydride gave 1-methyl-3-(2-hydroxypropyl) benzimidazoline (0.45g) as a colourless oil, b.p. 156°/0.3 mm, n_D^{26} 1.5758 (Found: C, 67.9; H, 8.3; N, 14.8%. $C_{11}H_{16}N_2O$ requires C, 68.7; H, 8.4; N, 14.6%). Light absorption in 95% ethanol: max. at 220 (ϵ 23,000), 269 (ϵ 4,900), and 315 mμ (ϵ 4,500); min. at 242 (ϵ 3,600) and 292 mμ (ϵ 2,800).

7-Bromo-4-ethyl-3,4-dihydro-3-oxoquinoxaline-2-carboxyureide.

The 4-bromo-2-nitro-N ethylaniline already described was hydrogenated over Raney nickel, and the diamine (1.7g) in ethanol (25 ml) was mixed with alloxan monohydrate (1.3g) in water (10 ml), and the mixture was heated under reflux for 5 min. The 7-Bromo-4-ethyl-3,4-dihydro-3-oxoquinoxaline-2-carboxyureide (1.6g, 47%) was collected and crystallized

from ethanol as yellow needles, m.p. 230-232° (Found: C, 42.9; H, 3.6%. $C_{12}H_{11}BrN_4O_3$ requires C, 42.5; H, 3.3%). Light absorption in 95% ethanol: max. at 245 (ϵ 28,900), 312 (ϵ 6,900), and 395 mμ (ϵ 4,500); min. at 227 (ϵ 13,000), 275 (ϵ 3,300), and 340 mμ (ϵ 2,200).

Part 2.

5,6-Dimethyldioxindole-3-carboxyureide (72; R=R'=Me)

This material was prepared by the method previously described by Berezovski, Rodionova and Gurko[67] for 5-(3',4'-dimethylphenylamino) dialuric acid. It was also prepared by gently warming a solution of 3,4-xylidene (1.21g) and anhydrous alloxan (1.43g) in acetic acid (10 ml) until the initial red colour had disappeared and then precipitation of the product with water. The 5,6-dimethyldioxindole-3-carboxyureide (72; R=R'=Me) (1.8 g, 68%) was washed with ethanol and ether and it crystallized from a large volume of ethanol or water as colourless needles or plates, m.p. 204° (Found: C 54.7; H, 5.1; N, 15.6%. $C_{12}H_{13}O_4N_3$ requires C, 54.7; H, 5.0; N, 16.0%). Carbonyl absorption (Nujol) occurred near 5.75 and 5.90 μ while -NH and -OH absorption was observed at 2.95 and 3.00 μ .

5,6-Dimethoxydioxindole-3-carboxyureide (72; R=R'=OMe).

3,4-Dimethoxynitrobenzene, m.p. 98° (lit.[109] m.p. 96°) was prepared by nitration of 1,2-dimethoxybenzene[110]. Reduction with sodium sulphide[111] gave 3,4-dimethoxyaniline m.p. 88°, b.p. 180°/25 mm (lit.[112] m.p. 87.5-88°, b.p. 174-176°/22 mm). 3,4-Dimethoxyaniline (1.53g) and alloxan monohydrate (1.6g) were dissolved in 50% aqueous acetic acid (25 ml) and

heated under reflux. The reaction mixture rapidly changed colour from red to yellow and the reaction was completed after 5 minutes. The solvent was removed under reduced pressure and the product washed with ethanol. 5,6-Dimethoxydioxindole-3-carboxyureide (72; R=R'=OMe) (2.8g, 95%) crystallized from ethanol or water as colourless needles, m.p. 198° (Found: C, 44.8; H, 5.0; O, 32.6; N, 13.9%. $C_{12}H_{13}O_6N_3$ requires C, 48.8; H, 4.4; O, 32.5; N, 14.2%). The above reaction was also carried out in aqueous-ethanol and in this case the yield was only slightly less. The infrared spectrum showed carbonyl absorption near 5.75 and 5.95 μ while -NH, -OH bands occurred near 2.90 and 3.05 μ .

5-Methyldioxindole-3-carboxyureide (72; R=Me, R'=H).

A solution of anhydrous alloxan (1.43g) and p-toluidine (1.07g) in acetic acid (20 ml) was allowed to stand (with occasional warming to dissolve any precipitated anil) for three days. The colour of the reaction changed from red to yellow during this period and the colourless product precipitated. It was collected by filtration and washed free of contaminating anil with water. 5-Methyldioxindole-3-carboxyureide (0.8g, 31%) crystallized from water as colourless needles, m.p. 200° (Found: C, 51.7; H, 4.5; N, 16.0%. $C_{11}H_{11}O_4N_3.\frac{1}{2}H_2O$ requires C, 51.2; H, 4.7; N, 16.3%). Carbonyl

absorptions occurred near 5.75 and 5.95 μ while -NH and -OH stretching absorptions appeared at 2.95, 3.0 and 3.10 μ .

5,6-Dimethoxyisatin (75; R=R'=OMe).

5,6-Dimethoxydioxindole-3-carboxyureide (72; R=R'=OMe) (2.95g) was heated under reflux with 5% aqueous hydrochloric acid (20 ml) for 1 hour. The reaction mixture at this stage contained a brown suspension and evapouration to dryness under reduced pressure gave a brown oily solid. This solid was dissolved in 10% aqueous potassium hydroxide (10 ml) and the resulting yellow solution was filtered from a small quantity of undissolved material and then aerated for 1 hour. The solution was finally acidified with concentrated hydrochloric acid (10 ml) and allowed to stand at 2 to 3° for 10 hours. The precipitated, deep red 5,6-dimethoxyisatin (1.1g, 53%) was filtered and washed with water. It crystallised from aqueous-ethanol in deep-red needles m.p. 254° (lit.[113] 254°) (Found: C, 57.44; H, 4.27; N, 6.93. Calc. for $C_{10}H_9O_4N$: C, 57.97; H, 4.38; N, 6.76%). Light absorption in 95% ethanol: max. at 269 (ε 22,000), 320 (ε 7,500), and 470 mμ (ε 1,400); min. at 290 (ε 2,000), and 372 mμ (ε 400). The infrared spectrum ($CHCl_3$) showed absorption at 5.70 and 5.80 μ .

5,6-Dimethylisatin (75; R=R'=Me).

Hydrolysis of 5,6-dimethyldioxindole-3-carboxyureide (72; R=R'=Me) with 5% aqueous hydrochloric acid for 2 hours and then basification and aeration followed by re-acidification, as described above for the 5,6-dimethoxy- compound, gave 5,6-dimethylisatin (37%) as orange-red needles, m.p. 214° (lit.[114] 214°). The infrared spectrum ($CHCl_3$) showed carbonyl absorption at 5.70 and 5.80 μ .

5,6-Dimethoxyoxindole-3-spiro-1'-(oxazolidine-2',4'-dione) (75; R=R'=OMe) and its potassium salt.

5,6-dimethoxydioxindole-3-carboxyureide (72; R=R'=OMe) (1.5g) was treated with 50% aqueous potassium hydroxide (10 ml). Ammonia was liberated immediately and the dioxindole dissolved on stirring. The dipotassium salt of 5,6-dimethoxyoxindole-3-spiro-1'-(oxazolidine-2'-4'-dione) (1.8g, 92%) and crystallized from water/ethanol as colourless needles, m.p.c. 330-335° (decomp.) (Found: C, 33.9; H, 3.1; N, 7.4% $C_{12}H_8N_2O_6K_2.2H_2O$ requires C, 33.8; H, 3.1; N, 7.2%). The nuclear magnetic resonance spectrum in deuterium oxide showed the two aromatic protons as unsplit one-proton peaks at 3.03 and 3.21 and the two methoxy groups appeared as two three-proton peaks at 6.07 and 6.17. Acidification of an aqueous

solution of the salt (1.0g) with dilute sulphuric acid gave 5,6-dimethoxyoxindole-3-spiro-1'-(oxazolidine-2',4'-dione) (0.7g, 92 %) which crystallized from water as colourless prisms m.p. 195-196° (Found: C, 48.1; H, 4.5; N, 9.4%. $C_{12}H_{10}O_6N_2 . H_2O$ requires C, 48.6; H, 4.1; N, 9.5%). Carbonyl absorption (Nujol) occurred near 5.5, 5.7 and 5.8 μ while -NH absorption appeared at 2.75 and 3.1 μ .

5,6-dimethyloxindole-3-spiro-1'-(oxazolidine-2',4'-dione) (76; R=R'=Me).

Treatment of 5,6-dimethyldioxindole-3-carboxyureide (72; R=R'=Me) (1.3g) with 50% aqueous potassium hydroxide (7 ml) yielded the dipotassium salt of 5,6-dimethyloxindole-3-spiro-1'-(oxazolidine-2',4'-dione (1.4g, 87%). Acidification of an aqueous solution of the potassium salt (1.4g) with dilute sulphuric acid gave 5,6-dimethyloxindole-3-spiro-1'-(oxazolidine-2',4'-dione) (1.0g, 92%) as a colourless solid which crystallized from water in prisms, m.p. 99-100° (Found: C, 57.9; H, 4.2; N, 11.2%. $C_{12}H_{10}N_2O_4 . \frac{1}{4}H_2O$ requires C, 57.5; H, 4.2; N, 11.2%). Carbonyl absorption (Nujol) appeared near 5.5, 5.7 and 5.8 μ and an -NH stretching absorption occurred near 3.1 μ .

5-Methyloxindole-3-spiro-1'-(oxazolidine-2',4'-dione) (76; R=Me, R'=H).

Treatment of 5-methyldioxindole-3-carboxyureide (72; R=Me, R'=H) (1.3g) with 50% aqueous potassium hydroxide (10 ml) liberated ammonia and gave the potassium salt of 5-methyloxindole-3-spiro-1'-(oxazolidine-2'-4'-dione) which precipitated as colourless plates. Acidification of an aqueous solution of the potassium salt gave 5-methyloxindole-3-spiro-1'-(oxazolidine-2',4'-dione) (0.9g, 77%) which crystallized from water as colourless needles, m.p. 287 (Found: C, 57.3; H, 3.6; N, 12.1%. $C_{11}H_8O_4N_2$ requires C, 56.9; H, 3.5; N, 12.1%). Infrared absorption (Nujol) occurred near 5.5, 5.65, and 5.85 μ (carbonyl) and 3.1 μ (-NH).

5,6-Dimethoxy-1,3'-dimethyloxindole-3-spiro-1'-(oxazolidine-2',4'-dione) (77; R=R'=OMe).

(a) A mixture of 5,6-dimethoxydioxindole-3-carboxyureide (72; R=R'=OMe) (1g), anhydrous potassium carbonate (5g) and methyl iodide (5g) in acetone (100 ml) was stirred continuously and heated under reflux for 18 hours. The acetone solution was separated from the suspended solid and on evapouration yielded 5,6-dimethoxy-1,3'-dimethyloxindole-3-spiro-1'-(oxazolidine-2',4'-dione) (0.85g, 82%) which cry-

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stallized from ethanol as colourless prisms, m.p. 250° (Found: C, 55.4; H, 4.8; N, 9.3%. $C_{14}H_{14}O_6N_2$ requires C, 54.9; H, 4.6; N, 9.2%). Carbonyl absorption (Nujol) occurred at 5.50, 5.70 and 5.80 μ .

(b) Methylation of 5,6-dimethoxyoxindole-3-spiro-1'-(oxazolidine-2',4'-dione) (76; R=R'=OMe) under conditions similar to those described in above gave the dimethylderivative (86%) in colourless prisms m.p. 250° alone and when mixed with that described under (a).

1,5,6-Trimethyloxindole-3-spiro-1'-(3'-methyloxazolidine-2',4'-dione) (77; R=R'=Me).

(a) 5,6-Dimethyoxindole-3-spiro-1'-(oxazolidine-2',4'-dione) (76: R=R'=Me) (1g), anhydrous potassium carbonate (5g); methyl iodide (5g) and acetone (100 ml) were heated under reflux with constant stirring for 15 hours. After filtration and evapouration of the filtrate the residue was crystallized from ethanol. 1,5,6-Trimethyloxindole-3-spiro-1'-(3'-methyloxazolidine-2',4'-dione) (0.95g, 94%) was obtained as colourless prisms, m.p. 219° (Found: C, 61.4; H, 5.2; N, 10.3%. $C_{14}H_{14}O_4N_2$ requires C, 61.3; H, 5.2; N, 10.2%). Carbonyl absorption (Nujol) occurred near 5.55, 5.70 and 5.85 μ but no absorption was found in the -NH region (2.5-3.1 μ).

7-(p-tolyl)uramil (83; R=Me, R'=H) and its p-toluidine salt (86; R=Me,R'=H).

(a) p-Toluidine (1.1g) in ethanol (40ml) was added to a solution of alloxan monohydrate (1.6g) in water (20ml) and the mixture was heated under reflux until the initial red colour of the solution had changed to a greenish-yellow (c. 2 hours). The p-toluidine salt of 7-p-tolyluramil (0.5g, 15%) which had precipitated as fine colourless needles, m.p. c. 230° (decomp.), was collected by filtration (Found: C, 63.0; H, 5.9; N, 16.2%. $C_{18}H_{20}O_3N_4$ requires C, 63.5; H, 5.9; N, 16.5%). Carbonyl absorption (Nujol) occurred near 5.95 μ. The salt was dissolved in concentrated hydrochloric acid and on dilution with water an almost quantitative yield of 7-p-tolyluramil was obtained. It was purified by repeated precipitation from 5% aqueous sodium hydroxide with dilute hydrochloric acid and by precipitation from dimethylsulphoxide or dimethylformamide with water. The colourless powder had m.p. 230° (decomp.) (Found: C, 55.9; H, 5.1; N, 17.4; O, 21.1%. $C_{11}H_{11}O_3N_3.\frac{1}{4}H_2O$ requires C, 55.6; H, 4.9; N, 17.7; O, 21.9%). Carbonyl absorption (Nujol) occurred near 6.00 and 6.20 μ and a sharp -NH or -OH absorption occurred near 3.15 μ. Ultraviolet light absorption in 95% ethanol: max. at 250 mμ (ε 18,000); min. 229 (ε 11,000).

(b) A solution of p-toluidine (0.5g) in 5% hydrochloric acid (15ml) was mixed with a solution of dialuric acid (0.7g) in water (300ml); alloxan monohydrate (0.050g) was added and the solution was heated under reflux. The product (0.7g, 60%) was collected after 3 hours and found to be identical (mixed m.p., and infrared and ultraviolet light absorption) with the material described under (a).

(c) Diethyl-p-toluidinomalonate (92)[115] crystallized from aqueous-ethanol as colourless prisms b.p.154°/0.8 mm. The diethylmalonate (1.33g) was added to a solution of sodium methoxide (containing 0.46g of sodium) in methanol (15ml) and the mixture was heated under reflux on a water-bath for 15 hours. After removal of the solvent at 100°, the residue was dissolved in water and filtered. Acidification of the filtrate yielded 7-(p-tolyl)uramil (1g, 83%) identical in all respects with the compound already described.

(d) 5-(p-tolylimino)barbituric acid (115) (0.5g) was added to a solution of sodium borohydride (0.5g) in water (15 ml) at room temperature. The colourless solution obtained was acidified with dilute hydrochloric acid and the precipitated 7-(p-tolyl)uramil (0.5g, 98%) was collected by filtration.

7-(4'-methoxyphenyl)uramil (83; R=OMe, R'=H) and its p-anisidine salt (86; R=Ome, R'=H).

p-anisidine (1.23g) in ethanol (40 ml) was heated under reflux with a solution of alloxan monohydrate (1.6g) in water (20 ml) until the initially red solution had changed to a yellow colour (c. 3 hours). The precipitated p-anisidine salt of 7-)4'-methoxyphenyl)uramil was dissolved in concentrated hydrochloric acid and the solution was diluted with water. The 7-(4'-methoxyphenyl)uramil (0.2g, 8%) which precipitated crystallized from dimethylformamide-water, m.p. c.180° (decomp.) (Found: C, 52.1; H, 4.7; N, 16.5%. $C_{11}H_{11}N_3O_4.\frac{1}{4}H_2O$ requires C, 52.1; H, 4.6; N, 16.6%.) Carbonyl absorption (Nujol) occurred near 6.00 and 6.20 μ and a sharp band occurred at 3.15 μ .

7-(3'-4'-dimethylphenyl)uramil (83; R=R'=Me).

This compound (8%) was prepared from 3,4-dimethylaniline and alloxan monohydrate in aqueous ethanol by a procedure similar to that described for the 7-phenyluramils above. It was purified by the usual method, m.p. 235°-240° (decomp.)

5-(methyl-p-tolylamino)-2,4,6-trimethoxypyrimidine (87).

A suspension of 7-p-tolyluramil (83, R=Me,R'=H) (1.0g)

in methanol (75 ml) was treated with an excess of ethereal diazomethane and the mixture kept at 0° overnight. Filtration and evapouration of the filtrate yielded 5 (methyl-p-tolylamino)-2,4,6-trimethoxypyrimidine (0.4g, 32%) which crystallized from ethanol as colourless prisms, m.p. 98-99° (Found: C, 62.7; H, 6.9; N, 14.6%. $C_{15}H_{19}O_3N_3$ requires C, 62.3; H, 6.6; N, 14.5%). The nuclear magnetic resonance spectrum in carbon tetrachloride showed the four aromatic protons as two doublets at 3.83, 3.68 and 3.24, 3.10; the aromatic methyl group absorbed at 7.08 and the N-methyl group at 6.99. The 2-methoxy group absorbed at 6.09 close to the absorption of the 4- and 6- methoxy groups which appeared as a single 6-proton peak at 6.14. The carbonyl region in the infrared spectrum (5.5 to 6.3 μ) was devoid of absorption except for a weak band at 6.0 μ . Ultraviolet light absorption in 95% ethanol: max. at 249 (ε 19,000), and 285mμ (ε 8,000); min. at 229 (ε 12,000) and 272 mμ (ε 7,900).

The p-toluidine salt of alloxanic acid (84; R=Me, R'=H).

(a) Alloxan monohydrate (1.6g) in water (20 ml) and p-toluidine (1.1g) in ethanol (40 ml) were heated under reflux until the initial red colour of the reaction mixture had changed to yellow. After filtering the precipitated uramil

salt the filtrate was evapourated to dryness under reduced pressure and the oily residue was treated with a small quantity of ethanol and induced to crystallize. The p-toluidine salt of alloxanic acid (1.5g, 60%) was collected and washed with a small quantity of cold ethanol. It crystallized from ethanol in colourless prisms, m.p. 148° (decarboxylation) (Found: C, 49.4; H, 5.1; N, 15.2; O, 30.3%. $C_{11}H_{13}O_5N_3$ requires C, 49.4; H, 4.9; N, 15.7; O, 29.9%). Infrared absorption occurred near 5.65, 5.70, 5.85, 6.00 and 6.20 μ and at 2.90 and 3.15 μ .

(b) Alloxanic acid (0.8g) in ethanol (4 ml) was treated with p-toluidine (0.54g) in ethanol (4ml) and the solution kept at 2 to 3° overnight. The precipitated p-toluidine salt of alloxanic acid (1.2g, 90%) was collected and crystallized from ethanol, m.p. 148° (decarboxylation). It was found to be identical (mixed m.p. and infrared absorption)with the material obtained as described under (a).

The 3,4-dimethylaniline salt of alloxanic acid (84, R=R'=Me).

(a) Alloxan monohydrate (1.6g) and 3,4-dimethylaniline (1.21g) were heated under reflux in 80% aqueous ethanol until the solution had acquired a yellow colour (C. 2½ hours). The precipitated amine salt of 7 (3',4'-dimethylphenyl) uramil

was filtered off and evapo ration of the filtrate under reduced pressure yielded an oil which eventually solidified and was crystallized from ethanol. The 3,4-dimethylaniline salt of alloxanic acid (1.4g, 52%) was obtained as colourless prisms, m.p. 148° (decarboxylation) (Found: C, 51.5; H, 5.4; N, 14.9%). $C_{12}H_{15}N_3O_5$ requires C, 51.2; H, 5.4; N, 14.9%). Infra red absorption occurred near 5.65, 5.80, 6.00 and 6.15 μ .

(b) The 3,4-dimethylaniline salt of alloxanic acid was further prepared (85%) by neutralization of an ethanolic solution of alloxanic acid with 3,4-dimethylaniline and found to be identical in all respects with the material described under (a).

The p-anisidine salt of alloxanic acid (84, R=OMe, R'=H).

(a) A mixture of p-anisidine (1.2g) and alloxan monohydrate (1.6g) in 50% aqueous ethanol was heated under reflux for 3/4 hour and after filtration of the precipitated uramil salt the reaction mixture was worked up as described for the salts above. The p-anisidine salt of alloxanic acid (1.0g, 38%) was obtained as colourless prisms from ethanol, m.p. 148° (decarboxylation). Infrared absorption was observed near 2.95, 5.65, 5.75, 5.85, 6.00 and 6.15 μ .

(b) It was also obtained from p -anisidine and allox-

anic acid in ethanol and it crystallized from ethanol in colourless prisms m.p. 148° (decarboxylation) alone and when mixed with that described under (a).

Diethyl-bis(p-methylaminophenyl)malonate (106, R=Me).

A solution of p-toluidine (1.07g) and diethyloxomalonate (1.78g) in 75% aqueous ethanol (20ml) was allowed to stand at room temperature for four days. Diethyl-bis-(p-methylaminophenyl)malonate (0.6g, 16%) precipitated during this period and was collected and crystallized from aqueous ethanol as colourless needles, m.p. 94° (Found: C, 68.1; H, 7.1; N, 7.5% $C_{21}H_{26}O_4N_2$ requires C, 68.1; H, 7.1; N, 7.6%). Carbonyl absorption occurred near 5.8 μ and -NH absorption was observed near 2.95 μ.

Diethyl-bis(o-dimethylaminoanilino)malonate (107).

o-Dimethylaminoaniline (1.4g) in ethanol (5ml) was treated with a solution of diethyloxomalonate (1.78g) in ethanol (10ml) and the mixture was allowed to stand at room temperature for two days. Diethyl-bis(o-dimethylaminoanilino)malonate (0.6g) which had precipitated was collected and a further quantity (0.75g) was isolated from the reaction mixture two days later. The product (1.35g, 64%) crystallized from ethanol as large rectangular plates, m.p. 118° (Found:

C, 64.3; H, 7.4; N, 12.9%. $C_{23}H_{32}N_4O_4$ requires C, 64.5; H, 7.5; N, 13.1%). The nuclear magnetic resonance spectrum in deuterochloroform/10% carbontetrachloride showed the four equivalent N-methyl groups as a 12-proton peak at 7.29; the triplet and quartet of the two ethyl groups appeared at 9.01 and 5.93, the aromatic and -NH protons formed a 10-proton multiplet centred at 3.09 which was not analysed. Carbonyl absorption occurred near 5.8 μ and -NH absorption at 3.00 μ.

o-Dimethylaminoaniline and Ninhydrin.

o-Dimethylaminoaniline (1.36g) and ninhydrin (1.78g) in 80% aqueous ethanol (20ml) were heated under reflux for half and hour. The solution was cooled to room temperature and the dark blue product (2.2g), possibly the anil (110), was collected and washed well with ethanol and ether. Carbonyl absorption (Nujol) occurred near 5.85 μ and the -NH region 2.5 to 3.3 μ was devoid of absorption. The compound was readily decolourised on treatment with warm dilute mineral acid.

5,5-bis(p-methylphenylamino)barbituric acid (104; R=Me) hydrate.

A cold solution of alloxan monohydrate (1.6g) in methanol (10ml) was added to a cold solution of p-toluidine (2.14g)

in methalon (15ml) and the mixture was diluted with water (15ml). After cooling at 2° to 3° for 10 hours the precipitated 5,5-bis(p-methylphenylamino)barbituric acid (3.1g, 87%) was collected by filtration. It crystallized from aqueous methanol as colourless plates which readily turned red, m.p. c. 256° (decomp.) (Found: C, 60.3; H, 5.6; N, 15.7%. $C_{18}H_{18}O_3N_4.H_2O$ requires C, 60.7; H, 5.7; N, 15.7%). Hydrolysis with 5% aqueous sodium hydroxide gave p-toluidine, which was identified by its m.p. and by it mixed m.p. with an authentic sample, as well as by its infrared absorption spectrum. Treatment of the hydrolysis solution with 10% aqueous barium hydroxide immediately precipitated the alloxanate anion as its barium salt, and this was identified by comparison of its infrared spectrum with that of an authentic sample. On boiling under reflux with aqueous ethanol the solution initially turned red and the 5,5-bis(p-methylphenylamino)barbituric acid was eventually (c. 2 hr.) converted into the p-toluidine salt of 7-(p-tolyl)uramil (86; R=Me, R'=H) and the p-toluidine salt of alloxanic acid (84; R=Me, R'=H).

5,5-bis(p-methoxyphenylamino)barbituric acid (104; R=OMe) Hydrate.

A cold solution of p-anisidine (2.46g) in methanol

(10ml) was added to a cold solution of alloxan monohydrate (1.6g) in methanol (5ml). The mixture was treated with water (15ml), and allowed to stand at 2-3° overnight. The precipitated 5,5-bis(p-methoxyphenylamino)barbituric acid (3.0g, 77%) crystallized from aqueous methanol as colourless plates m.p. c. 140° (decomp.) (Found: C, 55.4; H, 4.7; N, 14.2%. $C_{18}H_{18}O_5N_4.H_2O$ requires C, 55.7; H, 5.2; N, 14.4%). Boiling aqueous ethanol converted the product into the p-anisidine salt of the uramil (85; R=OMe, R'=H) and the salt of alloxanic acid (84; R=OMe, R'=H), while 5% aqueous sodium hydroxide gave p-anisidine and the alloxanate anion. The latter was identified as its insoluble barium salt by comparison of its infrared spectrum with that of an authentic sample of the salt.

5,5-bis(piperidino)barbituric acid (105).

A cold solution of piperidine (0.85g) in diglyme, (tetrahydrofuran or acetone) (20ml) was added dropwise to a solution of anhydrous alloxan (1.4g) in diglyme, (tetrahydrofuran or acetone) (20ml). The colourless 5,5-bis(piperidino)barbituric acid (1.4g, 43%) precipitated immediately from the pink solution and was collected by filtration and washed well with dry ethanol and ether; m.p. c.142° (decomp.) (Found: C, 52.8, 51.8; H, 7.7, 7.5; N, 17.4, 17.4,

17.6%. $C_{14}H_{22}N_4O_3.1\frac{1}{2}H_2O$ requires C, 52.3; H, 7.8; N, 17.4%). It was extremely insoluble and readily decomposed during attempted recrystallization to give deep red solutions. Alkaline hydrolysis afforded piperidine and the alloxanate anion (identified as its barium salt) and on boiling in water it was converted into the piperidine salt of alloxanic acid m.p. 152° undepressed by admixture with an authentic sample. Infrared absorption (Nujol) occurred near 3.15, 5.85, 6.00 and 6.15 μ. A similar compound was obtained from morpholine and anhydrous alloxan.

7-(o-carboxyphenyl)uramil (102).

(a) A mixture of anthranilic acid (1.4g) and alloxan monohydrate (1.6g) in 70% aqueous ethanol was heated under reflux for 3 hours. The crystalline product was filtered and washed with ethanol and ether. 7-(o-carboxyphenyl) uramil (0.3g, 11%) crystallized from dimethylformamide/ water as fine colourless needles, m.p. 290-295° (decomp.) (Found: C, 50.2; H, 3.9; N, 16.2%. $C_{11}H_9N_3O_5$ requires C, 50.2; H, 3.5; N, 16.0%). Carbonyl absorption (Nujol) occurred at 5.85, 6.05, and 6.25 μ.

Evapouration of the above aqueous solution gave a colourless compound (1.1g,39 %), possibly 5-(3'-carboxy-4'-aminophenyl) dialuric acid, which crystallized from water,

m.p. c. 250° (decomp.) (Found: C, 47.4; H, 3.6; N, 14.7%. $C_{11}H_9O_6N_3$ requires C, 47.3; H, 3.3; N, 15.0%).

(b) The benzoxazone (99) (1.3g) was added gradually to a solution of sodium borohydride (1g) in water (20ml). After the reaction had subsided the solution was filtered and the filtrate was acidified with dilute hydrochloric acid (6%). The product (1.0g, 77%) precipitated from the acid solution and was found to be identical (m.p., mixed m.p. and infrared spectrum) with the compound described in (a).

5-(3',4'-dimethylphenylamino)dialuric acid. (114; R=R'=Me).

Anhydrous alloxan (1.4g) in diglyme (10ml) at room temperature was added to a solution of 3,4-dimethylaniline (1.21g) in diglyme (5ml) and the mixture was kept at 2-3° overnight. 5-(3',4'-Dimethylphenylamino)dialuric acid (2.0g; 76 %), m.p. 226° (decomp.), crystallized as colourless prisms and it was collected by filtration and washed free of diglyme with dry ether, (Found: C, 54.4; H, 4.9; N, 15.8%. $C_{12}H_{13}N_3O_4$ requires C, 54.7; H, 5.0; N, 16.0%). Infrared absorption was observed near 3.10, 5.80 and 5.95 μ (with a weak band at 5.70 μ). On boiling with aqueous ethanol the dialuric acid was converted into the 3,4-dimethylaniline

salt of 7-(3,4-dimethylphenyl) uramil (86; R=R'=Me) and the 3,4-dimethylaniline salt of alloxanic acid (84; R=R'=Me), whereas treatment with 10% aqueous barium hydroxide gave 3,4-dimethylaniline and barium alloxanate.

5-(p-tolylimino)barbituric acid (115).

A mixture of anhydrous alloxan (0.40g) and p-toluidine (0.26g) in acetic acid (10ml) was heated under reflux for 10 min. The anil (0.30g, 46%) was rapidly deposited as dark red prisms from the deep red solution. It crystallized from acetone/light petroleum (b.p. 60°-80°) as almost black prisms, m.p. 256° (Found: C, 57.4; H, 4.0; N, 18.6%. $C_{11}H_9N_3O_3$ requires C, 57.1; H, 3.9; N, 18.2%). Carbonyl absorption occurred at 5.70, 5.85 and 5.90 μ and absorption also occurred at 3.10 and 3.20 μ. Ultraviolet light absorption in 95% ethanol: max. at 231 (ε 13,500), and 485 m μ (ε1,500); min. at 395 m μ (ε250).

1,2-dihydro-3,1,4H-benzoxaz-4-one-2-spiro-5'-(hexahydro-2',4',6'-trioxopyrimidine) (99).

A mixture of anthranilic acid (2.8g) and anhydrous alloxan (2.8g) in acetic acid (20ml) was heated under reflux for 5 min. During this time a highly crystalline, colourless compound precipitated and after the reaction mixture

had cooled the benzoxazone (3.1g, 60%) was collected by filtration. It crystallized from acetic acid or ethanol/light petroleum (b.p. 40-60°) as colourless prisms, m.p. 241° (Found: C, 50.8; H, 3.0%. $C_{11}H_7O_5N_3$ requires C, 50.6; H, 2.7%). Carbonyl absorption (Nujol) occurred near 5.65 and 5.8 μ. The benzoxazone was readily reduced to the corresponding phenyluramil (102) by sodium borohydride.

5-(1'-dibenzo-a,h-phenazinium)barbiturate (78) dihydrate.

β-naphthylamine (1.4g) in ethanol (5ml) was treated with a solution of alloxan monohydrate (1.6g) in 50% aqueous acetic acid (20ml) and the mixture was heated under reflux. The highly crystalline product began to precipitate from the boiling solution after c. 3 min. and heating was continued for a further 10 min. After cooling the 5-(1'-dibenzo-a,h-phenazinium)barbiturate (0.3g, 14%) was obtained as brown prisms with a green metallic lustre which decomposed slowly above c. 200° (Found: C, 65.7; H, 4.2; N, 12.3%. $C_{24}H_{14}O_3N_4.2H_2O$ requires C, 65.2; H, 4.1; N, 12.7%). When dried over phosphoric oxide at 100° and 0.1mm pressure for 24 hr. it gave a hemihydrate (Found: C, 69.7; H, 3.5; O, 13.1; N, 13.5%. $C_{24}H_{14}O_3N_4.\frac{1}{2}H_2O$ requires C, 69.4; H, 3.6; O, 13.5; N, 13.5%). Carbonyl absorption (Nujol) occurred near 5.90 u. When the barbiturate (0.44g) was treated with 10% aqueous

potassium hydroxide and the mixture warmed, ammonia was evolved and the precipitated yellow solid was isolated by filtration. Dibenzo-a,h-phenazine (0.21g, 75%) crystallized from acetone as lemon-yellow needles, m.p. 286° (lit.[116] 286°) undepressed by admixture with an authentic sample. (Found: C, 85.4; H, 4.2; N, 10.1%. $C_{20}H_{12}N_2$ requires C, 85.7; H, 4.3; N, 9.9%). Dibenzo-a,h-phenazine was also obtained by heating the barbiturate (78) at c. 230° and 0.1mm pressure when the phenazine sublimed as yellow needles identical in all respects, (m.p., mixed m.p. and ultraviolet and infrared absorption) with an authentic sample.

Part 3.

The anhydro salt of 5-hydroxyhydantoin and 5-(1'-piperidyl) dialuric acid (117).

A solution of anhydrous alloxan (8.4g) and piperidine (5.2g) in acetic acid (30ml) was heated under reflux. After a short time a vigorous reaction ensured and carbon dioxide (detected as barium carbonate) was evolved. Heating was discontinued until the reaction had subsided and then continued for a further 10 min. The highly coloured, crystalline salt (2.6g, 29%) was collected by filtration from the still warm, purple reaction mixture and washed with acetic acid (20ml), m.p. 345-350° (decomp.) (Found: C, 44.1, 44.1; H, 4.5, 4.9; N, 21.6%. $C_{12}H_{15}O_6N_5$ requires C, 44.3; H, 4.7; N, 21.5%). Infrared absorption (Nujol) occurred at 5.8, 5.95, 6.05 and 6.15 μ. Alkaline hydrolysis with 5% aqueous sodium hydroxide caused an initial deep blue colour and was accompanied by liberation of ammonia. The hydrolysis mixture eventually turned yellow and extraction with ether afforded piperidine. Addition of barium hydroxide to the hydrolysis mixture precipitated barium alloxanate which was identified by its infra red spectrum. Treatment of the salt (117) with warm, dilute hydrochloric acid caused loss of colour and after standing overnight the precipitated alloxantin was collected and crystallized from water as colourless prisms m.p. 234-6° (decomp.)

(lit.[76] m.p. 235° (decomp.)) (Found: C, 30.0; H, 3.4; N, 17.3%. Calc. for $C_8H_6N_4O_8.2H_2O$ C, 29.8; H, 3.1; N, 17.4%). The infrared absorption spectrum and general physical properties were identical to those reported by Tipson and Cretcher[76]. The ultraviolet light absorption of alloxantin initially showed a maximum at 260 m u but this rapidly disappeared (c.5 min.) on allowing the solution to remain in the light path.

5-(1'-piperidino)barbituric acid (123).

The salt (117) (2.6g) was heated under reflux with water (50ml) until the initial purple solution became colourless (c. 3-4 hr.). The insoluble material was filtered off and on cooling the filtrate the product (0.10g) precipitated as colourless plates. The insoluble material (which appeared to be easily oxidized back to a red colour) was warmed with water for a further 4 hrs. and filtered. On cooling the filtrate deposited a further 0.4g of product. 5-(1'-piperidino)barbituric acid (0.5g, 29%) crystallized from water (charcoal) as colourless plates, m.p. 345-350° (decomp.) (Found: C, 51.5; H, 6.3; N, 19.8%. $C_9H_{13}O_3N_3$ requires C, 51.2; H, 6.2; N, 19.9%). The barbituric acid was stable towards aqueous alkali and formed alkali metal salts. The nuclear magnetic resonance spectrum in deuterium oxide con-

taining sodium deuteroxide showed a 4-proton multiplet at 7.30 and a 6-proton multiplet at 8.81 due to the 2',6' and to the 3',4',5' protons respectively.

The anhydro salt of 5-hydroxyhydantoin and 5-(1'-benzimidazolyl)dialuric acid (118; R=H).

Benzimidazole (1.2g) and anhydrous alloxan (1.4g) in acetic acid (15ml) were warmed until the purple reaction mixture began to evolve carbon dioxide (detected as barium carbonate). After the evolution of carbon dioxide had moderated the reaction mixture was heated for 10 min. and the bluish-purple crystalline salt (1g, 59%) was collected by filtration from the warm solution and washed well with acetic acid, m.p. 284° (decomp.) (Found: C, 46.7; H, 3.2; N, 23.0%. $C_{14}H_{10}O_6N_6$ requires C, 46.9; H, 2.8; N, 23.5%). Alkaline hydrolysis of the salt (5g) with 10% aqueous potassium hydroxide (20ml) resulted in a transient deep blue colour which eventually disappeared (3/4 hr.) and benzimidazole (1.3g) crystallized on cooling the yellow solution. Acidification of the hydrolysis mixture (hydrochloric acid) precipitated a colourless, unidentified compound (0.7g) which was readily soluble in alkaline solution but reprecipitated on the addition of acid. It formed a crystalline hydrochloride in concentrated hydrochloric acid but this decomposed on dilution

of the acid solution with water. The salt (118; R=H) was decolourized by dilute hydrochloric acid and after standing overnight the precipitated solid was isolated, crystallized from water and identified as alloxantin by its infrared spectrum and characteristic properties[76].

5-(1'-benzimidazolyl)barbituric acid (124; R=H) Hydrate.

The above salt (5g) was heated under reflux with water (30 ml) until the purple colour had disappeared. The insoluble material (identical with the material obtained above on acidification of the alkaline hydrolysis mixture) was filtered from the boiling solution and on cooling the filtrated yielded 5-(1'-benzimidazolyl)barbituric aciddihydrate (0.6g, 15%) which crystallized from water (charcoal) as colourless plates or needles, m.p. 295-300° (decomp.) (Found: C, 47.2; H, 4.5; N, 20.2%. $C_{11}H_8N_4O_3.2H_2O$ requires C, 47.1; H, 4.3; N, 20.0%). When dried over phosphoric acid at 0.1mm and 100° for 24 hrs. it retained $\frac{1}{4}H_2O$ (Found: C, 52.9; H, 3.7; N, 22.5%. $C_{11}H_8N_4O_3.\frac{1}{4}H_2O$ requires C, 53.1; H, 3.4; N, 22.5%). Ultraviolet light absorption in 95% ethanol: max. at 259 (ε 8,700), 273 (ε 9,200), and 280 m μ (ε 7,500); min. at 225 (ε 5,000), 270 (ε 8,400) and 276 m μ (ε 6,400). The nuclear magnetic resonance spectrum in deuterium oxide containing sodium deuteroxide showed the 2'-proton as a single

1-proton peak at 2.28 while the aromatic protons absorbed as two 2-proton multiplets centred at 2.65 and 3.18.

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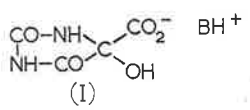
765. *Ring Contractions of Alloxan with Alicyclic Secondary Amines: Formation of Amine Salts of Alloxanic Acid.*

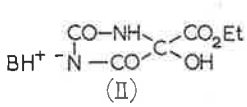
By J. W. Clark-Lewis and J. A. Edgar.

The so-called alloxanic acid amide hydrates formed from alloxan and secondary amines are shown to be amine salts of alloxanic acid. The adducts formed from anhydrous alloxan and morpholine or piperidine in ethanol are shown to be salts of the amine with the acidic imide group of ethyl alloxanate.

Fisher and Day [1] reported that alloxan reacts with secondary amines (morpholine, piperidine, pyrrolidine, and dimethylamine) to give amides of alloxanic acid, and that the same products were formed from ethyl alloxanate and the secondary amines in aqueous solution. The " amides " all retained an additional molecule of water and the obvious inference that the compounds are salts (I; B = base) and not amides has now been confirmed by preparation of morpholine and piperidine alloxanate by neutralising the acid with the amines. The products were identical with those prepared by Fisher and Day's methods, as judged by general physical properties, infrared spectra, and mixed melting-point determinations, and piperidine alloxanate in water showed the high equivalent conductance ($\Lambda = 51$) expected for such a salt. The reported [1] thermal decomposition of the morpholine compound into 5-hydroxyhydantoin, carbon dioxide, and morpholine is no longer surprising with the revised constitution, and both the morpholine and the piperidine salt gave an immediate and quantitative precipitate of barium alloxanate on addition of aqueous barium hydroxide.



(I)



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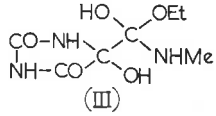
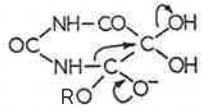


(III)

When piperidine was added to a solution of anhydrous alloxan in dry ethanol a compound $C_{11}H_{19}N_3O_5$ was obtained which formally is an adduct of alloxan, piperidine, and ethanol, and the same product was obtained from ethyl alloxanate and piperidine in dry ethanol (or dry acetone). Morpholine gave a similar product and these compounds we formulate as salts (II) of ethyl alloxanate. The equivalent conductance of the piperidine compound (II) in methanol was high ($\Lambda = 26$) as expected for a salt. A compound obtained from ethyl alloxanate and methylamine is evidently an analogous salt (although it was described by Biltz and Lachmann [2] as an " ethanolate " (III) of the methylamide. The structures (II) were established by warming the piperidine salt with water on a steam-bath for 15 minutes, which converted it into piperidine alloxanate (I; B = piperidine), and by precipitating the sodium salt of ethyl alloxanate from the piperidine salt with methanolic sodium methoxide and then liberating the ethyl ester from the precipitate with dry hydrogen chloride in tetrahydrofuran. Infrared measurements support the assigned structures as the salts (II; B = piperidine, morpholine) retained a band at 5·7 μ (ester-carbonyl) but lacked the absorption at 5·6—5·65 μ typical of the un-ionised alloxanate ring, and showed one instead of two peaks in the N–H stretching region. It was stated [2] that the methylamine salt of ethyl alloxanate (II; B = NH_2Me) (Biltz and Lachmann's " ethanolate," III), when warmed with water, yielded the hydrated amide which, like Fisher and Day's compounds, could not be dehydrated without decomposition, so that this " amide " is clearly the methylamine analogue (II; B = $NHMe_2$) of the piperidine and morpholine salts.

The revised constitution of the products from alloxan and secondary amines necessitates modification of the mechanism proposed by Fisher and Day for the ring contraction. Nucleophilic attack by solvent anions, or by solvent molecules followed by proton transfer to the amine, would give the intermediate (IV; R = H or Et) from which the products (V; R = H or Et) would arise by migration of nitrogen from C-4 to C-5. This migration is in agreement with radiotracer studies,[3] which established that formation of alloxanic acid from alloxan does not occur by C⟶C migration, as in rearrangements of the



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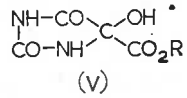

(V)

benzilic acid type. Ring contraction of alloxan under the influence of hydroxyl ions or amines (morpholine, piperidine, pyrrolidine, methylamine, and dimethylamine) in aqueous solution thus leads to the alloxanate anion. Alkoxides in dry alcohols give rise to the metal salts of alloxanate esters (*e.g.*, salt of V; R = Me),[1] and the amines in dry ethanol yield corresponding amine salts (II).

Experimental

Infrared spectra (2—15 μ) of Nujol mulls were recorded on an Infracord spectrometer, and positions of absorption in the region 5·5—6·5 μ were accurately measured (by Dr. R. A. Jones) with a Grubb–Parsons S4 spectrometer (calcium fluoride prism).

Ethyl alloxanate [2] gave carbonyl absorption bands at 5·55, 5·68, 5·76, and 5·82 μ.

Morpholine Alloxanate (I; B = C_4H_9NO).—(*a*) Morpholine (1·1 g.) was added to a solution of alloxanic acid (2 g.) in dry methanol (7 c.c.), and ether was added to produce a faint turbidity. After storage at 0° the *morpholine alloxanate* (2·8 g., 90%) was collected; it crystallised from aqueous ethanol (addition of ethanol to an aqueous solution) in prisms, m. p. 120° (lit.,[1] 119·8—120·8°) (Found: C, 36·4; H, 5·9; N, 15·8. $C_8H_{13}N_3O_6,H_2O$ requires C, 36·2; H, 5·7; N, 15·8%), $\nu_{max.}$ 5·66, 5·77, 6·07, and 6·23 μ.

(*b*) A solution of alloxan monohydrate (2 g.) and morpholine (1·1 g.) in water (15 c.c.) was boiled under reflux until it became yellow (5 min.). Ethanol (220 c.c.) was added and, after storage at 0° overnight, the salt (1·9 g., 62%) was collected. It crystallised from aqueous ethanol in prisms, m. p. 120° alone and when mixed with that described under (*a*).

(*c*) A solution of morpholine (1·1 g.) and ethyl alloxanate (2·3 g.) in water (15 c.c.) was heated on a steam-bath for 15 min. before addition of ethanol (220 c.c.) and cooling to 0°. Next day the salt (2·7 g., 90%) was collected; it crystallised from aqueous ethanol in prisms, m. p. and mixed m. p. 120°.

Piperidine Alloxanate (I; B = $C_5H_{11}N$).—The *salt* was prepared in the same way as the morpholine analogue by methods (*a*) (90%), (*b*) (68%), and (*c*) (86%) with piperidine in place of morpholine. It crystallised from aqueous ethanol in prisms, m. p. 153° (lit.,[1] 133°) (Found: C, 43·9; H, 6·4; N, 17·3. $C_9H_{15}O_5N_3$ requires C, 44·1; H, 6·2; N, 17·1%), $\nu_{max.}$ 5·62, 5·67, 5·78, 6·09, and 6·27 μ.

Morpholine Salt of Ethyl Alloxanate (II; B = C_4H_9NO).—(*a*) Morpholine (1·1 g.) was added to a solution of anhydrous alloxan (1·7 g.) in dry ethanol (10 c.c.), and the resulting suspension was cooled for 2 hr. The *morpholine salt* of ethyl alloxanate (1·9 g., 58%) was collected; it crystallised from ethanol in prisms, m. p. 126° (Found: C, 43·2; H, 6·1; N, 15·5. $C_{10}H_{17}N_3O_6$ requires C, 43·6; H, 6·2; N, 15·3%), $\nu_{max.}$ 5·77, 6·14, and 6·29 μ.

(*b*) Morpholine (1·1 g.) was added to a solution of ethyl alloxanate (2·3 g.) in dry ethanol (10 c.c.). The mixture was stored at 0° for 1 hr. and filtration then gave the morpholine salt (2·4 g., 71%). The salt was obtained almost quantitatively from ethyl alloxanate and morpholine in dry acetone.

Piperidine Salt of Ethyl Alloxanate (II; B = $C_5H_{11}N$).—(*a*) Piperidine (1·06 g.) was added to a solution of alloxan monohydrate (1·7 g.) in dry ethanol (10 c.c.), and the resulting suspension was cooled for 2 hr. before collection of the *piperidine salt* of ethyl alloxanate (2·1 g., 72%), which crystallised from dry ethanol in needles, m. p. 125—126° (Found: C, 48·3; H, 7·0; N, 15·4. $C_{11}H_{19}N_3O_5$ requires C, 48·3; H, 7·0; N, 15·4%), $\nu_{max.}$ 5·75s, 5·94w, 6·14, and 6·32 μ.

(*b*) Piperidine (1·06 g.) was added to a solution of ethyl alloxanate (2·3 g.) in dry ethanol (10 c.c.), and the solution was stored at 0° for 1 hr. before collection of the salt (2·7 g., 80%), which crystallised from ethanol in needles, m. p. and mixed m. p. 125—126°. A solution of the salt (2·7 g.) in water (5 c.c.) was heated on a steam-bath for 15 min. and then diluted with ethanol (75 c.c.) and stored at 0°. Next day piperidine alloxanate (1·4 g., 58%), m. p. and mixed m. p. 153°, was collected; its infrared absorption was indistinguishable from that of the sample described above

Liberation of Ethyl Alloxanate from its Piperidine Salt.—Sodium methoxide (0·54 g.) in methanol was added to a solution of the piperidine salt (2·7 g.) in the minimum of dry methanol. The immediate gelatinous precipitate of the sodium salt of ethyl alloxanate was collected and dried (2·0 g., 96%); its infrared absorption was indistinguishable from that of the sodium salt prepared from ethyl alloxanate and sodium ethoxide (absorption at 5·83 and 6·18 μ). The sodium salt was suspended in dry tetrahydrofuran in a flask protected from moisture, dry hydrogen chloride was passed in for 30 sec., and the mixture was shaken for 1½ hr. before filtration from sodium chloride. The filtrate was evaporated under reduced pressure, and re-evaporated after the addition of dry methanol. The residue was dissolved in a little warm, dry acetone, and the solution was diluted to incipient turbidity with dry chloroform. Ethyl alloxanate (1·4 g., 75%) crystallised in long plates pointed at both ends, m. p. 115—116° alone and when mixed with an authentic specimen.[2]

Electrical Conductivities.—0·1M-Solutions of the salts were measured at 20° with a Philips conductivity bridge, model GM 4249, and a dipping-electrode conductivity cell. We thank Dr. B. J. Steel for these measurements.

Microanalyses were performed under the supervision of Dr. W. Zimmermann, C.S.I.R.O. Microanalytical Laboratory, Melbourne. We thank Dr. R. A. Jones for infrared measurements.

UNIVERSITY OF ADELAIDE, SOUTH AUSTRALIA. [*Received, May 7th*, 1962.]

[1] Fisher and Day, *J. Amer. Chem. Soc.*, 1955, **77**, 4894.
[2] Biltz and Lachmann, *J. prakt. Chem.*, 1926, **113**, 309.
[3] Kwart, Spayd, and Collins, *J. Amer. Chem. Soc.*, 1961, **83**, 2579.

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QUINOXALINE DERIVATIVES

VIII. BETAINE STRUCTURES OF DIHYDROQUINOXALINIUM AND BENZIMIDAZOLIUM BARBITURATES FORMED FROM *o*-DIALKYLAMINOANILINES AND ALLOXAN

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By J. W. Clark-Lewis,† J. A. Edgar,† J. S. Shannon,‡ and M. J. Thompson§

[*Manuscript received March* 4, 1964]

Summary

Condensation of alloxan and *o*-dimethylaminoaniline gives 1,2,3,4-tetrahydro-4-methylquinoxaline-2-spiro-5-(hexahydro-2,4,6-trioxopyrimidine) (I) formed as a result of a unique ring-closure involving a methyl group of the *o*-dimethylamino substituent.[1] The structure of the closely related compound previously[2] formulated as its 3-hydroxy derivative (a carbinolamine) (II) is now revised to the corresponding betaine, a dihydroquinoxalinium barbiturate (III; R = H). The 6-methyl, 7-methyl, and 6,7-dimethyl analogues[3] of the spiran (I), like the parent compound,[4] were regarded as anils by Rudy and Cramer.[3,4] Betaine structures (cf. III) may be assigned to the 6,7-dimethyl[5] and 6,7-dichloro[2,6] analogue of the barbiturate (III; R = H). *o*-Diethylaminoaniline reacts differently from *o*-dimethylaminoaniline with alloxan in giving a benzimidazolium barbiturate (VIII; R = H). We propose a similar benzimidazolium barbiturate structure for the analogous product[5] from 4,5-dimethyl-2-dipropylaminoaniline. Mass spectra of the lowly volatile betaines and some of their deuterated derivatives were obtained and rationalized in terms of the assigned structures. Several dihydrobenzimidazoles have been prepared, and their n.m.r. and light absorption spectra recorded.

Condensation of *o*-aminodimethylaniline with alloxan in aqueous ethanol at room temperature gives the spiran (I) formed by participation of the *N*-methyl group in a unique ring-closure.[1] The spiran is accompanied by a second product (B) represented[2] as the carbinolamine (II), although its spectral properties and high melting point indicate that it exists as a hydrate of the betaine form (III; R = H), and this is confirmed below.

The present investigation was undertaken to clarify the structure of the product B, but we first consider the structure of the spiran (I) because merely aerating a hot aqueous solution of this compound gave B,[2] so that the two products are presumably closely related in structure. The spiran is stable to acid, which indicates

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† Department of Organic Chemistry, University of Adelaide.

‡ Division of Coal Research, CSIRO, Chatswood, N.S.W.

§ Department of Organic Chemistry, University of Adelaide. Present address: Department of Chemistry, University of Queensland.

[1] King, F. E., and Clark-Lewis, J. W., *J. Chem. Soc.*, 1951, 3080.

[2] King, F. E., and Clark-Lewis, J. W., *J. Chem. Soc.*, 1953, 172.

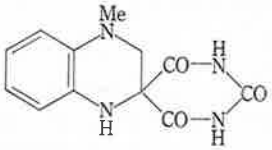
[3] Rudy, H., and Cramer, K. E., *Ber. dt. chem. Ges.*, 1939, **72**, 227.

[4] Rudy, H., and Cramer, K. E., *Ber. dt. chem. Ges.*, 1938, **71**, 1234.

[5] Rudy, H., and Cramer, K. E., *Ber. dt. chem. Ges.*, 1939, **72**, 728.

[6] Barlow, R. B., *J. Chem. Soc.*, 1951, 2225; Barlow, R. B., Ing, H. R., and Lewis, I. M., *J. Chem. Soc.*, 1951, 3242.

that the pyrimidine ring is intact, but boiling 30% aqueous sodium hydroxide converted it into the hydantoin (IV; R = H), the structure of which was confirmed by synthesis.[1] The spiran possessed one *N*-methyl group, and with diazomethane it gave a dimethyl derivative (V) which contained three *N*-methyl groups (Herzig–Meyer) and one active hydrogen (Zerewitinoff), and yielded an acetyl derivative with acetic anhydride. This evidence led to proposal[1] of the accepted structures for the spiran (I) and its dimethyl derivative (V) which are now confirmed by infrared and nuclear



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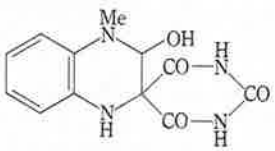

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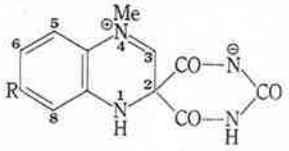

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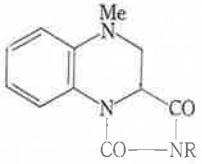

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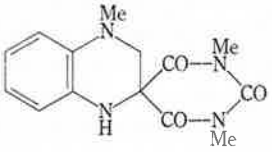

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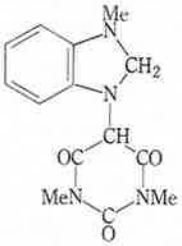


(VI)

magnetic resonance spectroscopy, and by a new degradation. The infrared spectrum of the dimethylspiran (V) confirmed that the carbonyl groups are located in amide functions in a six-membered ring and showed the presence of an NH group which was absent from the *N*-nitroso derivative of the spiran (V). The nuclear magnetic resonance spectrum of the dimethylspiran (V) in deuterochloroform showed four aromatic protons (single peak τ 3·23), a three-proton peak due to the N(4)Me group at τ 7·11, and a six-proton peak due to the N(1′)Me and N(3′)Me groups at τ 6·68. The methylene group absorbed as a single two-proton peak at τ 6·75, which decisively excludes a benzimidazoline formulation (VI) in which methylene absorption would be expected at lower field (τ *c.* 5·7; see below for models).[7] Mild alkaline degradation of the dimethylspiran (V) gave the hydantoin (IV; R = Me), identical with that prepared from the hydantoin (IV; R = H) by methylation with diazomethane, and

[7] Volpp, G., *Chem. Ber.*, 1962, **95**, 1493.

its formation from the spiran positively locates the active hydrogen on N(1) of the dimethylspiran (V). The nuclear magnetic resonance spectrum of the hydantoin (IV; R = Me) in carbon tetrachloride showed two peaks due to the *N*-methyl groups (τ 7·05, 6·98) and three quartets (τ 6·98, 6·37, 5·78) due to the $-CH_2-CH=$ system. The structure (I) for the spiran is therefore firmly established, although synthesis has not been achieved.[8] This yellow spiran was first obtained by Rudy and Cramer[4] who regarded it as an anil, and proposed anil structures for analogues[3] which should now be regarded as the 6-methyl, 7-methyl, and 6,7-dimethyl derivatives of the spiran (I).

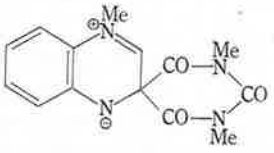
Formation of the product B, $C_{12}H_{12}O_4N_4$, can be understood as an oxidation by alloxan (or by air) of the spiran (I), $C_{12}H_{12}O_3N_4$, and although the oxidation product B is resistant to catalytic hydrogenation[2] it is quantitatively reduced to the spiran (I) once more by sodium borohydride. This reduction confirms that the oxidation product B is closely related to the spiran (I), and suggests that no rearrangement of the structural skeleton has occurred. The high melting point and absence[2] of carbinolamine properties favour formulation of B as a betaine (III; R = H) rather than as a carbinolamine (II), and its ultraviolet light absorption differs significantly from that of the spiran (I), but resembles that of benzimidazolium salts. The product B crystallizes with water of crystallization as $C_{12}H_{14}N_4O_5$, and can be dried to $C_{12}H_{10}N_4O_3.\frac{1}{2}H_2O$ (or $C_{24}H_{22}N_8O_7$), which is more easily understood on the betaine structure (III; R = H) as the dihydrate can lose $1\frac{1}{2}$ molecules of water of crystallization, whereas on the carbinolamine formulation (II) two molecules must lose three molecules of water with formation of an anhydride.[2] We therefore regard the crystalline product B as a dihydrate of the betaine (III; R = H); it was first obtained by Rudy and Cramer[5] and we propose a similar structure for their 6,7-dimethyl analogue[5] from 2-dimethylamino-4,5-dimethylaniline, for the 6,7-dichloro compound,[2,6] and for the 7-bromo derivative (III; R = Br) formed from 2-amino-4-bromodimethylaniline. In the case of the chloro- and bromo-compounds this has been confirmed by dehalogenation with Raney nickel to the parent betaine. The bromobetaine (III; R = Br) was prepared in the hope that its structure could be confirmed by X-ray diffraction studies, but it was not used as it appeared less suitable for this purpose than an apparently analogous but structurally different compound (VIII; R = Br) discussed below.

Methylation of the betaine (III; R = H) with diazomethane gave the 1′,3′-dimethyl derivative (VII), also prepared by oxidation of the dimethylspiran (V), and reduction of the betaine (VII) with sodium borohydride gave the dimethylspiran (V) once more. The 3-proton in the betaine (VII) absorbed at very low field (τ 0·37), close to the absorption of the 2-proton (τ 0·30) in 1,3-dimethylbenzimidazolium iodide (IX).

Use of *o*-diethylaminoaniline to investigate the scope of these interesting cyclizations, and to assist in clarifying the structures already discussed, disclosed that the reactions of *o*-dimethylaminoanilines are not general for *o*-dialkylaminoanilines but that alternative cyclizations occur. *o*-Diethylaminoaniline and alloxan did not yield an analogue of the spiran (I) but gave a product (VIII; R = H) with

[8] Clark-Lewis, J. W., and Thompson, M. J., *J. Chem. Soc.*, 1959, 2401.

physical properties closely resembling those of the betaine (III; R = H). The benzimidazolium barbiturate (VIII; R = H), m.p. *c.* 400° (decomp.), crystallized well from water although it was sparingly soluble, and it was less soluble in alcohols and in aprotic solvents. Its ultraviolet light absorption in dilute sulphuric acid was similar to that in water and remained unchanged in sulphuric acid concentrations up to 50%. The nuclear magnetic resonance spectrum of the barbiturate in trifluoroacetic acid showed peaks at τ 8·29 and τ 5·44 (triplet and quartet due to the *N*-ethyl group)



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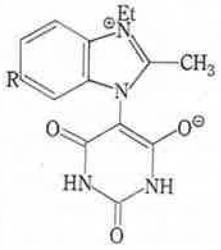

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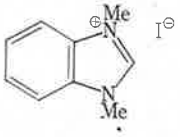


(IX)

and a singlet at τ 7·12 due to the 2′-methyl group. Methylation of the betaine (VIII; R = H) with diazomethane gave the 1,3-dimethyl derivative (X), and the n.m.r. spectrum of this compound dissolved in deuterochloroform showed peaks at τ 8·45 and τ 5·67 (triplet and quartet due to the *N*-ethyl group), a singlet at τ 7·29 due to the 2′-methyl group, and a six-proton peak at τ 6·64 (1,3-dimethyl groups).

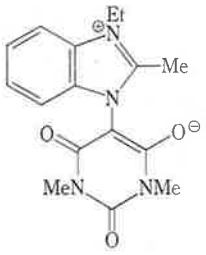
The betaine (VIII; R = H) was remarkably stable to both acid and alkali, and was recovered after being heated in concentrated sulphuric acid. It was also recovered after being boiled for several hours with 5N sodium hydroxide, and was recovered quantitatively from a solution in 30% aqueous sodium hydroxide after 3 days at room temperature. The surprising stability of the benzimidazolium barbiturate (VIII; R = H) towards alkali contrasts with the lability of the dihydroquinoxalinium barbiturate (III; R = H), which undergoes mild alkaline hydrolysis to 3,4-dihydro-4-methyl-3-oxoquinoxaline-2-carboxylic acid and formic acid.[2] This difference in chemical behaviour indicated that the two betaines possess different structures despite close similarity in physical properties. The structure of the 6′-bromobetaine (VIII; R = Br), obtained from 4-bromo-2-aminodiethylaniline and alloxan, was established by X-ray diffraction,[9] and debromination of the bromo-compound (VIII; R = Br) with Raney nickel gave the parent compound, so that its structure (VIII; R = H) is also defined by the X-ray work.

The ultraviolet light absorption of the benzimidazolium barbiturate (VIII; R = H) corresponds to superposition of the absorption of the barbiturate anion on that of simple benzimidazolium salts (e.g. IX).[10] The dihydroquinoxalinium barbiturate (III; R = H) has remarkably similar ultraviolet light absorption to that of the benzimidazolium barbiturate (VIII; R = H) and, moreover, introduction of bromine into the 7-position in the betaine (III; R = Br) caused a precisely similar

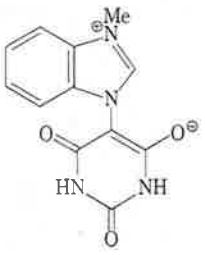
[9] Mathews, B. W., Ph.D. Thesis, Adelaide 1963; *Acta Crystallogr.* (in press).

[10] Maroni-Barnaud, Y., Wahl, H., and Maroni, P., *Bull. Soc. Chim. Fr.*, 1961, 1740, 1747.

bathochromic shift in the position of two subsidiary maxima as did indirect bromination of the barbiturate (VIII; R = H) to the 6′-bromo-compound (VIII; R = Br). The chromophores in the molecules (III) and (VIII) are evidently similar, but the very close correspondence in ultraviolet-light absorption of the two compounds necessitated further consideration of an alternative representation (XI) for the dihydroquinoxalinium barbiturate (III; R = H). This benzimidazolium structure (XI) appears to be eliminated by: (*a*) the difference between the barbiturates

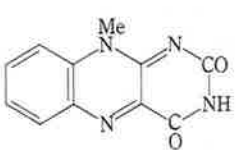


(X)

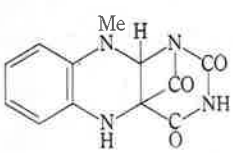


(XI)

(III; R = H) and (VIII; R = H) in their behaviour towards aqueous alkali; (*b*) the results of sodium borohydride reductions; (*c*) the effects of alkali fusions; and (*d*) the behaviour of the compounds (III; R = H), (VII), (VIII; R = H), and (X) in the mass spectrometer. The first of these has already been mentioned and we now discuss the remainder. Reduction of the barbiturate (III; R = H) with sodium borohydride gave the spiran (I) quantitatively, and although it is conceivable that a benzimidazolium compound (XI) could undergo ring expansion, the behaviour of the barbiturate (VIII; R = H) makes this improbable. The benzimidazolium barbiturate (VIII; R = H) was slowly reduced by sodium borohydride, but when reduction appeared from light-absorption changes to be complete, acidification yielded only recovered barbiturate (VIII; R = H). Model dihydrobenzimidazoles (see below) also proved unstable, and in acid solution they readily reverted to benzimidazolium salts. Fusion of the dihydroquinoxalinium barbiturate (III; R = H) with a mixture of sodium and potassium hydroxides gave 9-methylisoalloxazine (XII) in good yield, possibly by oxidative decarbonylation of an intermediate (XIII)



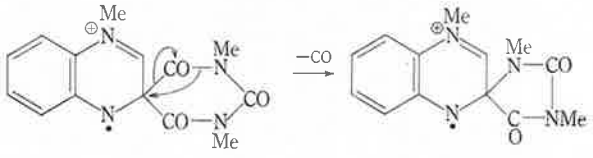
(XII)



(XIII)

or its equivalent. Transformation of the 6,7-dichloro derivative of the betaine (III) into 6,7-dichloro-9-methylisoalloxazine occurs under milder conditions,[2] and the revised formulation of the starting material makes this transformation more comprehensible. Alkali fusion of the benzimidazolium barbiturate (VIII; R = H) yielded mainly 1-ethyl-2-methylbenzimidazole and only traces of fluorescent material.

Despite their extremely low volatility, these barbiturates gave good mass spectra when they were introduced directly into the ion source and heated on the fringe of the ionizing electron beam. The chief difference noted in the mass spectral behaviour of these compounds was that the spectrum of the dimethyl derivative (VII) possessed an $M-28$ peak, attributed to loss of carbon monoxide, which was absent from the spectrum of the dimethyl derivative (X) of the barbiturate (VIII; R = H). A molecule with the structure (XI) would not be expected to lose carbon monoxide because its analogue (X) does not, but on the basis of the structure (VII) loss of carbon monoxide may be explained by the following transformation:



m/e 286 *m/e* 258

The parent benzimidazolium barbiturate (VIII; R = H) showed main peaks at *m/e* 286, 258, 172, 159 (most intense except for the molecular peak), 144, and 131. Metastable peaks confirmed the following transitions:

$$286^+ \rightarrow 258^+ + 28$$

$$258^+ \rightarrow 172^+ + 86$$

$$172^+ \rightarrow 144^+ + 28$$

$$159^+ \rightarrow 131^+ + 28.$$

These results, combined with those obtained for the deuterated molecule (see Experimental), can be explained by ion reactions shown in Figure 1, where *m/e* values in parentheses are those from the spectrum of the dimethyl derivative (X). In the mass spectrum of the deuterated betaine (VIII; with H = D and R = H), ion *b* had lost two to three deuterium atoms, ion *c* retained all deuterium, and ions *d* and *e* had both lost two atoms.

The mass spectrum of the betaine (III; R = H) was generally similar to that of the compound (VIII; R = H) except for a much more intense peak at *m/e* 241 (i.e. $M-17$) and a peak at *m/e* 198. Metastable peaks indicated the following transitions:

$$258^+ \rightarrow 241^+ + 17$$

$$241^+ \rightarrow 198^+ + 43$$

and from the spectrum of the deuterated betaine (III; R = H) (see below) it follows that the neutral fragment of mass 17 is OH and not NH_3. Possible ion reactions to account for these transformations are shown in Figure 2, where *m/e* values in parentheses are those from the spectrum of the dimethyl derivative (VII). The ion (*m/e* 172) in Figure 2 may arise from *b* via *g*, and the same ion is formed less directly from *a* via ions *c* and *d* (*m/e* 241) and *e* (*m/e* 198).

An alternative route to an ion *m/e* 172 is shown in Figure 3, and is consistent with the observation that peaks with *m/e* 198 and 172 are shifted by one mass unit in the spectrum of the deuterated molecule.

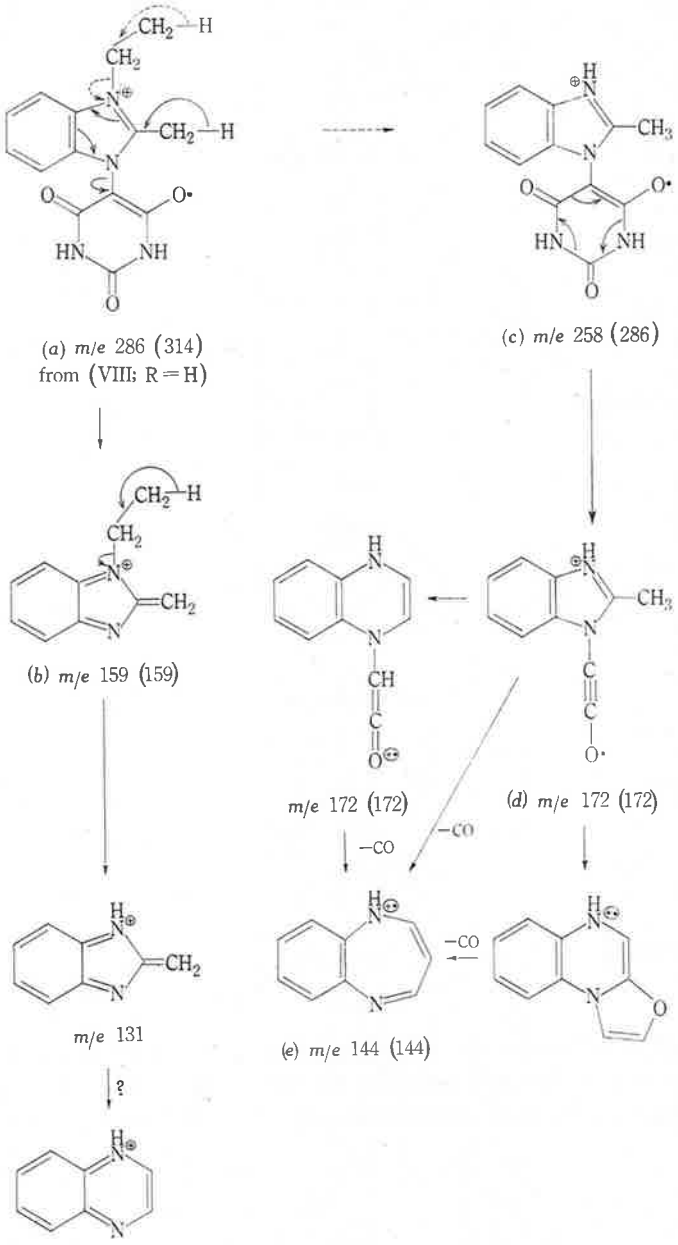


Fig. 1

Hydrogen exchange provided further evidence that the betaine is better formulated as (III; R = H) than as (XI): after recrystallization from deuterium

oxide the betaine was admitted into the mass spectrometer, together with a stream of deuterium oxide, and the resulting spectrum disclosed that three hydrogen atoms

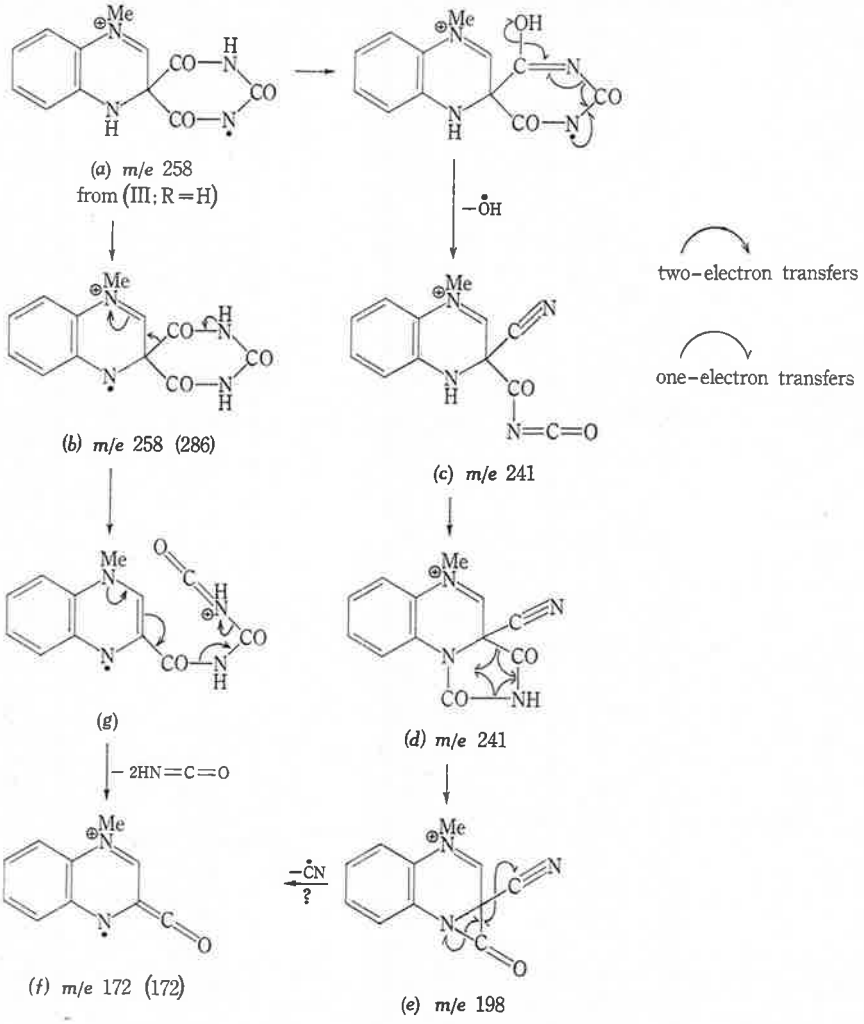
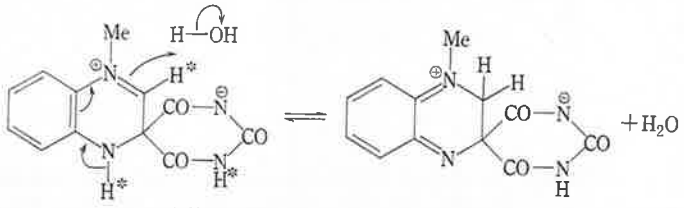


Fig. 2

had been replaced by deuterium. Exchange of the two *N*-hydrogen atoms would be expected on both formulae (III and XI), but the exchange of a third atom is more easily understood on the basis of structure (III; R = H), e.g. as shown below.



H*, exchangeable hydrogen atom.

Neutralization of the anionic charge in the isomeric barbiturates (III; R = H) and (XI) would be expected at different pH, but the compounds (III; R = H) and (VIII; R = H) proved too sparingly soluble for electrometric titration, so that the strengths of the conjugate acids could not be determined.

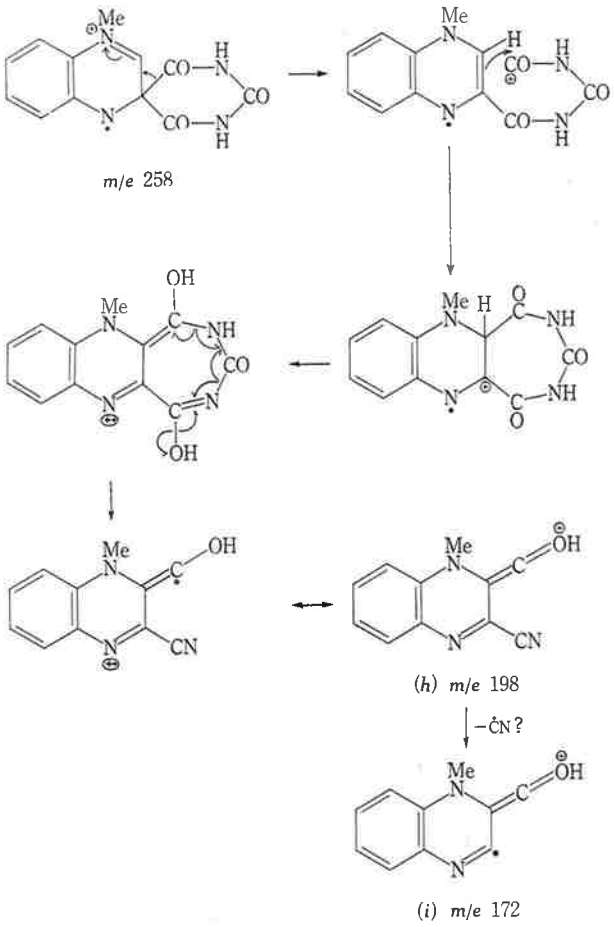


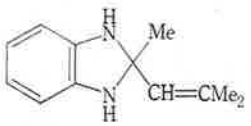
Fig. 3

Benzimidazolines and a tetrahydroquinoxaline were required as models for the putative dihydrobenzimidazole structure (VI) for the spiran (I). Very few benzimidazolines are known, but Bohlmann[11] obtained the parent compound as an unstable oil by vigorous reduction of benzimidazole with lithium aluminium hydride. Elderfield and McCarthy[12] prepared several compounds from ketones and *o*-phenylenediamines, and most of these were unstable oils which decomposed into hydrocarbons and

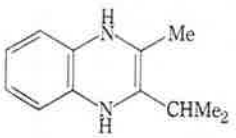
[11] Bohlmann, F., *Chem. Ber.*, 1952, **85**, 390.

[12] Elderfield, R. C., and McCarthy, J. R., *J. Amer. Chem. Soc.*, 1951, **73**, 975; see also Elderfield, R. C., and Kreysa, F. J., *J. Amer. Chem. Soc.*, 1948, **70**, 44.

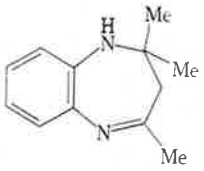
benzimidazoles when heated. One of these, which appeared to be a stable benzimidazoline (XIV), was obtained from *o*-phenylenediamine and acetone or mesityl oxide, and had previously been formulated as a dihydroquinoxaline (XV).[13] Its nuclear magnetic resonance spectrum showed, however, that the product must be regarded as the benzodiazepine (XVI) because absorptions characteristic of the isopropyl group and of vinyl protons were absent. It therefore seems likely that another supposed dihydrobenzimidazole (XVII)[12] obtained from pentan-2-one and *o*-phenylenediamine is also a benzodiazepine (XVIII). The trimethylbenzodiazepine (XVI) was prepared by Ried and Stahlhofen[14] but without reference to Elderfield and McCarthy.[12]



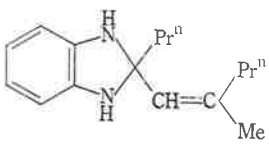
(XIV)



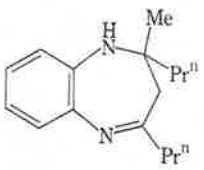
(XV)



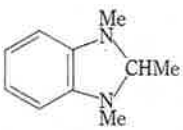
(XVI)



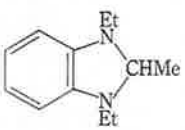
(XVII)



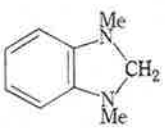
(XVIII)



(XIX)



(XX)



(XXI)

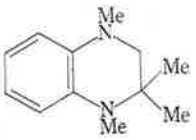
It has now been found that 1,3-disubstituted benzimidazolines (e.g. XIX–XXI) are readily obtained in good yields by reducing the appropriate alkiodide with sodium borohydride at room temperature. The products were purified by distillation under reduced pressure and obtained as colourless oils, which decomposed when exposed to air. A chloroform solution of 1,3-dimethylbenzimidazoline deposited 1-methylbenzimidazole methochloride on standing, and attempts to prepare picrates and hydrochlorides from benzimidazolines led to formation of the benzimidazolium picrates and chlorides. The picrate prepared by Bohlmann[11] from benzimidazoline is therefore probably benzimidazole picrate[15] which has the same m.p., and for which Bohlmann's analytical figures are in good agreement.

[13] Ekeley, J. B., and Wells, R. J., *Ber. dt. chem. Ges.*, 1905, **38**, 2259; cf. Ekeley, J. B., *Ber. dt. chem. Ges.*, 1906, **39**, 1646.

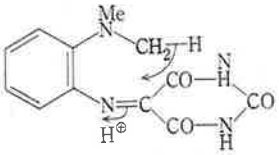
[14] Ried, W., and Stahlhofen, P., *Chem. Ber.*, 1957, **90**, 815.

[15] Skraup, S., *Liebigs Ann.*, 1918, **419**, 70.

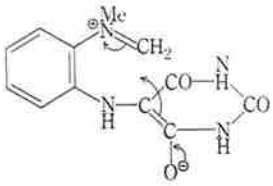
The absorption of the 2-proton in the n.m.r. spectrum of 1,2,3-trimethylbenzimidazoline (XIX) occurred as a quartet centred at τ 6·0, and the 2-methylene group in 1,3-dimethylbenzimidazoline (XXI) absorbed as a singlet at τ 5·77. The 3-methylene group of the spiran (I) absorbed at higher field (τ 6·75), and the methylene group of the reference tetrahydroquinoxaline (XXII) absorbed at τ 7·12.



(XXII)



(XXIII)



(XXIV)

During preparation of the bromo-*o*-phenylenediamines it was observed that bromination of *o*-nitrodiethylaniline to the oily 4-bromo-derivative was accompanied by de-ethylation and formation of crystalline 4-bromo-2-nitro-*N*-ethylaniline. Reduction of the latter gave 2-amino-4-bromo-*N*-ethylaniline which reacted with alloxan to give a quinoxaline-carboxyureide resembling the unbrominated ureide in light absorption and other properties. This formation of ureides by reaction with alloxan in neutral solution is typical of primary–secondary *o*-phenylenediamines,[16] but the closure of the tetrahydroquinoxaline ring in the spiran (I) through participation of the *N*-methyl group appears to be unique. This closure can be portrayed as an acid-catalysed cyclization of the anil (XXIII, arrows), or as cyclization of an intermediate (XXIV, arrows) derived from the anil by hydride shift. A similar ring-closure has recently been proposed for alkaloid biosynthesis.[17]

Experimental

Mass spectra were recorded with an Atlas CH4 mass spectrometer and the solid samples were introduced directly into the ion source. Deuterated derivatives were prepared by recrystallization of the samples from deuterium oxide and then introduced into the mass spectrometer together with a stream of deuterium oxide. Nuclear magnetic resonance spectra were determined with a Varian DP60 spectrometer and calibrated with side-bands generated by a Muirhead–Wigan decade oscillator (D890A) from the signal of tetramethylsilane used as an internal standard. Chemical shifts are given as τ values. Routine infrared spectra were recorded with an Infracord, and ultraviolet light absorption measurements were made with Optica and Unicam SP700 recording spectrophotometers and with a Hilger Uvispek.

1,2,3,4-Tetrahydro-4-methylquinoxaline-2-spiro-5′-(hexahydro-2′,4′,6′-trioxopyrimidine) (*I*) *and its 1′,3′-Dimethyl Derivative* (*V*)

(*a*) The spiran was obtained (19%) as previously described[1] and it crystallized from aqueous pyridine in small yellow plates, m.p. 250° (decomp.). Carbonyl absorption occurred near 5·72, 5·80, and 5·95 μ, and N–H stretching absorption near 3·06 and 3·11 μ (Nujol). The 1′,3′-dimethyl derivative[1] (V) crystallized from ethanol in pale yellow prisms, m.p. 194°, and its n.m.r. spectrum ($CDCl_3$) showed four sharp peaks at 3·23 (four aromatic protons), 6·68 (six protons of 1′,3′-methyl

[16] King, F. E., and Clark-Lewis, J. W., *J. Chem. Soc.*, 1951, 3379; Clark-Lewis, J. W., and Thompson, M. J., *J. Chem. Soc.*, 1957, 430.

[17] Barton, D. H. R., Hesse, R. H., and Kirby, G. W., *Proc. Chem. Soc.*, 1963, 267; Battersby, A. R., *Proc. Chem. Soc.*, 1963, 189; Barton, D. H. R., *Proc. Chem. Soc.*, 1963, 293.

groups), 6·75 (two protons of the 3-methylene group) and 7·11 (three protons of the 4-methyl group). Carbonyl absorption occurred near 5·95 μ (with a weak band at 5·75 μ), and N–H stretching absorption near 2·95 μ ($CHCl_3$).

(*b*) An excess of sodium borohydride (0·5 g) was added in small portions, with shaking, to a suspension of the quinoxalinium barbiturate (III; R = H) (1 g) in water (20 ml), and the solid dissolved during 30 min. Acidification with acetic acid precipitated the spiran (0·87 g, 98%) in small yellow plates, m.p. 250° (decomp.) alone and when mixed with that described under (*a*). The dimethyl derivative was similarly obtained by reduction of the dimethylbarbiturate (VII) (0·1 g) during *c.* 2 hr with sodium borohydride, and the product crystallized from ethanol in pale yellow prisms (0·05 g, 53%), m.p. 194° alone and when mixed with that described under (*a*).

The nitroso-derivative was prepared by adding sodium nitrite (0·17 g) in water (2 ml), dropwise to the dimethylspiran (0·65 g) dissolved in acetic acid (6 ml). The product crystallized in golden yellow needles (0·6 g, 85%) from the deep yellow solution, after chilling, and recrystallization from ethanol gave *1,2,3,4-tetrahydro-4-methyl-1-nitroso-2-spiro-5′-(hexahydro-2′,4′,6′-trioxo-1′,3′-dimethylpyrimidine)* in needles, m.p. 176° (Found: C, 53·4; H, 5·1; N, 22·3%. $C_{14}H_{15}N_5O_4$ requires C, 53·0; H, 4·8; N, 22·1%). The infrared spectrum ($CHCl_3$) was devoid of absorption in the region 2·5–3·1 μ; carbonyl absorption occurred near 5·95 μ (with a weak band at 5·75 μ).

1,2,3,4,2′,4′-Hexahydro-2′,4′-dioxo-4,3′-dimethylglyoxalino(1′,5′ : 1,2)quinoxaline (IV; R = Me)

Methylamine was evolved and potassium carbonate precipitated almost immediately when the dimethylspiran (V) (1 g) was boiled with 5% alcoholic potassium hydroxide (20 ml). The solution was acidified after 3–5 min with dilute hydrochloric acid before extraction with chloroform, and evaporation of the extract left a residue of the hydantoin (0·5 g, 62%), which crystallized from ethanol in prisms, m.p. 154° alone and when mixed with a synthetic[1] sample. The infrared spectra of the two samples (in Nujol) were indistinguishable (carbonyl absorption near 5·70 and 5·88 μ). The n.m.r. spectrum (CCl_4 with *c.* 10% $CDCl_3$) revealed the 8-proton as a doublet with secondary splitting at very low field (centre 2·11) due to deshielding by the 2′-carbonyl group. The remaining three aromatic protons formed a multiplet which was not analysed; the 2H-quartet was centred at 5·78, one of the quartets due to the 3-methylene protons at 6·37, and only the outside peaks of the remaining quartet (centre 6·97) were visible owing to overlap with absorptions by the two *N*-methyl groups (6·98 and 7·05).

1,2-Dihydro-4-methylquinoxalinium-2-spiro-5′-barbiturate (III; R = H) Dihydrate

(*a*) This was obtained from alloxan and *o*-dimethylaminoaniline, or from the spiran (I), as previously recorded[2] for the product described as the 3-hydroxyspiran (II). It crystallized from water in prisms, m.p. 370–375° (decomp.). Light absorption in ethanol (95%): max. 248 (ϵ 18,700), 268 (ϵ 7400), and 275 mμ (ϵ 5900); min. 228 (ϵ 7300), 266 (ϵ 7200), and 272 mμ (ϵ 5800).

(*b*) The 7-bromoquinoxalinium barbiturate (see below) (0·1 g) was warmed for 2 hr with an aqueous suspension of W7 Raney nickel and after filtration the solution was acidified with acetic acid (2 drops) and evaporated. Recrystallization from water gave the debrominated barbiturate (0·05 g, 60%) identical (mixed m.p. and ultraviolet light absorption) with that described under (*a*).

(*c*) The 6,7-dichloroquinoxalinium betaine (0·4 g) was warmed with a suspension of W7 Raney nickel in water (20 ml) for 3–4 hr. Evaporation of the filtrate from the catalyst and crystallization of the residue from water yielded the betaine (III) dihydrate (0·12 g, 35%) identical (mixed m.p. and light absorption) with that described under (*a*).

9-Methylisoalloxazine

The barbiturate (III; R = H) (0·5 g) was fused with a 1 : 1 mixture of sodium hydroxide and potassium hydroxide for a few minutes. Acidification of an aqueous solution of the residue with phosphoric acid precipitated 9-methylisoalloxazine (0·35 g), m.p. above 300° (decomp.), with light absorption in 95% ethanol identical with that of an authentic specimen:[18] max. at

[18] Kuhn, R., and Weygand, F., *Ber. dt. chem. Ges.*, 1934, **67**, 1409.

266 (ε 26,250), 333–336 (ε 5300), and 434–436 mμ (ε 7600); min. at 234 (ε 5500), 295 (ε 1550), and 372 mμ (ε 2200).

6,7-Dichloro-1,2,3,4-tetrahydro-4-methylquinoxaline-2-spiro-5′-(hexahydro-2′,4′,6′-trioxopyrimidine)

An excess of sodium borohydride was added to a suspension of the dichlorobetaine (previously described[2] as a 6,7-dichloro-3-hydroxyquinoxaline) (300 mg) in water (20 ml). After 3 hr the starting material had dissolved, and the solution was then acidified and stored at 4°. Next day the precipitated *dichlorospiran* (0·28 g, 98%) was collected by filtration and washed with ethanol; it crystallized from aqueous pyridine in small, pale yellow plates, m.p. 238° (Found: C, 44·4; H, 3·3; Cl, 20·9; N, 17·1%. $C_{12}H_{10}Cl_2N_4O_3$ requires C, 43·8; H, 3·1; Cl, 21·5; N, 17·0%). Light absorption in 95% ethanol: max. 230 (ε 21,600) and 312 (ε 4200), and shoulder at 260 mμ (ε 5500); min. 295 mμ (ε 1900).

1,2-Dihydro-4-methyl-2-spiro-5′-(hexahydro-1′,3′-dimethyl-2′,4′,6′-trioxopyrimidine) Betaine (VII)

A large excess of ethereal diazomethane was added to a suspension of the barbiturate (III; R = H) (1 g) in methanol (100 ml) and kept at 0°. Next day the suspension was filtered from unreacted material (0·7 g) and the filtrate was evaporated. Crystallization of the residue from methanol gave the *betaine* (VII) in needles (0·1 g), m.p. 331–333°, alone and when mixed with a sample previously prepared[2] by oxidation of the dimethylspiran (Found: 55·2; H, 5·4; N, 18·5%. $C_{14}H_{14}N_4O_3.H_2O$ requires C, 55·2; H, 5·3; N, 18·4%). Recrystallization of the earlier preparation, m.p.[2] 306–307°, from methanol raised its m.p. to 331–333°, and the two samples of higher m.p. gave identical infrared spectra (Nujol; carbonyl absorption at 6·0 μ). The 2-proton absorbed at τ 0·37 (dimethylsulphoxide solution).

7-Bromo-1,2-dihydro-4-methylquinoxalinium-2-spiro-5′-barbiturate Hydrate (III; R = Br)

Bromination[19] of 2-nitrodimethylaniline in acetic acid gave 4-bromo-2-nitrodimethylaniline, m.p. 68°, which was reduced by tin and hydrochloric acid to 2-amino-4-bromodimethylaniline, b.p. *c.* 170°/25 mm, acetyl derivative, m.p. 111° (lit.[20] b.p. 165°/23 mm, deriv. m.p. 111°). The amine (5 g) in ethanol (25 ml) was added to alloxan monohydrate (5 g) dissolved in water (10 ml) containing concentrated hydrochloric acid (3 drops). The solution deposited solid after 15 hr and the product (4 g) was collected after 3 days. It was extracted with boiling water and with pyridine, and crystallization of the water-soluble, pyridine-insoluble fractions from water (charcoal) gave the *barbiturate hydrate* (1·4 g, 19%), in long needles, m.p. 360–365° (decomp.), *d* 1·752 (Found: C, 40·7; H, 3·2; N, 15·2; O, 18·4%. $C_{12}H_9BrN_4O_3.H_2O$ requires C, 40·6; H, 3·1; N, 15·8; O, 18·0%). Light absorption in 95% ethanol: max. at 210 (ε 29,100), 247 (ε 21,000), 278 (ε 8000), and 286 mμ (ε 7100); min. at 231 (ε 12,000), 267 (ε 6000), and 282 mμ (ε 7000). The dimensions of the unit cell of the triclinic crystals were found[9] to be *a* 7·23; *b* 9·08; *c* 12·07 Å; α 63·5°; β 106°; γ 99·5°. The molecular distribution was possibly non-centric.

5-(3′-Ethyl-2′-methylbenzimidazolium)barbiturate (VIII; R = H) Trihydrate

o-Nitrodiethylaniline[20,21] distilled as a red oil, b.p. 114–116°/1 mm (bath temp. 150°) without decomposition, and gave a picrate, m.p. 122° (lit.[21] m.p. 122–123°). Hydrogenation of the nitro-compound (24·8 g) over palladized calcium carbonate gave the diamine (17·0 g, 81%), b.p. 130–131°/30 mm (bath temp. 170°) (lit.[21] b.p. 127°/25 mm), which gave a picrate,[21] m.p. 162°; the reported dipicrate[20] could not be obtained. Alloxan monohydrate (15 g) in water (40 ml) was added to a solution of *o*-aminodiethylaniline (10 g) in ethanol (70 ml) containing hydrochloric acid (10 drops). After 4 days at room temperature the sparingly soluble product was collected by filtration, and washed with ethanol. Crystallization from water gave the *barbiturate trihydrate* (5·2 g, 25%) in large prisms, m.p. *c.* 396° (decomp.) (Found: C, 49·2; H, 5·9; N, 16·5; O, 28·9%. $C_{14}H_{14}N_4O_3.3H_2O$ requires C, 49·4; H, 5·9; N, 16·5; O, 28·2%). Light absorption in water: max. at 247 (ε 22,100), 270 (ε 9500), and 276 mμ (ε 8900); min. at 228

[19] Aitken, F., and Reade, T. H., *J. Chem. Soc.*, 1926, 1896.
[20] Weissenberger, G., *Mh. Chem.*, 1912, **33**, 821.
[21] Hall, D. M., and Turner, E. E., *J. Chem. Soc.*, 1945, 694.

(ϵ 8700), 266 (ϵ 8500), and 273 mμ (ϵ 6700). When dried over phosphoric oxide it gave a *hemihydrate*, m.p. *c.* 396° (decomp.) (Found: C, 56·6; H, 5·1; N, 19·0; O, 19·0%. $C_{14}H_{14}N_4O_3.\frac{1}{2}H_2O$ requires C, 56·9; H, 5·1; N, 19·0; O, 18·9%). The n.m.r. spectrum of the barbiturate in trifluoroacetic acid showed four aromatic protons as a multiplet centred at 2·28, the methylene and methyl protons of the ethyl group at 5·44 and 8·29, and a single peak at 7·12 due to the 2′-methyl group. The betaine was recovered (65%) after being boiled with 20% aqueous sodium hydroxide for 3½ hr, and it was recovered quantitatively from a solution in 30% aqueous sodium hydroxide which had been stored at room temperature for 3 days. The betaine was also recovered after it had been heated in concentrated sulphuric acid. Reduction of the betaine with sodium borohydride occurred slowly and after 12 hr the ultraviolet light absorption of the solution corresponded to that of a benzimidazoline, but acidification yielded the original benzimidazolium betaine.

Alkali Fusion of 5-(3′-Ethyl-2′-methylbenzimidazolium)barbiturate

The barbiturate trihydrate (2 g) was fused with a 1 : 1 mixture of sodium and potassium hydroxides (2 g) for several minutes. The residue was dissolved in water (25 ml) and extracted several times with ether. The dried (Na_2SO_4) extract was evaporated and distillation of the residue under reduced pressure gave a pale yellow viscous oil (0·2 g, 21%) with light absorption typical of benzimidazoles. The hydrochloride crystallized from methanol–ether mixture in prisms; m.p. 191° not depressed when mixed with the hydrochloride (m.p. 193–194°) prepared from authentic 1-ethyl-2-methylbenzimidazole (see below).

5-(3′-Ethyl-2′-methylbenzimidazolium)-1,3-dimethylbarbiturate (*X*)

A large excess of ethereal diazomethane was added to the foregoing betaine (0·9 g) suspended in methanol (100 ml), and the mixture was stirred at 0°. Next day unreacted material (0·6 g) was removed by filtration and the filtrate was evaporated. The *dimethylbarbiturate* (0·2 g, 23%) crystallized from acetone in prisms, m.p. 285–286° (Found: C, 60·8; H, 6·2%. $C_{16}H_{18}N_4O_3.H_2O$ requires C, 60·7; H, 6·4%). The dimethylbarbiturate in $CDCl_3$ gave an n.m.r. spectrum with a peak at 2·5 (single peak due to four aromatic protons), the *N*-ethyl group quartet at 5·67 and triplet at 8·45, a six-proton peak at 6·64 (1,3-dimethyl groups) and a three-proton peak at 7·29 (2′-methyl group).

4-Bromo-2-nitrodiethylaniline and 4-Bromo-2-nitro-N-ethylaniline

Bromine (5·2 g) in acetic acid (10 ml) was added during 45 min to *o*-nitrodiethylaniline (6 g) in acetic acid (20 ml), and the mixture was stirred at 60° for 12 hr. Thin-film chromatography on silica gel plates developed with benzene–hexane (1 : 9) mixture indicated the presence of two products, and the mixture was then separated by chromatography on an alumina column with hexane as eluent. 4-Bromo-2-nitro-*N*-ethylaniline[22] (1·9 g, 25%) crystallized from hexane or ethanol in orange-red prisms, m.p. 91° (Found: C, 39·4; H, 4·0; Br, 31·1%. Calc. for $C_8H_9BrN_2O_2$: C, 39·2; H, 3·7; Br, 32·6%). *4-Bromo-2-nitrodiethylaniline* (4·1 g, 49%) was obtained as an orange-red oil, b.p. 129–130°/0·7 mm, n_D^{25} 1·5943 (Found: C, 44·1; H, 4·8; Br, 29·1%. $C_{10}H_{13}BrN_2O_2$ requires C, 44·0; H, 4·8; Br, 29·3%). Reduction of the nitro-compound with tin and hydrochloric acid gave *2-amino-4-bromodiethylaniline* (82%) as a colourless oil, b.p. 150°/2·5 mm, n_D^{26} 1·5810 (Found: C, 49·2; H, 6·0; Br, 33·0%. $C_{10}H_{15}BrN_2$ requires C, 49·4; H, 6·2; Br, 32·9%).

5-(6′-Bromo-3′-ethyl-2′-methylbenzimidazolium)barbiturate (*VIII*; *R* = *Br*) *Hydrate*

Alloxan hydrate (12 g) in water (40 ml) was added to a mixture of 2-amino-4-bromodiethylaniline (10 g), ethanol (70 ml), and hydrochloric acid (5 drops), and the solution was kept at room temperature. Filtration after three days yielded *5-(6′-bromo-3′-ethyl-2′-methylbenzimidazolium)barbiturate* (1·2 g, 8%) which crystallized from water (charcoal) in large prisms, m.p.

[22] Blanksma, J. J., *Rec. Trav. Chim. Pays-Bas*, 1902, **21**, 273; Feitelson, B. N., Mamalis, P., Moualim, R. J., Petrow, V., Stephenson, O., and Sturgeon, B., *J. Chem. Soc.*, 1952, 2389.

about 400° (decomp.), *d* 1·652 (Found: C, 44·0; H, 3·8; Br, 21·4; N, 14·1; O, 17·2%. $C_{14}H_{13}BrN_4O_3.H_2O$ requires C, 43·9; H, 3·9; Br, 20·9; N, 14·6; O, 16·7%). Light absorption in 95% ethanol: max. at 209 (ε 40,300), 247 (ε 23,700), 279 (ε 10,000), and 287 mμ (ε 9200); min. at 233 (ε 13,300), 266 (ε 6600), and 284 mμ (ε 8100). The unit cell of the monoclinic prisms (space group $P2_1/n$) was found[9] to contain eight molecules and to have the dimensions *a* 8·687± 0·004, *b* 14·995±0·003, *c* 23·730±0·004 Å, and β 95° 5·3±1·5′. The bromo-compound (0·05 g) was warmed for 1½ hr with an aqueous suspension of W7 Raney nickel, and the filtrate from the catalyst was acidified with acetic acid and stored at 2–3°. 5-(3′-Ethyl-2′-methylbenzimidazolium) barbiturate (0·02 g, 45%) crystallized in prisms, m.p. *c.* 396° (decomp.) identical (m.p., infrared and ultraviolet spectra) with the material already described.

5,7,7-Trimethyl-2,3-benzo-1,4-diazepine (*XVI*)

This compound was prepared according to Elderfield and McCarthy[12] (compare ref.[13]) and it crystallized from light petroleum, b.p. 40–60°, in large prisms, m.p. 125° (lit.[12,14] m.p. 125°). The benzodiazepine structure was confirmed by the n.m.r. spectrum ($CDCl_3$) which showed four aromatic protons in a multiplet, a single proton peak at 7·08 (NH), a three-proton peak at 7·63 (5-methyl group), a two-proton peak at 7·76 (6-methylene group), and a six-proton peak at 8·66 (7,7-dimethyl group).

1,2,3-Trimethylbenzimidazoline (*XIX*)

1,2,3-Trimethylbenzimidazolium iodide[23] crystallized from ethanol in plates, m.p. 256°. An excess of sodium borohydride was added during 45 min to an aqueous solution (*c.* 25 ml) of the iodide (2 g). The reaction mixture was extracted with ether, and evaporation of the dried ($MgSO_4$) extract left a residue which on distillation gave *1,2,3-trimethylbenzimidazoline* (1·6 g, 90%) as an oil, b.p. 110°/3 mm, n_D^{27} 1·5710, unstable on exposure to air (Found: C, 74·0; H, 8·8%. $C_{10}H_{14}N_2$ requires C, 74·0; H, 8·7%). Light absorption in 95% ethanol: max. 218 (ε 33,100), 266 (ε 5700), and 310 (ε 5700); min. 243 (ε 4200) and 286 mμ (ε 3100). The n.m.r. spectrum of the compound (in CCl_4) showed a four-proton multiplet (aromatic protons), a quartet at 6·0 due to the 2-H, a six-proton peak at 7·38 (*N*-methyl groups), and a three-proton doublet (5 c/s splitting) at 8·54 (*C*-methyl group). Addition of dry hydrogen chloride to an ethereal solution of the benzimidazoline gave 1,2,3-trimethylbenzimidazolium chloride, which crystallized from ethanol–ether as a dihydrate in prisms, m.p. 227° (lit.[24] m.p. 225–230°) (Found: C, 51·7; H, 7·9; N, 11·8%. Calc. for $C_{10}H_{13}ClN_2.2H_2O$: C, 51·6; H, 7·4; N, 12·0%).

1,3-Diethyl-2-methylbenzimidazoline (*XX*)

1-Ethyl-2-methylbenzimidazole hydrochloride,[25] m.p. 193–194°, was converted into 1,3-diethyl-2-methylbenzimidazolium iodide[26] which crystallized from ethanol in prisms, m.p. 200°, and reduction of this compound with sodium borohydride as described for the trimethyl analogue gave *1,3-diethyl-2-methylbenzimidazoline* as a colourless oil, b.p. 74–75°/0·5 mm, n_D^{26} 1·6376 (Found: C, 75·9; H, 9·4%. $C_{12}H_{18}N_2$ requires C, 75·7; H, 9·5%). Light absorption in 95% ethanol: max. at 220 (ε 26,400), 268 (ε 5000), and 315 mμ (ε 4600); min. at 242 (ε 3700) and 292 mμ (ε 2800).

1,3-Dimethylbenzimidazoline (*XXI*)

1,3-Dimethylbenzimidazolium iodide (IX) prepared according to Fischer and Fussenegger[27] crystallized from methanol in colourless prisms, m.p. 200–201° (lit.[28] m.p. 200–201°). The 2-proton

[23] Shriner, R. L., and Boermans, P. G., *J. Amer. Chem. Soc.*, 1944, **66**, 1810.

[24] Pinnow, J., and Sämann, C., *Ber. dt. chem. Ges.*, 1899, **32**, 2181.

[25] Weidenhagen, R., and Train, G., *Ber. dt. chem. Ges.*, 1942, **75**, 1942.

[26] Brooker, L. G. S., Sklar, A. L., Cressman, H. W. J., Keyes, G. H., Smith, L. A., Sprague, R. H., Van Lare, E., Van Zandt, G., White, F. L., and Williams, W. W., *J. Amer. Chem. Soc.*, 1945, **67**, 1875.

[27] Fischer, O., and Fussenegger, E., *Ber. dt. chem. Ges.*, 1901, **34**, 936.

[28] Breslow, R., *J. Amer. Chem. Soc.*, 1958, **80**, 3725.

absorbed as a singlet at τ 0·30 (dimethylsulphoxide solution). Reduction with sodium borohydride gave *1,3-dimethylbenzimidazoline* (81%) as a colourless oil, b.p. 86°/1·5 mm, n_D^{27} 1·5850 (Found: C, 72·7; H, 8·0%. $C_9H_{12}N_2$ requires C, 72·9; H, 8·2%). The n.m.r. spectrum (CCl_4) showed four aromatic protons in a multiplet, a two-proton peak (5·77) due to the methylene group, and a six-proton peak (7·34) due to the *N*-methyl groups. Light absorption in 95% ethanol: max. 217 (ϵ 36,900), 265 (ϵ 5700); min. at 241 (ϵ 3400) and 286 mμ (ϵ 3100). The benzimidazoline and ethanolic picric acid yielded 1,3-dimethylbenzimidazolium picrate, which crystallized from ethanol in needles, m.p. 195–196°, alone and when mixed with an authentic specimen. The light absorption of the picrate in 95% ethanol showed the sharp maxima at 270 and 278 mμ typical of benzimidazolium salts.

1-Methyl-3-(2-oxopropyl)benzimidazolium Iodide and 1-Methyl-3-(2-hydroxypropyl)benzimidazoline

A mixture of benzimidazole (3 g), chloroacetone (5 ml), anhydrous potassium carbonate (5 g), and acetone (250 ml) was stirred under reflux for 19 hr and then filtered. Evaporation of the filtrate left an oil, which solidified (2 g, 45%), and recrystallization from ethyl acetate gave *1-(2-oxopropyl)benzimidazole* in needles, m.p. 131° (Found: C, 69·1; H, 5·8; N, 15·8%. $C_{10}H_{12}N_2O$ requires C, 69·0; H, 5·8; N, 16·1%). The *methiodide* crystallized from ethanol in plates, m.p. 196° (Found: C, 42·4; H, 4·5; N, 8·4%. $C_{11}H_{13}IN_2O$ requires C, 41·8; H, 4·1; N, 8·9%). When reduced with sodium borohydride the methiodide (0·5 g) gave *1-methyl-3-(2-hydroxypropyl)benzimidazoline* (0·45 g) as a viscous, colourless oil, b.p. 156°/0·3 mm, n_D^{26} 1·5758 (Found: C, 67·9; H, 8·3; N, 14·8%. $C_{11}H_{16}N_2O$ requires C, 68·7; H, 8·4; N, 14·6%). Light absorption in 95% ethanol: max. at 220 (ϵ 23,000), 269 (ϵ 4900), and 315 mμ (ϵ 4500); min. at 242 (ϵ 3600) and 292 mμ (ϵ 2800).

1,2,3,4-Tetrahydro-2,2,4-trimethyl-3-oxoquinoxaline and 1,2,3,4-Tetrahydro-1,2,2,4-tetramethyl-3-oxoquinoxaline

1,2,3,4-Tetrahydro-2,2-dimethyl-3-oxoquinoxaline (4·6 g, 58%), prepared from methyl α-bromoisobutyrate and *o*-phenylenediamine, crystallized from benzene in plates, m.p. 175–176° (lit.[29] m.p. 175–176° and 177°) (Found: C, 68·3; H, 6·7; N, 16·1%. Calc. for $C_{10}H_{12}N_2O$: C, 68·2; H, 6·9; N, 15·9%). Light absorption in 95% ethanol: max. at 223–224 (ϵ 38,500), 263–266 (ϵ 2800), and 306 mμ (ϵ 4400); min. at 251 (ϵ 2400) and 281–282 mμ (ϵ 2200). The quinoxaline (3·7 g) was methylated with methyl iodide–potassium carbonate–acetone at the b.p. for 19 hr and gave *1,2,3,4-tetrahydro-2,2,4-trimethyl-3-oxoquinoxaline* (1·38 g, 35%), which crystallized from hexane in plates, m.p. 113–114° (Found: C, 69·4; H, 7·1; N, 15·0; NMe, 5·4%. $C_{11}H_{14}N_2O$ requires C, 69·5; H, 7·4; N, 14·7; NMe, 7·9%). Light absorption in 95% ethanol: max. at 225–226 (ϵ 36,600), 270–272 (ϵ 3200), and 307 mμ (ϵ 4300); min. at 252 (ϵ 2100) and 287 mμ (ϵ 2800). The hexane mother liquors were chromatographed with hexane on alumina, and evaporation of the eluate (600 ml) left a residue of *1,2,3,4-tetrahydro-1,2,2,4-tetramethyl-3-oxoquinoxaline* which distilled as an oil (1·8 g, 42%), b.p. 114°/0·05 mm, n_D^{25} 1·5771 (Found: C, 70·5; H, 7·9; N, 13·7%. $C_{12}H_{16}N_2O$ requires C, 70·6; H, 7·9; N, 13·7%). The compound dissolved in dilute acid but was sparingly soluble in water. Light absorption in 95% ethanol: max. at 225 (ϵ 37,100), 264–266 (ϵ 3400), and 307 mμ (ϵ 4200); min. at 253–254 (ϵ 2950) and 284 mμ (ϵ 2100). The tetramethylquinoxalone (2·6 g, 50%) was also obtained as an oil, b.p. 132°/0·7 mm, n_D^{25} 1·5769, from methyl α-bromoisobutyrate (4·6 g) and *NN'*-dimethyl-*o*-phenylenediamine[30] (7·5 g) at 150° for 3 hr (Found: N, 14·2%). The ultraviolet light and infrared spectra of samples prepared by the two methods were indistinguishable.

1,2,3,4-Tetrahydro-1,2,2,4-tetramethylquinoxaline (XXII)

The tetramethylquinoxalone (1·0 g) in anhydrous ether (20 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0·4 g) in ether (15 ml) and the mixture was then boiled for 2 hr. The excess of hydride was decomposed with water and the precipitated hydroxide was removed by filtration. The filtrate was dried ($MgSO_4$) and evaporation left *1,2,3,4-tetrahydro-1,2,2,4-tetramethylquinoxaline* which distilled as an oil (0·76 g, 80%), b.p.

[29] Banti, G., *Gazz. Chim. Ital.*, 1929, **59**, 819 (*Chem. Abstr.*, 1930, **24**, 1632).

[30] Cheeseman, G. W. H., *J. Chem. Soc.*, 1955, 3308; Stetter, H., *Chem. Ber.*, 1953, **86**, 161.

156°/16 mm, n_D^{25} 1·5791 (Found: C, 75·7; H, 9·4%. $C_{12}H_{18}N_2$ requires C, 75·7; H, 9·5%). The n.m.r. spectrum of the compound (in CCl_4) showed a multiplet centred at 3·57 (four aromatic protons), a two-proton peak at 7·12 (3-methylene group), three-proton peaks at 7·19 and 7·31 (*N*-methyl groups), and a six-proton peak at 8·87 (*C*-methyl groups). Light absorption in 95% ethanol: max. at 227 (ε 31,600), 270 (ε 6400), and 313 mμ (ε 5200); min. at 247 (ε 3500) and 293–294 (ε 3700). The compound reduced ammoniacal silver nitrate rapidly. The *picrate* crystallized from ethanol in needles, m.p. 152° (Found: C, 51·6; H, 5·2%. $C_{18}H_{21}N_5O_7$ requires C, 51·6; H, 5·1%).

4-Ethyl-3,4-dihydro-3-oxoquinoxaline-2-carboxyureide and -2-carboxylic Acid

Catalytic hydrogenation of *o*-nitro-*N*-ethylaniline,[25] b.p. 122–124°/0·8 mm, n_D^{27} 1·6768, gave *N*-ethyl-*o*-phenylenediamine.[31] The diamine (10 g) in ethanol (50 ml) was added to alloxan hydrate (10 g) in water (25 ml), and the *ureide* (13·8 g, 72%) was collected after 3 hr; it crystallized from acetic acid in yellow needles, m.p. 235° (Found: C, 55·3; H, 4·5; N, 21·3%. $C_{12}H_{12}N_4O_3$ requires C, 55·4; H, 4·7; N, 21·5%). Hydrolysis of the ureide (1 g) with boiling 2N hydrochloric acid for 30 min gave *4-ethyl-3,4-dihydro-3-oxoquinoxaline-2-carboxylic acid,* which crystallized from the cold solution in yellow plates (0·6 g, 71%), m.p. 175° (decomp.) raised to m.p. 177° (decomp.) by recrystallization from water (Found: N, 12·9%. $C_{11}H_{10}N_2O_3$ requires N, 12·8%).

7-Bromo-4-ethyl-3,4-dihydro-3-oxoquinoxaline-2-carboxyureide

The 4-bromo-2-nitro-*N*-ethylaniline already described was hydrogenated over Raney nickel, and the diamine (1·7 g) in ethanol (25 ml) was mixed with alloxan monohydrate (1·3 g) in water (10 ml), and the mixture was heated under reflux for 5 min. The *ureide* (1·6 g, 47%) was collected; it crystallized from ethanol in yellow needles, m.p. 230–232° (Found: C, 42·9; H, 3·6%. $C_{12}H_{11}BrN_4O_3$ requires C, 42·5; H, 3·3%). Light absorption in 95% ethanol: max. at 245 (ε 28,900), 312 (ε 6900), and 395 mμ (ε 4500); min. at 227 (ε 13,000), 275 (ε 3300), and 340 mμ (ε 2200).

Deuterium Exchange

When deuterium oxide was admitted to the ion source of the mass spectrometer the betaines exchanged extremely slowly, and the deuterated betaines were therefore obtained by crystallizations from deuterium oxide prior to introduction into the mass spectrometer. When crystallized from deuterium oxide the spiran (I) and the betaine (III) each quickly exchanged three atoms and the dimethyl derivative (VII) exchanged one hydrogen atom; the betaine (VIII; R = H) exchanged five hydrogen atoms and its dimethyl derivative did not undergo exchange. The dimethylbarbiturate (VII) very slowly acquired 5–7 deuterium atoms and the dimethylbarbiturate (IX) three deuterium atoms by exchange.

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[31] Hempel, A., *J. prakt. Chem.* [2], 1889, **39**, 199; 1890, **41**, 164.