# Dihydrobenzimidazole Chemistry. Part III.† Acid-catalysed Cyclisations of *o*-Pyrrolidino Anils

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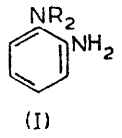
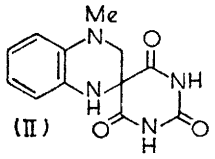
Anils derived from *o*-pyrrolidinoaniline and a wide variety of aldehydes are shown to undergo a rapid cyclisation in the cold with acid catalysts to give dihydrobenzimidazoles. Alloxan is shown to react in a similar manner with various anilines to give benzimidazolium salts. The scope and limitations of the reaction are discussed and the mechanism is shown to involve intramolecular proton transfer. The formation of both benzimidazolium salts and spiro-quinoxalines in the alloxan reactions is shown to occur by way of a common dihydrobenzimidazole intermediate. The ring expansion of dihydrobenzimidazoles to quinoxalines constitutes a new type of rearrangement reaction.



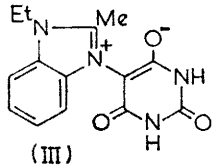
In the presence of suitable *ortho*-substituents, the otherwise unreactive dialkylanilines often show a surprising reactivity at the *N*-alkyl position. Thus numerous [3] workers have noted the formation of benzimidazoles during the reduction of *ortho*-nitro-dialkylanilines to the *ortho*-amino-analogues. Pyrolysis of these nitro-compounds also results in benzimidazoles,[4] while the action of zinc chloride and acetic anhydride gives benzimidazolones and 2-acetoxymethylbenzimidazoles [5d] (not quinoxalines as originally proposed [5a-c]). Photolysis of *N*-2,4-dinitrophenyl derivatives of amino-acids (*e.g.* leucine) in neutral media results in 2-nitroso-4-nitro-*N*-methylaniline and isobutyraldehyde.[6a,b]. In acid



(I)



(II)



(III)

solution a benzimidazole *N*-oxide is formed by recombination of the two primary products.[6c-f] *o*-Aminodialkylanilines (I) or their acyl derivatives have been shown to give benzimidazoles with peracids [7] *via* the corresponding *N*-oxide.[7b] The same amines (I) react readily with alloxan. However instead of the expected anil, the dimethyl compound (I; R = Me) gave a spiro-quinoxaline (II) while the diethyl analogue gave the benzimidazolium barbiturate (III).[8] Dealkylation accompanies the formation of benzimidazoles by action of chloral hydrate and hydroxylamine in acidic solution on the amines (I). The polymethylene-analogues (I; $R_2 = [CH_2]_n$) react similarly with concomitant ring-opening.[9] The prolonged action of acetic anhydride [3a,c,e,10a,b] on the amines (I) or of polyphosphoric acid [10c,d] on their *N*-acyl derivatives results in benzimidazoles with loss of an alkyl substituent. The polymethyleno-analogues are again ring-opened but the chain recyclises to give a tricyclic benzimidazole.[10c,d] *o*-Dialkylaminoazobenzenes undergo acid-catalysed ring-closure to give a benzimidazole and the corresponding *o*-aminodialkylaniline.[1,11] The reaction is also brought about by transition-metal salts. The *o*-dialkylaminophenylazosulphonates are similarly cyclised with acid to give a mixture of a benzimidazolium salt and a triazine.[12] Quinones and quinone-imides bearing an *ortho*-tertiary amino-substituent undergo photolytic cyclisation to give benzoxazolines [13a,b,d] and benzimidazoles.[13c,e] Both

† Two previous short communications [1,2] are considered as Parts I and II of this series.

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[2] R. K. Grantham and O. Meth-Cohn, *Chem. Comm.*, 1968, 500.

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[4] H. Suschitzky and M. E. Sutton, *Tetrahedron Letters*, 1967, 3933.

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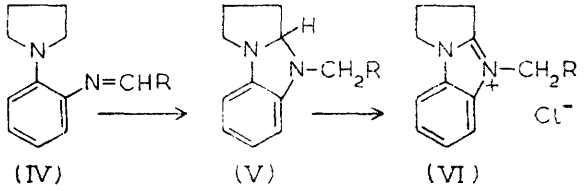
[13] (*a*) E. P. Fokin and E. P. Prudchenko, *Izvest. sibirsk. Otdel. Akad. Nauk S.S.S.R., Ser. khim. Nauk*, 1966, 98 (*Chem. Abs.*, 1967, **66**, 37,809); (*b*) D. W. Cameron and R. G. F. Giles, *Chem. Comm.*, 1965, 573; (*c*) I. Baxter and D. W. Cameron, *Chem. and Ind.*, 1967, 1403; (*d*) D. W. Cameron and R. G. F. Giles, *J. Chem. Soc.* (*C*), 1968, 1461; (*e*) I. Baxter and D. W. Cameron, *J. Chem. Soc.* (*C*), 1968, 1747.

thermal and photolytic action of 1-t-aminoanthraquinone yields the corresponding oxazine.[14]

All these reactions involve compounds in which an unsaturated *ortho*-substituent is either initially involved or is a key intermediate in a ring-closure reaction with the adjacent nitrogen atom or the *N*-methylene or methyl group. We now report more fully on the acid-catalysed formation of dihydrobenzimidazoles (V) from the anils of *ortho*-substituted amines (IV).

In an earlier communication we noted that when a mixture of *o*-pyrrolidinoaniline (I; $R_2 = [CH_2]_4$) and an aldehyde, or the anil (IV) derived from these reactants, was treated with a catalytic amount of acid in cold ethanol solution, a rapid cyclisation ensued to give high yields of the product (V). When these products are warmed with carbon tetrachloride (or if the cyclisation is performed in this solvent with trifluoroacetic acid as catalyst) a ready oxidation to the benzimidazolium salt (VI) is observed with elimination of hydride ions and the formation of chloroform. El'tsov and his co-workers [15] have commented on the hydride lability of dihydrobenzimidazoles and shown the generality of this aromatisation. In a similar manner the reduction of acetone to isopropyl alcohol accompanies the aromatisation of the dihydrobenzimidazoles when they are heated under reflux in this solvent in the presence of acid. The benzimidazolium salts are readily reconverted into their dihydro-analogues with sodium borohydride.



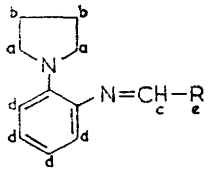

(IV) (V) (VI)

This ready cyclisation can be brought about with aliphatic, olefinic, aromatic, or hetero-aromatic aldehydes with equal facility the only limitation being with those compounds which do not readily form anils (*e.g.* 2,4-dinitrobenzaldehyde). Some ketones have also been employed, though the same limitation applies and further reaction is possible which is discussed later in this paper (Tables 1—3 summarise the relevant details). The nature of the aromatic ring containing the amine function appears to be critical. Thus, while the presence of a nitro-group *para* to the pyrrolidine ring does not inhibit the ring-closure, the acid treatment of the pyridine system (VII) did not effect cyclisation. Variation of the tertiary amine was also critical and, although with rings larger than that of pyrrolidine no significant reaction was observed under the conditions employed in this paper (*i.e.* catalytic quantities of acid), further research (see following paper) revealed an interesting series of reactions. Anils of the corresponding *o*-dialkylaminoanilines (I) also failed to cyclise under these conditions. Finally, variation of the acid catalyst only affected the ease with which cyclisation took place, in qualitative order of acid strength. Thus, even benzoic acid (in the small quantity present in commercial benzaldehyde) brought about the formation of the corresponding dihydrobenzimidazole when unpurified benzaldehyde and *o*-pyrrolidinoaniline were warmed together.

Analogies to this reaction are found in the literature. The cyclisation of azo-compounds [1,11] to benzimidazoles with acid has already been referred to. We also found that when 2,2′-dipiperidinoazobenzene was heated with

TABLE 1

Properties of the anils (IV) and (VII)




| R (XVIII) | Form * (solvent) | M.p. or b.p. (mm.) | N.m.r. shifts (τ) a | b | c | d | e | Coupling constants $J$ (Hz) | Found (%) C | H | N | Formula | Requires (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ph | Yellow liq. | 165° (0·5) | 6·55c | 8·13c | 1·75s | | 2·0—3·6c | | 81·8 | 7·3 | 11·0 | $C_{17}H_{18}N_2$ | 81·55 | 7·25 | 11·2 |
| *o*-$O_2N{\cdot}C_6H_4$ | Red n. (L.P.) | 87 | 6·52c | 8·11c | 1·13s | | 1·6—2·5c | | 68·9 | 5·6 | 14·7 | $C_{17}H_{18}N_2O_2$ | 69·1 | 5·8 | 14·2 |
| *m*-$O_2N{\cdot}C_6H_4$ | Red n. (L.P.) | 60 | 6·50c | 8·08c | 1·55s | | 1·3—3·5c | | 69·0 | 5·8 | 14·6 | $C_{17}H_{17}N_3O_2$ | 69·1 | 5·8 | 14·2 |
| *p*-$O_2N{\cdot}C_6H_4$ | Maroon n. (L.P.) | 159 | 6·49c | 8·05c | 1·50s | 2·6—3·4 | 2·01d 1·67d | 9·0 | 68·75 | 5·9 | 14·3 | $C_{17}H_{17}N_3O_2$ | 69·1 | 5·8 | 14·2 |
| PhCH=CH α β | Orange n. (EtOH) | 101 | 6·59c | 8·10c | 1·81dd | | 2·3—3·4c | $J_{\beta,c}$ 5·5 $J_{\alpha,c}$ 3·5 | 82·4 | 7·45 | 9·95 | $C_{19}H_{20}N_2$ | 82·6 | 7·3 | 10·1 |
| 2-Cl, 5-$NO_2{\cdot}C_6H_3$ | Maroon n. (EtOH) | 114 | 6·48c | 8·05c | 1·18s | 2·7—3·5c | 2·46d (3) 1·86dd (4) 1·00d (5) | $J_{3,4}$ 9·0 $J_{4,6}$ 3·0 | 62·1 | 4·8 | 12·6 | $C_{17}H_{16}ClN_3O_2$ | 62·1 | 4·9 | 12·7 |
| (XXI) | Maroon p. (EtOH) | 158—160 | 6·23c | 8·05c | 1·45s | | 1·5—3·5c | | 64·6 | 5·3 | 18·65 | $C_{16}H_{16}N_4O_3$ | 64·8 | 5·4 | 18·9 |

* L.P. = light petroleum; c = complex; d = doublet; dd = double doublet; n = needles; p = plates; s = singlet.

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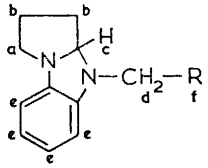
TABLE 2

Properties of the dihydrobenzimidazoles (V)

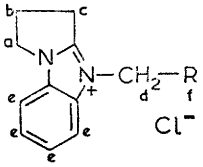


| R | Yield (%) | Form and solvent † | M.p. or b.p. (mm.) | N.m.r. chemical shift (τ) † a | b | c | d | e | f | Coupling constant J (Hz) | Found (%) C | H | N | Formula | Requires (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ph | 89 | Yellow liq. | 164° (0·6) | 6·2—7·2c | 8·3c | 4·97c | 5·78s | 2·5—3·9c | 2·77s | | 81·15 | 7·4 | 10·6 | $C_{17}H_{18}N_2$ | 81·55 | 7·25 | 11·2 |
| Ph(HCl) | 89 | White n. | 135 | 6·65/6·0c | 7·88c | 4·36c | 5·60 | 2·3—3·5c | 2·64s | | 71·0 | 6·65 | 9·7 | $C_{17}H_{19}ClN_2$ | 71·1 | 6·7 | 9·8 |
| o-$O_2N{\cdot}C_6H_4$ | 86 | Red pr. (EtOH) | 64 | 6·75 | 8·22c | 4·88 | 5·33q | 3·2—4·0c | 1·8—2·8c | $J_{d,d}$ 17 | 69·0 | 5·7 | 14·7 | $C_{17}H_{17}N_3O_2$ | 69·1 | 5·8 | 14·2 |
| o-$O_2N{\cdot}C_6H_4$(HCl) | 89 | Yellow pr. (EtOH) | 155 | 6·7/5·95c | 7·90c | 4·35c | 5·18q | 1·8—3·5c | | $J_{d,d}$ 17 | 61·0 | 5·0 | 12·45 | $C_{17}H_{18}ClN_3O_2$ | 61·5 | 5·5 | 12·7 |
| m-$O_2N{\cdot}C_6H_4$ | 82 | Red pr. (L.P.) | 92 | 6·7c | 8·2c | 4·89c | 5·62q | 3·0—3·9c | 1·7—2·7c | $J_{d,d}$ 17 | 68·8 | 5·5 | 14·1 | $C_{17}H_{17}N_3O_2$ | 69·1 | 5·8 | 14·2 |
| p-$O_2N{\cdot}C_6H_4$ | 85 | Red pr. (L.P.) | 91 | 6·8c | 8·2c | 4·90c | 5·63q | 3·2—3·9c | 2·53d 1·85d | $J_{d,d}$ 17; $J_f$ 8·5 | 69·2 | 5·65 | 14·6 | $C_{17}H_{17}N_3O_2$ | 69·1 | 5·8 | 14·2 |
| 3,4-$Cl_2C_6H_3$(HCl) | 84 | White n. (EtOH) | 125—130 | 6·65/5·95c | 7·78c | 4·32c | 5·57s | 2·4—3·5c | | | 56·8 | 4·65 | 7·7 | $C_{17}H_{17}Cl_3N_2$ | 57·45 | 4·8 | 7·9 |
| m-HO·$C_6H_4$(HCl) * | 81 | White n. (EtOH) | 156 | 5·95c | 7·6c | 4·0c | 5·3 | 3·0 | 4·1c | | 66·9 | 6·3 | 9·00 | $C_{17}H_{19}ClN_2O$ | 67·4 | 6·3 | 9·25 |
| 2-Cl, 5-$NO_2{\cdot}C_6H_3$ | 96 | Red-brown pr. (EtOH) | 125 | 6·69c | 8·15c | 4·86c | 5·56q | 3·2—3·9c | 2·48d (3) 1·92dd (4) 1·72d (6) | $J_{3,4}$ 9·0; $J_{d,d}$ 18; $J_{4,6}$ 2·5 | 62·1 | 4·8 | 12·5 | $C_{17}H_{16}ClN_3O_2$ | 62·1 | 4·9 | 12·7 |
| 2-Thienyl | 85 | Yellow liq. | 160—165 (1) | 6·9c | 8·29c | 4·99c | 5·67s | 2·8—3·8c | | | 70·2 | 6·6 | 10·85 | $C_{15}H_{16}N_2S$ | 70·55 | 6·3 | 10·95 |
| 4-Pyridyl | 87 | Yellow liq. | 165—170(1) | 6·81c | 8·23c | 4·95c | 5·76s | 2·8—4·0c | 2·78d 1·47d | $J_f$ 6·0 | 76·1 | 7·0 | 16·55 | $C_{16}H_{17}N_3$ | 76·55 | 6·8 | 16·7 |

* N.m.r. in $D_2O$ solution, chmical shifts relative to HOD (τ 5·3). † c = complex; d = doublet; dd = double doublet; L.P. = light petroleum; q = quartet; s = singlet.

TABLE 3

Properties of the benzimidazolium salts (VI)

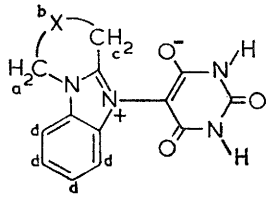


| R | Yield (%) | M.p. or b.p. (mm.) | N.m.r. chemical shift (τ) ‡ a | b | c | d | e | f | Others | Coupling constant J (Hz) | Found (%) C | H | N | Formula | Requires (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ph($2H_2O$) * | 86 | 219—220° | 5·66tr | 7·15qi | 6·65tr | 4·75s | 2·2—2·8c | 2·6s | | $J_{a,b} \simeq J_{b,c} \simeq 7·5$ | 63·9 | 6·5 | 9·6 | $C_{17}H_{21}ClN_2O_2$ | 63·65 | 6·6 | 9·3 |
| Me($H_2O$+) * | 79 | 140 | 5·51tr 5·52tr | 7·02qi 7·16qi | 6·46tr 6·40tr | 5·53q 5·54q | 2·0—2·5c 1·8—2·6c | 8·43tr 8·53tr | | $J_{d,f}$ 7·2 ≃ $J_{a,b}$ $J_{b,c}$ $J_{d,f}$ 7·2 ≃ 7 | 59·5 | 7·3 | 11·5 | $C_{12}H_{17}ClN_2O$ | 59·8 | 7·1 | 11·6 |
| 3,4-$(MeO)_2C_6H_3$ (0·5$H_2O$) * | 82 | 240(d) | 5·60tr | 6·6 | 7·4c | 4·58s | | 2·2—3·1c | OMe 6·20/6·25s | $J_{a,b} \simeq 7$ | 64·9 | 6·0 | 7·5 | $C_{19}H_{22}ClN_2O_{2·5}$ | 64·7 | 6·2 | 7·9 |
| p-HO·$C_6H_4$ (0·5$H_2O$) * | 80 | 252 | 5·60tr | 7·12c | 6·82tr | 4·57s | 2·3—2·6c | 3·12d 2·69d | | $J_f$ 9·0 | 65·3 | 6·2 | 8·6 | $C_{17}H_{18}ClN_2O_{1·5}$ | 65·5 | 5·85 | 9·0 |
| 3-HO, 4-MeO·$C_6H_3$ (0·5$H_2O$)† | 81 | 240(d) | 5·55c | Overlaid by solvent | | 4·45s | | 1·8—3·5c | OMe 6·22 | | 64·0 | 5·7 | 7·8 | $C_{18}H_{20}ClN_2O_{2·5}$ | 63·8 | 5·9 | 8·2 |
| 2-Cl, 5-$O_2N{\cdot}C_6H_3$ (0·25$H_2O$) * | 84 | 290(d) | 5·43tr | 6·95qi | 6·61tr | 4·15s | | 1·5—2·4c | | $J_{a,b} \simeq J_{b,c} \simeq 6·5$ | 55·5 | 4·3 | 10·9 | $C_{17}H_{15·5}Cl_2N_3O_{2·25}$ | 55·5 | 4·25 | 11·4 |
| PhCH=CH· * | 86 | 258—260 | 5·72br,tr | 7·23c | 6·72br,tr | 5·12br,d | | 2·3—3·0c | CH=CH 3·4—4·15c | $J_d \simeq 7$ | 73·2 | 5·9 | 8·9 | $C_{19}H_{19}ClN_2$ | 73·4 | 6·2 | 9·0 |
| 2-Pyridyl (HCl,$H_2O$) * | 75 | 163 | 5·45br,tr | 7·0c | 6·5br,tr | 3·82s | | 1·4—2·7c | | | 53·5 | 5·3 | 11·8 | $C_{16}H_{19}Cl_2N_3O$ | 54·2 | 5·4 | 11·8 |
| 3-Pyridyl (HCl,$H_2O$) * | 75 | 169(d) | 5·43tr | 7·05qi | 6·50tr | 4·02 | | 1·0—2·45c | | $J_{ab} \simeq J_{bc} \simeq 7$ | 57·0 | 6·0 | 11·4 | $C_{16}H_{19}Cl_2N_3O$ | 56·5 | 5·6 | 12·4 |

* N.m.r. in $D_2O$, chemical shifts relative to HOD (5·3). † N.m.r. in DDMSO. ‡ br = Broad; c = complex; d = doublet; q = quartet; qi = quintet; s = singlet; tr = triplet.

TABLE 4

Properties of the barbituryl benzimidazolium salts *

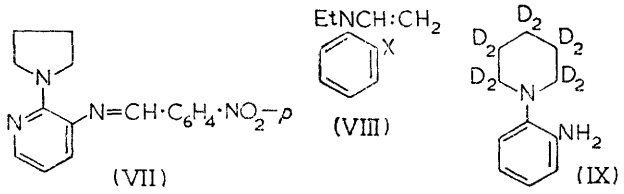


| X | Form and solvent | M.p.† | N.m.r. chemical shift (τ) ‡ a | b | c | d | Others | Coupling constants J (Hz) | Found (%) C | H | N | Formula | Requires (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $CH_2$ HOAc | § | >300(d) | 5·40tr | 6·81qi | 6·51tr | 2·33br | Me, 7·60s | $J_{ab} \simeq J_{bc} \simeq 7$ | 55·2 | 4·7 | 16·6 | $C_{16}H_{16}N_4O_5$ | 55·8 | 4·7 | 16·3 |
| $[CH_2]_2$ 0·5 HOAc | § | >300(d) | 5·66br | 7·73br | 6·87br | 2·4c | Me, 7·83s | | 58·6 | 4·9 | 17·5 | $C_{16}H_{16}N_4O_4$ | 58·55 | 4·9 | 17·05 |
| $[CH_2]_3$ | § | >300(d) | 5·47br | 7·90br | 6·79br | 2·4c | | | 61·1 | 5·1 | 18·2 | $C_{16}H_{16}N_4O_3$ | 61·5 | 5·2 | 17·9 |

* N.m.r. spectra in $CF_3CO_2D$. † These compounds slowly decompose above 300°. ‡ br = Broad; c = complex; qi = quintet; s = singlet. § White needles from aqueous acetic acid.

ethanolic hydrochloric acid, the corresponding benzimidazole and amine (I; $R_2 = [CH_2]_5$) was obtained.

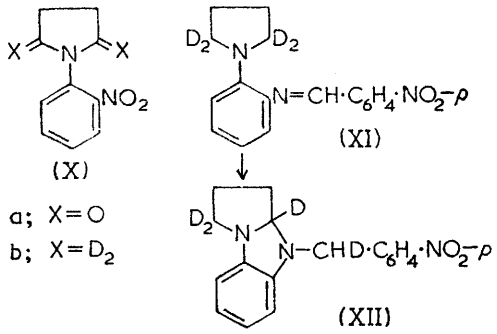
A closer analogy is found in the cyclisation which results when *o*-dialkylaminoanilines (I) are treated with alloxan. Rudy and Cramer,[8a-c] who originally investigated this reaction, inferred that *o*-dialkylaminoanilines reacted in the same way as the *para*-isomers to give the corresponding anils. However, although King and Clark-Lewis[10e] showed that the product from the *o*-dimethylaminoaniline was the quinoxaline (II) and that of the diethylaminoaniline was the barbituryl benzimidazolium salt (III)[10] they were unable to isolate an anil



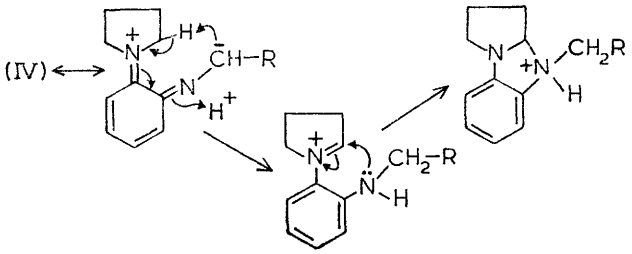

intermediate. They preferred one of several homolytic pathways,[10i] alternative to the primary formation of the anil, to explain the reaction sequences invoking, in the case of the diethylaminoaniline, the intermediacy of the enamine (VIII). However, when the diethylaminoaniline was treated with alloxan in methan[$^2$H]ol, no incorporation of deuterium into the alkyl groups was observed, thus excluding the enamine as a possible intermediate. To further clarify the mechanism we prepared *o*-[$^2H_{10}$]piperidinoaniline (IX) and subjected it to the action of alloxan.

Alloxan was found to react with *o*-pyrrolidino-, piperidino-, and perhydroazepino-aniline (I; $R_2 = [CH_2]_4$, $[CH_2]_5$, and $[CH_2]_6$ respectively) in an exactly analogous way as the diethylaminoaniline, to give the corresponding barbituryl benzimidazolium salts (Table 4).

No loss of deuterium was observed from the β-position in the piperidine ring, again excluding an enamine intermediate. When isotopic labelling experiments were performed on the dihydrobenzimidazole synthesis from anils, it became evident that an intramolecular hydrogen transfer was involved. Thus, no incorporation of deuterium in either the pyrrolidine ring or the benzylic methylene group occurred when the anil (IV) was cyclised in methan[$^2$H]ol, with deuterium chloride catalyst, to compound (V; R = *p*-nitrophenyl). The deuteriated anil (XI) was prepared from the corresponding amine (Xb) [made by reduction of *N*-(*o*-nitrophenyl)-succinimide (Xa) with perdeuterio-diborane (derived *in situ* from sodium borodeuteride and boron trifluoride etherate in diglyme) followed by reduction of the nitro-group] and cyclised in the usual way. The product, (XII), contained one proton and one deuteron at the benzylic position as shown by n.m.r. spectroscopy, thus supporting the intramolecular mechanism. Furthermore, preliminary kinetic studies[16] revealed that the deuteriated anil (XI) cyclised at a rate 5·9 times slower than the protonated analogue, thus supporting the




supposition that the scission of a C–H (or C–D) bond at the α-position of the pyrrolidine ring is involved in the rate-determining step of the reaction. We therefore propose the mechanism outlined below (Scheme 1) to




SCHEME 1

account for the cyclisation. A similar mechanism will explain the formation of the barbituryl benzimidazolium salts, alloxan performing the role of both the acid-catalyst and the oxidant to aromatise the intermediate dihydro-compound in accordance with its known properties. An alternative mechanism in which abstraction of hydride from the pyrrolidine ring α-position is also a possibility.

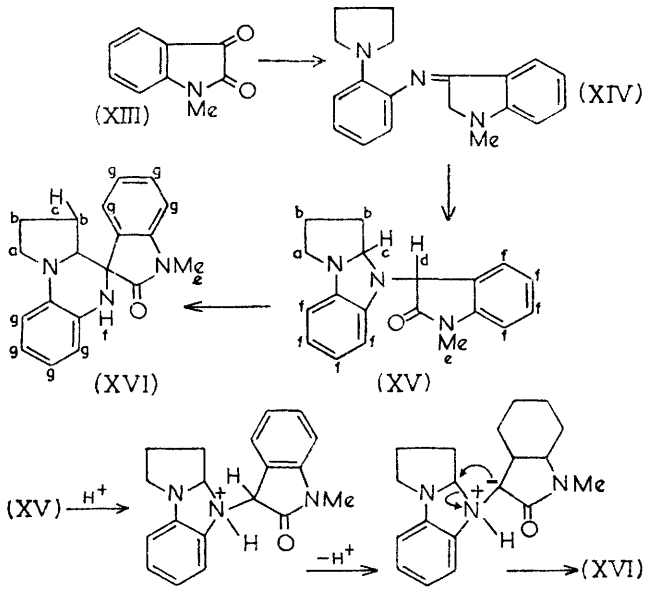
In order to throw light on the formation of the spiro-quinoxaline (II) we examined the interaction of other similar ketones with *o*-pyrrolidinoaniline, since no intermediates are isolable from alloxan reactions owing to its diverse reactivity. We found *N*-methylisatin (XIII) to be an ideal ketone for this purpose. In ethanol, in the absence of acid, this ketone reacted slowly with the *o*-pyrrolidinoaniline to give a purple anil (XIV). Similar reactions in the presence of 0·05, 0·15, and 1·0 molar proportions of hydrochloric acid resulted in the rapid formation of a transient purple colour (the anil) followed by the precipitation in each case of a white, crystalline solid. The three solids were each different and pure! Spectral analysis revealed the first to be the expected dihydrobenzimidazole (XV). Thus, the i.r. spectrum showed the cyclic amide carbonyl (1700 cm.$^{-1}$), while the n.m.r. spectrum ($CDCl_3$) confirmed the presence of two new methine protons, a triplet at τ 4·90 (N–CH–N) and a singlet at τ 4·98, in accord with the suggested structure.

The second compound was an isomer of the first and from its spectral properties was clearly the spiro-quinoxaline (XVI) analogous to that reported by Clark-Lewis and his co-workers. Thus i.r. spectroscopy

[16] D. Barraclough, O. Meth-Cohn, and E. Warburton, unpublished results.

showed a sharp NH absorption (3270 cm.$^{-1}$) while the n.m.r. spectrum both satisfied the required structure (see Experimental section) and underlined the fixed geometry of the spiro-rings by the presence of a complex one-proton resonance at high-field ($\tau$ 9·15); this was due to one of the pyrrolidine ring protons [starred in (XVI)] being held in the shielding cone of the oxindolyl aromatic ring. The third product proved to be the hydrochloride of this spiro-quinoxaline.

The spiro-compound was also obtained when either the anil (XIV) or the dihydrobenzimidazole (XV) was treated with acid. Indeed, when the latter intermediate was merely warmed in solution a rapid transformation to the quinoxaline occurred.* It would thus appear that the two different systems derived from alloxan and the *o*-t-aminoanilines (I) represent two alternative pathways from the dihydrobenzimidazole intermediate. On the one hand oxidation (with alloxan) or hydride transfer (see following paper) results in a benzimidazolium salt, while on the other hand the acid-catalysed rearrangement indicated above results in the quinoxaline. The fact that the dimethylaniline (I; R = Me) gave the spiro-compound while the diethyl analogue gave the benzimidazolium salt points to the greater hydride lability of the 2-proton in the dihydrobenzimidazole in the latter case. The ring-enlargement of dihydrobenzimidazoles to quinoxalines is a new type of rearrangement of considerable scope. The mechanism (Scheme 2) is basically similar to a Stevens rearrangement, requiring the presence of an acidic hydrogen (*i.e.* adjacent to both the carbonyl group and the aromatic ring) to facilitate the ready reaction. This reaction will be the subject of a further paper in this series. The isolation of both a benzimidazolium salt and a triazene from the previously mentioned azosulphonate [12] could also be explained by the intermediate formation of a dihydrobenzimidazole which reacts further as in the above examples.




SCHEME 2

* *Note added in proof:* The thermal rearrangement did not occur with the dihydrobenzimidazole (XV) after washing with alkali, indicating that it was, in fact, catalysed by adventitious traces of acid.

## EXPERIMENTAL

I.r. spectra were recorded on a Perkin–Elmer 257 spectrometer as Nujol mulls or liquid films. $^1$H N.m.r. spectra were taken on a Varian A60A spectrometer with tetramethylsilane as internal reference in deuteriochloroform unless otherwise indicated.

*Preparation of Amines* (I).—The amines were prepared according to literature methods [17] and purified by vacuum distillation in the presence of zinc dust.

*Purification of Aldehydes.*—The commercial aldehydes in ether solution were washed with aqueous sodium hydrogen carbonate and then distilled or recrystallised prior to use.

*Cyclisation Reactions.*—(1) *Preparation of anils* (IV). Equimolar proportions of the amine and aldehyde were warmed in ethanol solution and the mixture was set aside overnight. Removal of the solvent gave the anil which was purified either by distillation or recrystallisation. Physical properties and other data are recorded in Table 1.

(2) *Preparation of dihydrobenzimidazoles* (V). (*a*) The amine (0·01 mole) and aldehyde (0·01 mole) in ethanol (10 ml.) were treated with one drop of hydrochloric acid (*d* 1·18) and set aside overnight. The solvent was removed and the product was purified either by distillation, recrystallisation, or chromatography (see Table 2).

(*b*) The anil (IV) (0·01 mole) in ethanol (10 ml.) was treated as in (*a*).

(*c*) The amine hydrochloride (0·01 mole) and aldehyde (0·01 mole) in ethanol (10 ml.) were set aside overnight. Evaporation of the solvent gave the dihydrobenzimidazole hydrochloride, which was crystallised from ethanol and diethyl ether (see Table 2).

(3) *Preparation of benzimidazolium salts* (VI). (*a*) The dihydrobenzimidazole [from (2a) or (2b)] was heated under reflux in carbon tetrachloride for 1 hr. The salt was filtered off and recrystallised as indicated in Table 3.

(*b*) The amine (0·01 mole) and aldehyde (0·01 mole), or the anil (IV) (0·01 mole), were heated under reflux in carbon tetrachloride (25 ml.) with trifluoroacetic acid (one drop) for 1 hr.; the product was isolated as in (3a).

(*c*) The hydrochloride salt prepared in (2c) was heated under reflux with acetone for 1 hr., cooled, and filtered, and further treated as in (3a).

(*d*) The benzimidazole (0·01 mole) and the alkyl halide (0·01 mole) were heated together at 100° for 2 hr. and the product was crystallised as above.

(*e*) The amine (0·01 mole) (I; $R_2$ = $[CH_2]_4$, $[CH_2]_5$, or $[CH_2]_6$) and alloxan (0·01 mole) in ethanol (20 ml.) were set aside overnight in the presence of hydrochloric acid (3 drops; *d* 1·18). The precipitated product was filtered off, washed with ethanol, and crystallised as shown in Table 4.

*Reduction of Benzimidazolium Salts.*—The salt (VI) (0·01 mole) in water (20 ml.) at 0°, was treated with sodium borohydride (0·38 g., 0·01 mole). The dihydrobenzimidazole (V) formed immediately and was extracted from solution with ether; the extract was dried and evaporated to give the pure product in quantitative yield.

*Reactions of* N-(2-*Amino-4-nitrophenyl*)*pyrrolidine.*—*N*-

[17] O. Meth-Cohn, R. K. Smalley, and H. Suschitzky, *J. Chem. Soc.*, 1963, 1666.

(2-Amino-4-nitrophenyl)pyrrolidine (1·95 g., 0·01 mole) n.p. 79°, prepared according to Ainsworth and Suschitzky [18]) and *p*-nitrobenzaldehyde (1·51 g., 0·01 mole) in hanol (20 ml.) were set aside overnight. Removal of the olvent gave the *anil*, as red needles from light petroleum .p. 100—120), m.p. 228° (Found: C, 59·8; H, 4·75; N, 3·3; $C_{17}H_{16}N_4O_4$ requires C, 60·0; H, 4·7; N, 16·5%). he above anil (1 g.) in ethanol (20 ml.) was treated with ne drop of hydrochloric acid (*d* 1·18) and then set aside vernight; the solvent was removed and the residue was rystallised from methanol to give the *nitrodihydrobenzimidazole* (0·82 g., 82%), m.p. 241° (Found: C, 60·0; , 4·8; N, 16·6. $C_{17}H_{16}N_4O_4$ requires C, 60·0; H, 4·7; , 16·5%), τ 6·61 (2H, complex, $NCH_2CH_2$), 8·13 (4H, mplex $CH_2CH_2$), 4·73br (1H, t, NCH, *J* 6Hz), 5·47 (2H, s, $CH_2$), 1·8—3·6 (7H, complex Ar).

*Preparation and Cyclisation of* 2,2-*Dipiperidinoazobenzene* IIb; R = $C_5H_{10}N$).—*N*-(*o*-Nitrophenyl)piperidine (2·06 g., 01 mole) in dry ether (20 ml.) was added dropwise to a fluxing solution of lithium aluminium hydride (0·57 g., 015 mole) in dry ether (100 ml.) and the mixture was eated under reflux for a further 2 hr. Ethyl acetate was lded dropwise to the solution to destroy the excess of the hium aluminium hydride and the resulting solution was ashed well with water, dried ($MgSO_4$), and evaporated. he remaining red product was eluted through an alumina lumn in benzene and the red band was collected; evaporion of the solvent and crystallisation of the residue from hanol gave the *azo-compound* as red plates (1·2 g., 69%), .p. 164—165° (Found: C, 75·5; H, 8·1; N, 16·5: $_2H_{28}N_4$ requires C, 75·8; H, 8·1; N, 16·1%).

A solution of this compound (1 g.) in ethanol (15 ml.) was eated under reflux in the presence of one drop of hydroloric acid (*d* 1·18) until the red colour disappeared (4 hr.). he resulting solution was evaporated and triturated with ght petroleum (b.p. 30—40°). From the triturate was otained *o*-piperidinoaniline (0·4 g.), leaving a residue of peridino[1,2-*a*]benzimidazole (0·45 g.), both products eing identical with authentic specimens (i.r. spectrum .p. and mixed m.p.).

*Preparation and Reactions of* N-(o-*Aminophenyl*)*perdeuteriopiperidine*.—To perdeuteriopyridine (10 g.) in reixing deuteriomethanol (MeOD, 60 ml.) was added in nall portions clean sodium (18 g.). The precipitated dium methoxide crystallised above the liquid level llowing further addition of sodium. When all the sodium as added the volatile products were distilled off and the sulting solution was treated with *o*-fluoronitrobenzene 6·8 g.); the mixture was heated under reflux for 1 hr. and en the solvent was removed. The crude product was tracted from ether solution with 6N-hydrochloric acid, e acid extracts were basified, and then re-extracted with her, dried, and evaporated. The orange solid (12·8 g., %) crystallised from light petroleum (b.p. 30—40°) as ange needles, m.p. 76°. The n.m.r. spectrum confirmed at no significant proportion of aliphatic protonated aterial was present. Catalytic reduction of the *nitrompound* in the usual way [17] gave the corresponding *amine* X) which was treated in the manner described for the otium analogue. No protons were found in the aliphatic gion of the n.m.r. spectrum of the resulting product.

*Preparation and Cyclisation of* N-(o-*Nitrophenyl*)-2,2,5,5-*radeuteriopyrrolidine* (Xb).—*N*-(*o*-Nitrophenyl)succinide [19] (1 g.) and freshly distilled boron trifluoride diethyletherate (0·5 g.) were dissolved in dry 1,2-dimethoxyethane (20 ml.) and a suspension of sodium borodeuteride (0·2 g.) in the same solvent (20 ml.) was added dropwise during 20 min., with stirring at 0°. The resultant mixture was heated under reflux for 2 hr., cooled, and carefully acidified with 4N-hydrochloric acid. The acidified solution was heated under reflux for 5 min., cooled, basified, and thoroughly extracted with ether. The ether extract was dried ($MgSO_4$), evaporated, and the residue chromatographed on Silica gel, with benzene. The first orange band was removed and gave the *nitro-compound* (0·52 g., 47%), m.p. 36° as orange needles. The n.m.r. spectrum lacked the pyrrolidine ring α-protons. A similar reduction with sodium borohydride gave *N*-(*o*-nitrophenyl)pyrrolidine, identical (i.r. spectrum, m.p. and mixed m.p.) with an authentic specimen.[17]

Reduction as described previously [17] gave the corresponding *deuteriated amine* which, with *p*-nitrobenzaldehyde, gave the *anil* (XI), m.p. 160°. N.m.r. τ 8·05 (4H, complex, $CH_2{\cdot}CH_2$), 1·50 (1H, s, CH), 1·6—3·4 (8H, complex, Ar).

The above anil was cyclised by treatment with acid as described earlier to give the *dihydrobenzimidazole* (XII), m.p. 91°. N.m.r. τ 8·2 (4H, complex, $CH_2{\cdot}CH_2$), 5·63br (1H, CHD), 1·8—3·9 (8H, complex, Ar).

*Reactions with* N-*Methylisatin*.—(*a*) *N*-Methylisatin (0·5 g., 0·0031 mole) and *N*-(*o*-aminophenyl)pyrrolidine (0·5 g., 0·0031 mole) in ethanol solution (20 ml.) were set aside overnight; the solvent was removed and the purple product was crystallised from ethanol to give the *anil* (XIV) as purple needles, m.p. 159—160° (Found: C, 74·3; H, 6·1; N, 13·45. $C_{18}H_{19}N_3O$ requires C, 74·6; H, 6·3; N, 13·7%). N.m.r. τ 6·70 (4H, complex, a), 8·18 (4H, quintet, b), 6·69 (3H, s, c), and 2·4—3·5 (8H, complex, d).

(*b*) Three mixtures of the same quantities of *N*-methylisatin and the amine in ethanol as in (*a*) were treated respectively with (i) one drop (0·05M) (ii) 3 drops (0·15M) and (iii) 0·625 ml. (1M proportion) of hydrochloric acid (*d* 1·18) and were then set aside overnight. The white crystalline mass precipitated in each case was filtered off, washed with cold ethanol, dried, and examined spectroscopically. (i) Gave the *dihydrobenzimidazole* (XV), m.p. 145—150° (decomp.) (Found: C, 73·9; H, 6·45; N, 13·6. $C_{18}H_{19}N_3O$ requires C, 74·6; H, 6·3; N, 13·7%). N.m.r. τ 6·85 (2H, complex, a), 8·15 (4H, complex, b), 4·90 (1H, t, c, $J_{b,c}$ 5·0 Hz), 4·98 (1H, s, d), 6·80 (3H, s, e), and 2·5—4·0 (8H, complex, f).

(ii) Gave the *quinoxaline* (XVI) as white needles from ethanol, m.p. 215° (Found: C, 74·4; H, 6·5; N, 13·6. $C_{18}H_{19}N_3O$ requires C, 74·6; H, 6·3; N, 13·7%). N.m.r. τ 6·59 (2H, t, a, $J_{a,b}$ 7·0 Hz), 8·2 (3H, complex, b), 9·15 (1H, complex, c), 6·23 (1H, quartet, d, $J_{b,d}$ 9·0, $J_{c,d}$ 6·0 Hz), 6·77 (3H, s, e), 2·5—3·6 (9H, complex, f, g).

(iii) Gave the *hydrochloride* of XVI as white clusters from ethanol, m.p. 218° (decomp.).

When the dihydrobenzimidazole (XV) was warmed briefly in ethanol solution (15 min.) or treated with hydrochloric acid it was rapidly converted into the quinoxaline (XVI).

We thank Dr. R. K. Smalley for a sample of the pyridine (VII) and Geigy (U.K.) Ltd., for a generous research grant which made this work possible.

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[19] R. Meyer and J. Maier, *Annalen*, 1903, **327**, 6.