## 312. *Syntheses of Heterocyclic Compounds. Part III.*[1] *Pyrolytic Cyclisation of Aromatic Azides.*

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By thermal decomposition of suitable *ortho*-substituted phenyl and 2- and 4-substituted 3-pyridyl azides a number of tricyclic compounds, some of which represent new ring systems, have been prepared.

Aryl azides decompose thermally by various routes depending on environment and structure.[2] Such decompositions can be of preparative value for azides with *ortho*-substituents. For instance, cyclisation on to a methylene group of a saturated ring occurs in good yield when the intermediate (RN) derived from a decomposing $RN_3$ group is suitably placed.[3-5] By this procedure we prepared the oxazino[4,3-*a*]- (I; X = $CH_2$·O·$CH_2$) and pyrrolo[1,2-*a*]-benzimidazole (I; X = $[CH_2]_2$) from (*N*-*o*-azidophenyl-morpholine and -pyrrolidine) in hot nitrobenzene. Both of these ring systems have been prepared by other methods in substantially similar yields.[6-8]

Cyclisation of 1-*o*-azidophenyl-2-methylpiperidine could conceivably give rise to several isomeric products depending upon the point of ring-closure. We obtained only one product, $C_{12}H_{14}N_2$. It showed no NH band in its infrared spectrum, and its ultraviolet spectrum was similar to that of the benzimidazole (I; X = $[CH_2]_3$). It was therefore assigned the benzimidazole structure (IV) which was further supported by its non-identity (m. p. and infrared spectrum) with the isomeric quinoxaline [9] that might have been formed.

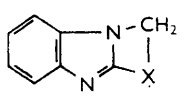
This reaction was then extended to the 2- and 4-substituted 3-azidopyridines. These

[1] Part II, Higginbottom and Suschitzky, *J.*, 1962, 2367.
[2] Smith and Hall, *J. Amer. Chem. Soc.*, 1962, **84**, 480.
[3] Saunders, *J.*, 1955, 3275.
[4] Schmutz and Künzle, *Helv. Chim. Acta*, 1956, **39**, 1149.
[5] Smolinsky, *J. Amer. Chem. Soc.*, 1961, **83**, 2489.
[6] Reppe and co-workers, *Annalen*, 1955, **596**, 209.
[7] Nair and Adams, *J. Amer. Chem. Soc.*, 1961, **83**, 3518.
[8] De Selms, *J. Org. Chem.*, 1962, **27**, 2165.
[9] Meth-Cohn and Suschitzky, unpublished result.

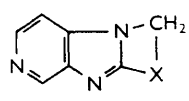
were readily obtained from condensation in benzene of 4-chloro-3-nitro- or 2-chloro-3-nitro-pyridine with the required base; the resulting nitro-compounds were quantitatively reduced as benzene solutions in hydrogen over Raney nickel to the corresponding amines; conversion into the azides was by diazotisation and addition of sodium azide. Cyclisation was effected, without isolation of the azides, by heating them in nitrobenzene at 170°. The products could not be purified directly by recrystallisation, but gave colourless crystalline compounds on sublimation *in vacuo*.

Yields in the series (II; X = $[CH_2]_2$, $[CH_2]_3$, $[CH_2]_4$, and $CH_2{\cdot}O{\cdot}CH_2$) increased with increasing size of the saturated ring (40—70%), a trend which was also observed by Saunders for the analogous benzene series (I). Yields in the other pyridine series (III; X = as above) were uniformly low (10—15%), possibly because azides were derived from very unstable diazonium compounds.

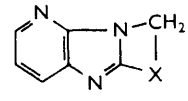
The mechanism of ring formation in the thermal decomposition of an aromatic azide has been discussed by various workers.[2,3,5] Whether the intermediate is electrophilic (R–$\dot{\ddot{N}}$:) or biradical(R–$\dot{\ddot{N}}{\cdot}$) in nature, it probably combines with a methylene group to form initially a dihydro-heterocycle, as was observed with *o*-azidophenylcyclohexane which gave hexahydrocarbazole on pyrolysis.[5] Saunders suggested that dihydrobenzimidazoles were intermediates in his preparation of benzimidazoles of type (I) from phenyl azides in nitrobenzene. An attempt by us to isolate such a dihydro-compound from the decomposition of *N*-*o*-azidophenylpyrrolidine and of 3-azido-4-piperidinopyridine yielded much tar, a little primary amine, and a small amount of benzimidazole (II; X = $[CH_2]_3$) in the latter case. The dihydro-compound appears to be unstable under the reaction conditions. With the intention of " trapping " the dihydro-compound as a stable derivative, decomposition was carried out in boiling acetic anhydride. Analytical and spectral data are consistent with the products' being the respective acylated benzimidazoles (V; R = Ac, $n = 3$; VI; R = Ac, $n = 4$). Similary, in propionic anhydride the *N*-propionyl



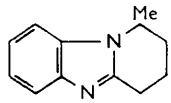
(I)



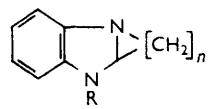
(II)



(III)



(IV)



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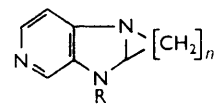

(VI)

derivative (V; R = EtCO, $n = 3$) was obtained. This constitutional assignment is supported by the ease with which the dihydro-compounds (V; R = Ac or EtCO, $n = 3$) were changed into the parent benzimidazole (I; X = $[CH_2]_2$) on treatment with hydrogen peroxide in formic acid, causing oxidative deacylation.

## Experimental

*4-Chloro-3-nitropyridine.*—4-Hydroxypyridine-2,6-dicarboxylic acid (100 g.) was heated at 250° until carbon dioxide evolution was complete. On treatment of the crude 4-hydroxypyridine with water (30 ml.) and nitric acid (40 ml.; *d* 1·42) the nitrate (75 g.) separated. After being washed with ethanol and acetone it had m. p. 199°. Koenigs and Greiner [10] record m. p. 205°. It was converted into 4-chloro-3-nitropyridine by the method of Kruger and Mann.[11]

[10] Koenigs and Greiner, *Ber.*, 1931, **64**, 1049.
[11] Kruger and Mann, *J.*, 1955, 2755.

*Condensations.*—(*a*) *o*-Chloronitrobenzene (1 mol.) and the appropriate amine (2·1 mol.) were heated for 3—4 hr. on a water-bath. The mixture was then poured into ice–water and the red oil made to solidify. Recrystallisations were from light petroleum (b. p. 60—80°). Condensation with 2-methylpiperidine took 12 hr. and gave 2-*methyl*-1-o-*nitrophenylpiperidine* (15%) as orange needles, m. p. 75° (Found: C, 65·4; H, 7·1. $C_{12}H_{16}N_2O_2$ requires C, 65·4; H, 7·3%). Its *picrate* had m. p. 141—142° (from ethanol) (Found: C, 48·2; H, 4·7. $C_{18}H_{19}N_5O_9$ requires C, 48·1; H, 4·3%). 1-*o*-Nitrophenylpyrrolidine, which has been reported [7] as a liquid, was obtained as an orange solid, m. p. 34—35° (Found: C, 62·8; H, 6·3. Calc. for $C_{10}H_{12}N_2O_2$: C, 62·5; H, 6·3%).

(*b*) A 25% solution of 4-chloro-3-nitro- or 2-chloro-3-nitro-pyridine (commercially available) was run dropwise into an ice-cooled 30% solution of the appropriate amine (2·1 mol.) in benzene with agitation. Stirring was continued for 1 hr. before the base hydrochloride was filtered off. The filtrate was washed with cold water and the solvent driven off under a vacuum leaving usually an oil which was readily solidified and was recrystallised from light petroleum. Yields were practically quantitative. Results are recorded in Table 1.

TABLE 1.

Substituted pyridines and their picrates.

| | | | | | | | | | | | Picrate | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 3- | | M. p. | Found (%) | | | Reqd. (%) | | | | Found (%) | | Reqd. (%) | |
| 2-Subst. | Subst. | 4-Subst. | (b. p.) | C | H | Formula | C | H | M. p. | | C | H | C | H |
| — | $NO_2$ | $C_5H_{10}N$– | 61° | 58·3 | 6·25 | $C_{10}H_{13}N_3O_2$ | 58·0 | 6·3 | 171° | | 43·8 | 3·9 | 44·0 | 3·7 |
| $C_5H_{10}N$– | $NO_2$ | — | 51 [a] | — | — | — | — | — | — | | — | — | — | — |
| — | $NO_2$ | $C_4H_8N$– | 88 | 55·9 | 5·8 | $C_9H_{11}N_3O_2$ | 56·0 | 5·7 | 200 | | 42·6 | 3·4 | 42·7 | 3·3 |
| $C_4H_8N$– | $NO_2$ | — | 42 | 55·7 | 5·6 | $C_9H_{11}N_3O_2$ | 56·0 | 5·7 | 141 | | 43·1 | 3·5 | 42·7 | 3·3 |
| — | $NO_2$ | $C_6H_{12}N$– | 69 | 59·8 | 6·7 | $C_{11}H_{15}N_3O_2$ | 59·7 | 6·8 | 169 | | 45·9 | 4·1 | 45·3 | 4·0 |
| $C_6H_{12}N$– | $NO_2$ | — | 35 | 60·0 | 6·4 | $C_{11}H_{15}N_3O_2$ | 59·7 | 6·8 | 119 | | 45·4 | 3·85 | 45·3 | 4·0 |
| — | $NO_2$ | $OC_4H_8N$– | 139 | 51·2 | 5·3 | $C_9H_{13}N_3O_3$ | 51·8 | 5·3 | 214 | | 40·75 | 3·2 | 41·0 | 3·2 |
| $OC_4H_8N$– | $NO_2$ | — | 86 | 51·9 | 5·3 | $C_9H_{13}N_3O_3$ | 51·8 | 5·3 | — | | — | — | — | — |
| — | $NH_2$ | $C_5H_{10}N$– | 55 | 61·2 | 8·4 | $C_{10}H_{17}N_3O$ [b] | 61·5 | 8·7 | 158 | | 47·6 | 4·7 | 47·3 | 4·5 |
| $C_5H_{10}N$– | $NH_2$ | — | 62 [c] | — | — | — | — | — | 164 | | 47·4 | 4·2 | 47·3 | 4·5 |
| — | $NH_2$ | $C_4H_8N$– | 150/[c] 1·1 mm. | — | — | — | — | — | 170 | | 45·8 | 4·0 | 45·9 | 4·1 |
| $C_4H_8N$– | $NH_2$ | — | 70 | — | — | — | — | — | 184 | | 45·6 | 3·8 | 45·9 | 4·1 |
| — | $NH_2$ | $C_6H_{12}N$– | 159/[c] 1·2 mm. | — | — | — | — | — | 138 | | 48·4 | 4·7 | 48·5 | 4·7 |
| $C_6H_{12}N$– | $NH_2$ | — | 118/[c] 0·3 mm. | — | — | — | — | — | 146 | | 48·9 | 4·7 | 48·5 | 4·7 |
| — | $NH_2$ | $OC_4H_8N$– | 136 | 59·8 | 7·1 | $C_9H_{13}N_3O$ | 60·3 | 7·3 | 181 | | 43·7 | 4·0 | 44·1 | 3·95 |
| $OC_4H_8N$– | $NH_2$ | — | 127 | 60·5 | 7·2 | $C_9H_{13}N_3O$ | 60·3 | 7·3 | 130 | | 44·2 | 3·95 | 44·1 | 3·95 |

[a] Chapman and Rees, *J.*, 1954, 1190, give m. p. 52°. [b] This amine crystallises with 1 mol. of $H_2O$. [c] Slowly decomposes and hence is unsuitable for analysis.

*Reductions.*—(*a*) The nitro-compounds were reduced as 15% benzene solutions with Raney nickel (prepared by Mishimura's method [12]) and hydrogen at atmospheric pressure and room temperature. The amine was extracted with 2N-hydrochloric acid and taken up in ether after precipitation with sodium hydroxide. Evaporation of the solvent yielded the crude amine which was purified either by distillation *in vacuo* or by recrystallisation from light petroleum. The amines were usually too unstable for analysis and were kept as hydrochlorides. Yields were 60—90% and results are summarised in Table 1. Picrates were obtained from ethanol.

(*b*) To a boiling and stirred mixture of reduced iron (3·2 mol.) and ammonium chloride (0·4 mol. as a 10% aqueous solution) was added the nitro-compound (1 mol.) in small portions. When addition was complete heating was continued for 2 hr. The resulting amine was purified by steam-distillation and collected by filtration or ether-extraction. 1-o-*Aminophenyl*-2-*methylpiperidine* (89%) had m. p. 45° (Found: C, 75·3; H, 9·2. $C_{12}H_{18}N_2$ requires C, 75·6; H, 9·5%).

*Preparation of Azides.*—The amine was diazotised in 5N-hydrochloric acid with sodium nitrite in the usual way. The cold solution of diazonium hydrochloride was slowly added to a well-stirred aqueous solution of sodium azide (equimolar) containing sodium acetate (20% w/w).

[12] Mishimura, *Bull. Chem. Soc. Japan*, 1959, **32**, 61.

The organic azide was extracted with chloroform and the extract dried ($MgSO_4$). On evaporation of the solvent the azide was taken up in the decomposition medium without further purification.

*Cyclisation of Azides.*—(*a*) A 5% solution of the azide (50 ml.) in nitrobenzene was added dropwise to nitrobenzene (100 ml.) maintained at 170°. Heating was continued until nitrogen evolution ceased (about 0·5 hr.). Solvent and aniline (formed in the reaction) were removed by vacuum-distillation below 100° leaving the required product as a dark oil. This was usually made to solidify by contact with light petroleum (b. p. 40—60°). Purification was effected from the same solvent followed by sublimation at 100°/0·2 mm. 2,3-Dihydro-1*H*-pyrrolo-[1,2-*a*]benzimidazole (68%), m. p. 115° (Reppe *et al.*[6] record 115°), and 3,4-dihydro-1*H*-[1,4]-oxazino[4,3-*a*]benzimidazole (69%), m. p. 130° (Nair and Adams [7] give m. p. 130°), were obtained as white needles. 1,2,3,4-*Tetrahydro*-1-*methylpyrido*[1,2-*a*]*benzimidazole* (50%), obtained as white prisms, had m. p. 98° (Found: C, 76·9; H, 7·5. $C_{12}H_{14}N_2$ requires C, 77·4; H, 7·6%).

TABLE 2.

Imidazopyridines (II) and (III).

| Compound | X | M. p. | Yield (%) | Found (%) C | Found (%) H | Formula | Reqd. (%) C | Reqd. (%) H | Picrate M. p. | Picrate Found (%) C | Picrate Found (%) H | Picrate Reqd. (%) C | Picrate Reqd. (%) H |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| II | $[CH_2]_3$ | 136° | 56·5 | 69·2 | 6·8 | $C_{10}H_{11}N_3$ | 69·3 | 6·4 | 203° | 48·0 | 3·6 | 47·8 | 3·5 |
| III | $[CH_2]_3$ | 100 | 10·3 | 69·0 | 6·8 | $C_{10}H_{11}N_3$ | 69·3 | 6·4 | 195 | 47·3 | 4·0 | 47·8 | 3·5 |
| II | $[CH_2]_2$ | 167 | 41·0 | 68·2 | 6·0 | $C_9H_9N_3$ | 67·9 | 5·7 | 185 | 46·7 | 3·2 | 46·4 | 3·1 |
| III | $[CH_2]_2$ | 125 | 12·8 | 68·4 | 6·0 | $C_9H_9N_3$ | 67·9 | 5·7 | 185 | 46·2 | 3·45 | 46·4 | 3·1 |
| II | $[CH_2]_4$ | 155 | 72·0 | 70·5 | 6·8 | $C_{11}H_{13}N_3$ | 70·5 | 6·9 | 177 | 49·2 | 3·9 | 49·0 | 3·85 |
| III | $[CH_2]_4$ | 93 | 15·3 | 70·1 | 6·9 | $C_{11}H_{13}N_3$ | 70·5 | 6·9 | 191 | 49·1 | 3·85 | 49·0 | 3·85 |
| II | $CH_2{\cdot}O{\cdot}CH_2$ | 170 | 51·0 | 61·55 | 5·5 | $C_9H_9N_3O$ | 61·7 | 5·1 | 196 | 44·9 | 3·4 | 44·6 | 2·9 |
| III | $CH_2{\cdot}O{\cdot}CH_2$ | 128 | 12·5 | 61·4 | 5·0 | $C_9H_9N_3O$ | 61·7 | 5·1 | 192 | 44·7 | 2·6 | 44·6 | 2·9 |

(*b*) By a similar procedure of decomposition and purification, in which acetic or propionic anhydride was used as the solvent the following compounds were obtained: 4-*acetyl*-2,3,3a,4-*tetrahydro*-1H-*pyrrolo*[1,2-a]*benzimidazole* (V; R = Ac, $n$ = 3) (32%) as white prisms, m. p. 85—86° (Found: C, 71·5; H, 7·0; N, 13·9. $C_{12}H_{14}N_2O$ requires C, 71·3; H, 7·0; N, 13·9%); the 3-*propionyl* derivative (V; EtCO, $n$ = 3) (30%) as white needles, m. p. 90° (Found: C, 72·7; H, 7·4; N, 12·8. $C_{13}H_{16}N_2O$ requires C, 72·2; H, 7·5; N, 13·0%); 9-*acetyl*-4b,5,6,7,8,8a-*hexahydro*-2,4b,9-*triazafluorene* (VI; R = Ac, $n$ = 4), m. p. 66° (Found: C, 66·1; H, 7·1. $C_{12}H_{15}N_3O$ requires C, 66·3; H, 6·95%).

*Oxidation of Acyldihydrobenzimidazoles.*—The acyltetrahydropyrrolobenzimidazoles (2 g.) (V; R = Ac, $n$ = 3 and R = EtCO, $n$ = 3) were each treated with formic acid (12 ml., 98%) and hydrogen peroxide (6 ml., 30%). The reaction mixture was heated on the water-bath for 10 min. then diluted with water (50 ml.), made alkaline (NaOH), and extracted with chloroform. A practically quantitative yield of the pyrrolo[1,2-*a*]benzimidazole (I; X = $[CH_2]_2$) was obtained in each case.

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