893. *Syntheses of Heterocyclic Compounds. Part IV.*[1] *Oxidative Cyclisation of Aromatic Amines and their* N*-Acyl Derivatives.*

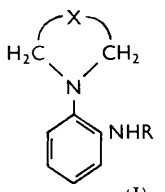
By O. Meth-Cohn and H. Suschitzky.

Formation of benzimidazoles from 2-substituted aniline derivatives of type (I; R = H or acyl) on treatment with formic acid and hydrogen peroxide is shown to be related to a Polonovski reaction.

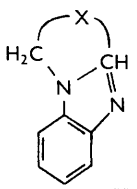
Nair and Adams [2] recently cyclised the amines (I; R = H; X = $[CH_2]_2$, $[CH_2]_3$, $CH_2{\cdot}O{\cdot}CH_2$, and $[CH_2]_4$) with peroxytrifluoroacetic acid to the corresponding benzimidazoles (II) in high yields. By contrast, the benzoyl derivative (I; R = Bz, X = $[CH_2]_3$) gave only a little of the benzimidazole under these conditions. As we have been engaged on similar work we report additional results at this stage.

A mixture of 98—100% formic acid and 30% hydrogen peroxide (called below performic acid) was found to be as good as peroxytrifluoroacetic acid for producing the benzimidazoles (II). Moreover, performic as well as peroxytrifluoroacetic acid cyclised the acyl derivatives (I; R = CHO, Ac, or Bz; X = $[CH_2]_2$, $[CH_2]_3$, $\cdot CH_2{\cdot}O{\cdot}CH_2$, $[CH_2]_4$) under the same conditions in high yields to the benzimidazoles (II) with loss of the acyl group. The benzoyl derivatives, for instance, eliminated benzoic acid quantitatively. The diacetamido-compound (III; R = NHAc) furnished the pentacyclic structure (IV) which has been previously made [3] from the nitro-compound (III; R = NO_2) by a longer and less profitable synthesis.

Contrary to report,[2] *NN*-dimethyl-*o*-phenylenediamine (V; R = H) and its benzoyl derivative (V; R = Bz) cyclised in high yields to 1-methylbenzimidazole (VI) in performic or peroxytrifluoroacetic acid.



(I)



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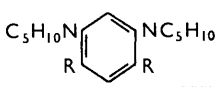

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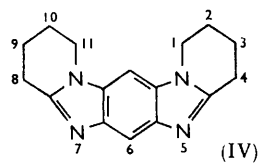
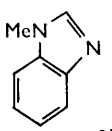


(IV)

(V)



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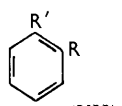

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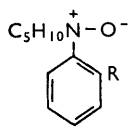
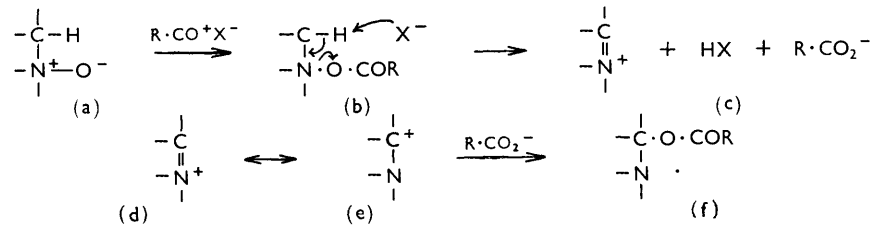


(VIII)

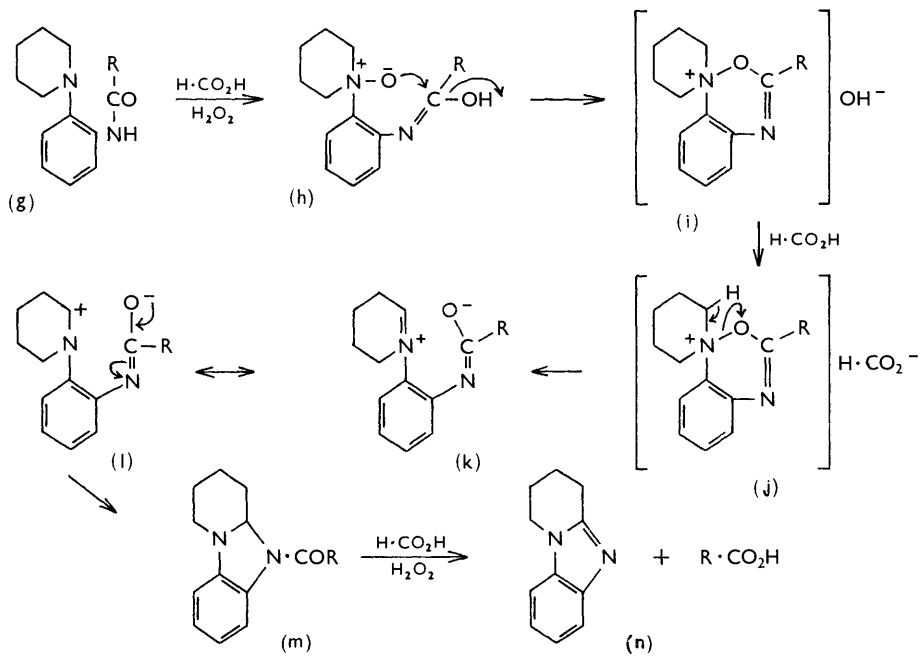
Oxidative cyclisation of *o*-substituted anilines (*e.g.*, I; R = H) is believed to occur through a nitroso- or hydroxyamino-intermediate.[2] This route, however, cannot be operative for the acyl derivatives since we observed that formyl-, acetyl-, and benzoylaniline remain unchanged on treatment with peracids under the reaction conditions. 1-Phenylpiperidine (VII; R = H, R' = $C_5H_{10}N$) and 1-*o*-nitrophenylpiperidine (VII; R = NO_2, R' = $C_5H_{10}N$), on the other hand, yield the amine oxides (VIII; R = H or NO_2). Moreover, since neither acylated 2-aminobiphenyls (*e.g.*, VII; R = NHBz, R' = Ph) nor various acylated *o*-cyclohexylanilines (*e.g.*, VII; R = NHBz, R' = C_6H_{11}) could be made to cyclise by means of a peracid, the presence of a tertiary nitrogen in the 2-position seems indispensable to cyclisation. The evidence points to an amine oxide as

[1] Part III, Meth-Cohn, Smalley, and Suschitzky, *J.*, 1963, 1666.
[2] Nair and Adams, *J. Amer. Chem. Soc.*, 1961, **83**, 3518.
[3] Saunders, *J.*, 1955, 3275.

the essential primary product and on this basis the cyclisation can be visualised as following the pattern of a Polonovski rearrangement.[4,5] In this reaction *N*-oxides are converted into carbinolamines or their derivatives by an acid anhydride, acid chloride, or other reagent [4-6] and this may be followed by dealkylation. The mechanism of the reaction has recently been the subject of considerable research [6-8] and according to Huisgen *et al.*[9] involves a mesomeric immonium ion (d ⟷ e) produced by an E_2-type attack of the acylate anion (X^-)(b) to give a carbinolamine ester (f), as set out in the Scheme.



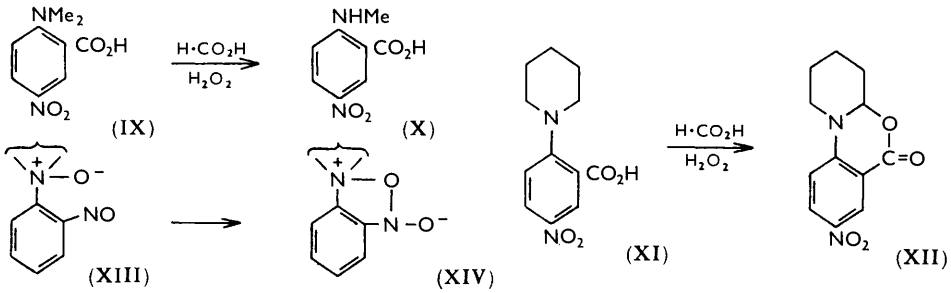
Thus if oxidative benzimidazole formation proceeds by a Polonovski reaction, it must entail formation of an *N*-oxide (a) and its acylation (b). The first stage is clearly ensured by the nature of the oxidising agent, as explained above. However, the second, acylation, is not brought about by the nature of the cyclising medium, because we found that various *N*-oxides such as those of 1-phenyl- and 1-*o*-nitrophenyl-piperidine and *NN*-dimethyl-aniline are unchanged by performic acid. Another acylating source could be the acyl moiety of the acylamino-group (cf. I; R = acyl). Whether intramolecular acylation is a feasible step in the Polonovski reaction was tested by treating the acids (IX and XI)



[4] Polonovski and Polonovski, *Bull. Soc. chim. France*, 1927, **41**, 1190.
[5] Wenkert, *Experientia*, 1954, **10**, 346.
[6] Craig, Dwyer, Glazer, and Horning, *J. Amer. Chem. Soc.*, 1961, **83**, 187; Sweeley and Horning, *ibid.*, 1957, **79**, 2620.
[7] Oae, Kitao, and Kitaoka, *J. Amer. Chem. Soc.*, 1962, **84**, 3366.
[8] Walter, Steffen, and Heyns, *Chem. Ber.*, 1961, **94**, 2462.
[9] Huisgen, Bayerlein, and Heydkamp, *Chem. Ber.*, 1959, **92**, 3223.

with performic acid in the usual way. The first gave the demethylated amine (X), the second the lactone (XII), which are both products expected from a successful Polonovski reaction. It is noteworthy that the lactone (XII) is another rare example [8,10] of a stable carbinolamine ester, a structure lending support to the suggested course of the Polonovski reaction (cf. species f).

A likely mechanism for benzimidazole formation which satisfies the previous observations can be given as outlined (g—n), for an acylated *o*-piperidinoaniline as example. Acylation of the *N*-oxide (h) by the adjacent acylamino-group is followed by an E_2 elimination (j) resulting in the mesomeric immonium ion (k ⟷ l). Its ring-closure leads to 1-acyldihydrobenzimidazole (m) previously described [1] and readily convertible into the parent benzimidazole (n) with elimination of the acyl portion when treated with performic acid.



A similar reaction scheme can be applied to the conversion of the amines (I; R = H) into the benzimidazoles (II) through the intermediate nitroso-*N*-oxide (XIII). This is feasible since it is known [11] that the reagent produces a nitroso-compound from a primary amine apart from the observed *N*-oxide. Subsequent changes analogous to the scheme (g ⟶ m) possibly involving the hydrofurazanoxide (XIV) would lead to a benzimidazole *N*-oxide. Benzimidazole *N*-oxide itself was found to be deoxygenated readily under the reaction conditions and could, in fact, not be prepared directly by peracid oxidation.

Experimental

o-*Substituted Anilines*.—The required compounds (I; R = H) were prepared by condensation of *o*-chloronitrobenzene (1 mol.) and the appropriate amine (2·1 mol.), followed by reduction of the product as described.[1]

o-*Substituted Acylanilides*.—Acylation of the compounds (I; R = H) was done in the usual way with formic acid, acetic anhydride, or benzoyl chloride, yielding the *products* listed in the Table.

1,1′-(4,6-*Diacetamido*-m-*phenyleneid*)*piperidine* (III; R = NHAc).—The dinitro-compound (10 g.) (III; R = NO_2) obtained by Saunders's method [3] was reduced in acetic anhydride (100 ml.) with Raney nickel and hydrogen. The *diamide* (9·4 g., 88%) precipitated after filtration and neutralisation, with 2N-aqueous sodium hydroxide, of the reaction mixture, formed needles (from aqueous ethanol), m. p. 228—229° (Found: C, 66·8; H, 8·35. $C_{20}H_{30}N_4O_2$ requires C, 67·0; H, 8·4%).

Oxidative Cyclisation.—The compounds (I; R = H) or their acyl derivatives (I; R = acyl) (2 g. in each case) were heated with 98% formic acid (12 ml.) and 30% hydrogen peroxide (6 ml.) on the steam-bath for 10—15 min. Colour changes occurred and the solution became finally red-brown to pale yellow. Dilution and neutralisation with aqueous ammonia precipitated the tricyclic benzimidazole derivative. Chloroform-extraction of the mother-liquor gave a further small amount, bringing the total yield to 85—95% for compounds (II;

[10] Bell and Childress, *J. Org. Chem.*, 1962, **27**, 1691.
[11] Baeyer and Villiger, *Ber.*, 1900, **33**, 1569; D'Ans and Kneip, *Ber.*, 1915, **48**, 1136; Ibne-Rasa and Edwards, *J. Amer. Chem. Soc.*, 1962, **84**, 763.

N-o-Acylaminophenyl derivatives (I) of pyrrolidine, piperidine, morpholine, and hexahydroazepine.

X	R	M. p. or b. p./mm.	Found (%) C	Found (%) H	Formula	Reqd. (%) C	Reqd. (%) H
$[CH_2]_2$	CHO	63°	69·7	7·1	$C_{11}H_{14}N_2O$	69·4	7·4
$[CH_2]_2$	Ac	124	70·3	7·8	$C_{12}H_{16}N_2O$	70·6	7·9
$[CH_2]_2$	Bz	129	76·3	6·8	$C_{17}H_{18}N_2O$	76·7	6·8
$[CH_2]_3$	CHO	104	71·0	7·7	$C_{12}H_{16}N_2O$	70·6	7·9
$[CH_2]_3$	Ac	66 *	72·0	8·3	$C_{13}H_{18}N_2O$	71·5	8·3
$[CH_2]_3$	Bz	98 †	77·1	7·5	$C_{18}H_{20}N_2O$	77·1	7·2
$CH_2{\cdot}O{\cdot}CH_2$	CHO	152	65·0	7·0	$C_{11}H_{14}N_2O_2$	64·7	6·8
$CH_2{\cdot}O{\cdot}CH_2$	Ac	87	65·6	7·4	$C_{12}H_{16}N_2O_2$	65·4	7·3
$CH_2{\cdot}O{\cdot}CH_2$	Bz	110	72·2	6·6	$C_{17}H_{18}N_2O_2$	72·3	6·4
$[CH_2]_4$	CHO	79	71·9	8·4	$C_{13}H_{18}N_2O$	71·5	8·3
$[CH_2]_4$	Ac	120°/0·1	72·5	8·9	$C_{14}H_{20}N_2O$	72·4	8·7
$[CH_2]_4$	Bz	79	77·7	7·3	$C_{19}H_{22}N_2O$	77·5	7·5

* Lellmann and Geller (*Ber.*, 1888, **21**, 2281) record this compound as a liquid. † Nair and Adams [2] report m. p. 79—80°.

X = $[CH_2]_2$, $[CH_2]_3$, $[CH_2]_4$, and $CH_2{\cdot}O{\cdot}CH_2$). 1-Methylbenzimidazole was obtained from *NN*-dimethyl-*o*-phenylenediamine and its benzoyl derivative in 80% and 70% yield, respectively. Products derived from the amines were less pure than those from the acyl compounds. Trifluoroacetic acid gave similar yields. Treatment of the dipiperidine (III; R = NHAc) with performic acid in the above manner gave 1,2,3,4,8,9,10,11-octahydrobenzodi-[1″,2″-2,3:4″,3″-2′,3]imidazolo[1,2-*a*]pyridine (IV) (74%) which sublimed *in vacuo* as cream-coloured needles, m. p. 285—286°. Saunders [3] gives m. p. 279—280°. However, 2-benzamidobiphenyl and *N*-benzoyl-2-cyclohexylaniline were recovered when treated with performic acid.

Oxidation of Tertiary Amines.—(*a*) 1-Phenylpiperidine (2 g.), on treatment with performic acid as above, gave 1-*phenylpiperidine* N-*oxide monohydrate* (1·8 g., 74%) as plates, on extraction of the mother-liquor with chloroform. It had m. p. 113° (Found: C, 67·6; H, 9·3; N, 7·2. $C_{11}H_{17}NO_2$ requires C, 67·7; H, 8·8; N, 7·2%). On dehydration at 100° the *N*-oxide, m. p. 169°, was obtained as a white, hygroscopic solid. 1-o-*Nitrophenylpiperidine* N-*oxide* was obtained in a similar way, as needles (from ethyl acetate), m. p. 166° (70%) (Found: C, 59·55; H, 6·3. $C_{11}H_{14}N_2O_3$ requires C, 59·4; H, 6·35%). *NN*-Dimethylaniline yielded the *N*-oxide (86%) which gave a picrate, m. p. 137° (Bamberger and Tschirner [12] give m. p. 138°).

(*b*) 5-Nitro-2-piperidinobenzoic acid (2 g.), m. p. 201°, made by Le Fèvre and Turner's method,[13] was treated with 98% formic acid (12 ml.), and 30% hydrogen peroxide (6 ml.) on the water-bath for a few min. Evaporation of the mother-liquor and extraction of the residue with light petroleum (b. p. 100—120°) gave 2-2′-*hydroxypiperidino*-5-*nitrobenzoic acid lactone* (0·45 g., 23%) as yellow needles, m. p. 125°, $\nu_{max.}$ (in Nujol) 1730 cm.$^{-1}$ (lactone-carbonyl) (Found: C, 58·3; H, 5·3; N, 11·2. $C_{12}H_{12}N_2O_4$ requires C, 58·1; H, 4·9; N, 11·3%). The residue after extraction was starting material (1·5 g.).

(*c*) 2-*Dimethylamino*-5-*nitrobenzoic acid* was made by condensing aqueous 40% w/w dimethylamine (15 ml.) with 2-chloro-5-nitrobenzoic acid (5 g.) at 50° for 15 min. and then keeping the mixture at room temperature overnight. It recrystallised from water as yellow needles, m. p. 164° (4·5 g., 86%) (Found: C, 51·0; H, 4·6. $C_9H_{10}N_2O_4$ requires C, 51·4; H, 4·8%). No analysis or m. p. is given in the literature.[14] On oxidation of the acid (2 g.) as in (*b*) 2-methylamino-5-nitrobenzoic acid [15] (91%), m. p. 276°, was formed.

(*d*) *Benzimidazole* N-*oxide*. This was prepared by the method of Kuhn and Blau [16] and on treatment with formic acid and hydrogen peroxide yielded benzimidazole. Attempts to oxidise benzimidazole with any peracid failed.

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[12] Bamberger and Tschirner, *Ber.*, 1899, **32**, 1905.
[13] Le Fèvre and Turner, *J.*, 1927, 1117.
[14] G.P. 124,907/1901.
[15] Thieme, *J. prakt. Chem.*, 1891, [2], **43**, 471.
[16] Kuhn and Blau, *Annalen*, 1958, **615**, 99.