297. *The Synthesis of Benziminazoles from* ortho-*Phenylenediamines and Imino-ethers.*

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A synthesis of benziminazoles from imino-ethers and *o*-phenylenediamines, used by Wheeler (*Amer. Chem. J.*, 1895, **17**, 397) to prepare 2-phenylbenziminazole, has been further investigated, and the optimum reaction conditions have been determined. The method has been applied to *N*-alkylbenziminazoles, *e.g.*, 6-*chloro*-2-*methyl*-1-(3′-*diethylaminopropyl*)*benziminazole*, but a side reaction leading to amidines of the type (II) limits the formation of analogues containing a 5-chloro-substituent.

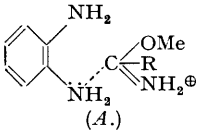
The condensation of ethylenediamines with imino-ether hydrochlorides is a well-established method for the preparation of dihydroglyoxalines (*e.g.*, dimethyl penillate-G, Merck, C.P.S., 365) and takes place under mild conditions with considerable ease (see *Chem. Zentr.*, 1929, II, 2970; Klarer and Urech, *Helv. Chem. Acta*, 1944, **27**, 1762; Delaby and Harispe, *Bull. Soc. chim.*, 1944, [v], **11**, 277). An interest in the synthesis of certain benziminazoles, unobtainable by the usual comparatively drastic methods owing to the presence of labile substituents, led us to investigate the analogous reaction between *o*-phenylenediamines and some simple imino-ethers.

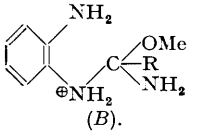
Wheeler (*Amer. Chem. J.*, 1895, **17**, 397) has already prepared 2-phenylbenziminazole from *o*-phenylenediamine and benzimino methyl ether, and the corresponding phenylbenzoxazole from *o*-aminophenol. It is reported that, without heating, little if any reaction occurs, but no yields are given to indicate the efficacy of the synthesis, and further examples of its application appear not to have been described.

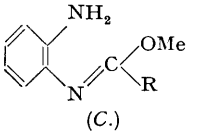
Experiments with phenacetimino methyl ether and *o*-phenylenediamine have confirmed the importance of temperature in this reaction. Heating the reagents in methanol failed to induce appreciable cyclisation (cf. Ashley *et al.*, J., 1942, 103), but when they were heated alone at 115° slow evolution of ammonia was observed which became rapid above 130°, and 2-benzylbenziminazole was obtained in 35% yield. On the other hand, with the addition of small quantities of the imino-ether hydrochloride a perceptible reaction occurred in boiling methanol, and when cold methyl-alcoholic solutions containing equivalent amounts of the imino-ether hydrochloride and *o*-phenylenediamine were mixed the heat of reaction caused the solvent to boil and the yield of benziminazole reached 84%. In presence of two equivalents of acid, the yield of benziminazole was again high, but with three equivalents, and even after prolonged heating, the formation of benziminazole was approximately only 50%. Similar results were obtained with *N*-methyl-*o*-phenylenediamine, leading to 1-*methyl*-2-*benzylbenziminazole* which was conveniently isolated as a *picrate*. Phenacetimino benzyl thioether hydrochloride readily formed benziminazoles with both *o*-diamines, but the use of *o*-phenylenediamine dihydrochloride again resulted in a diminished yield of the 2-benzylbenziminazole.

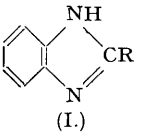
The retardation caused by a total of three equivalents of acid is readily explained in terms of the following scheme, in which the affinity of the imino-ether cation for the unshared electrons of either aromatic amino-group initiates the reaction. Formation of the complex (*B*)

is followed by loss of an ammonium ion giving a substituted imino-ether (*C*) capable of intramolecular condensation to the benziminazole (I) by elimination of methanol. Conversion of the *o*-diamine into a diquaternary salt hinders the process by removing the attractive force leading to the complex (*B*).


(*A*.)


(*B*).


(*C*.)

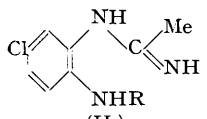

(I.)

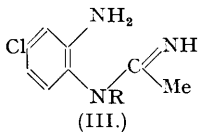
Stages (*A*)—(*C*) of this scheme are identical with those involved in the synthesis of *N*-substituted imino-ethers, *e.g.*, $OEt{\cdot}CR{:}N{\cdot}CH_2{\cdot}CO_2Et$, from the simple imino-compounds $OEt{\cdot}CR{:}NH$ and glycine ethyl ester hydrochloride (Schmidt, *Ber.*, 1914, **47**, 2545; Cornforth and Cornforth, *J.*, 1947, 96).

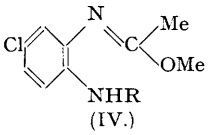
o-Aminophenol and the hydrochlorides of acetimino methyl ether and of the analogous thiobenzyl compound also reacted easily giving 2-methylbenzoxazole, which was identified by its picrate. In view of the mechanism proposed for these reactions it is probable that the condensation of imino-ether hydrochlorides with ethanolamines will yield oxazolines. This conclusion is at variance with the observation of Drozov and Bekhli (*J. Gen. Chem. Russia*, 1944, **14**, 480) that the compound obtained by the action of palmitimino ethyl ether hydrochloride on 3-piperidino-2-hydroxy-*n*-propylamine is a dihydroglyoxaline, but the recorded analytical figures for the picrate, by which the product was characterised, do not altogether exclude the oxazoline structure.

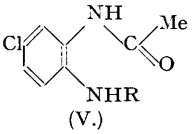
In addition to the purpose for which it was originally intended, the imino-ether method was also of interest in connexion with the synthesis of some *N*-dialkylaminoalkylbenziminazoles. Compounds of this type so far prepared (see King, Beer, and Waley, *J.*, 1946, 92) are without plasmodicidal properties, but those tested do not contain the chlorinated aromatic nucleus characteristic of most successful synthetic antimalarials. Three chloro-derivatives representative of the series of basically-substituted benziminazoles were therefore selected for synthesis, *viz.*, 5-chloro-, 6-chloro-, and 5 : 6-dichloro-2-methyl-1-(3′-diethylaminopropyl)benziminazole. The necessary monochloro-*o*-diamines were obtained from the chloro-*o*-nitroanilines (King and Acheson, *J.*, 1946, 811; King, Acheson, and Yorke-Long, *J.*, 1948, 1926) by catalytic reduction; their cyclisation to benziminazoles was first carried out with acetic acid by heating in 4N-hydrochloric acid, the method of Phillips (*J.*, 1928, 2393). The 5 : 6-*dichlorobenziminazole* was similarly prepared, the requisite diamine being obtained by condensation of 1 : 2-dichloro-4 : 5-dinitrobenzene with 3-diethylaminopropylamine and reduction of the resulting 4 : 5-dichloro-2-nitro-*N*-(3′-diethylaminopropyl)aniline. The products were either straw-coloured oils or low-melting solids forming stable *dipicrates* and *dipicrolonates*.

The preparation of these benziminazoles by the imino-ether method was fully successful only when applied to 5-chloro-2-amino-*N*-(3′-diethylaminopropyl)aniline, which readily combined with acetimino benzyl thioether hydrochloride to give the 6-chlorobenziminazole in good yield. 4-Chloro-2-amino-*N*-(3′-diethylaminopropyl)aniline and acetimino methyl ether, on the other hand, gave only a small amount of the required benziminazole, isolated as the dipicrate. The principal product separated as a *hydrochloride*, and from analyses appeared to be an amidine for which structures (II) and (III) are possible. The base, a distillable but easily oxidisable oil, was characterised by *mono-* and *di-picrates*. These derivatives did not analyse satisfactorily for nitrogen, and other possible structures were considered, *e.g.*, the imino-ether (IV) and its hydrolysis product (V), but these alternatives do not appear to be feasible. The results of


(II.)


(III.)


(IV.)


(V.)

R = $\cdot[CH_2]_3{\cdot}NEt_2$

attempted diazotisation and coupling with alkaline β-naphthol, although not conclusive, appear to favour structure (II). The amidine gave the corresponding 5-chlorobenziminazole in nearly theoretical amount on boiling it with acetyl chloride. All attempts to acetylate 4-chloro-2-nitro-*N*-(3′-diethylaminopropyl)aniline, in the hope of preparing an isomer of (V) for comparative purposes, were unsuccessful.

A *base* similar to that regarded as (II) was the principal product when acetimino methyl ether hydrochloride reacted with 4 : 5-dichloro-2-amino-*N*-(3′-diethylaminopropyl)aniline.

The ready formation of the 6-chlorobenziminazole, but not of the 5-chloro- and 5 : 6-dichlorobenziminazoles, suggests that ease of ring-closure may depend on the relative basicity of the alkylated *N*-atom, which will be lower when *para* to chlorine. If, in accordance with the mechanism already outlined, a substituted imino-ether of type (*C*) is involved, the formation of amidines implies a competitive side reaction with the ammonium chloride produced in the previous stage, and this would most likely be of significance only when the *o*-amino-group is weakly basic. In support of this explanation it was found that 4-methoxy-2-amino-*N*-(3′-diethylaminopropyl)aniline reacted with acetimino methyl ether hydrochloride giving without difficulty 5-methoxy-2-methyl-1-(3′-diethylaminopropyl)benziminazole, which was also synthesised for comparison by the method of Phillips.

Experimental.

2-Benzylbenziminazole (I; R = CH_2Ph).—(i) When *o*-phenylenediamine (0·54 g., 1 mol.) and phenylacetimino methyl ether (0·75 g., 1·1 mols.) were heated under reflux in methyl alcohol (3 c.c.) for 1 hour, there was no evolution of ammonia or separation of product on cooling and seeding with 2-benzylbenziminazole. Heating alone for 2½ hours, finally at 150—160°, and crystallisation from ethanol (charcoal) gave the benziminazole as a dark brown solid, m. p. 183—184° (35%).

(ii) Boiling the reactants under reflux in methanol for 6 hours after the addition of a minute amount of the imino-ether hydrochloride gave a product (26%) of m. p. and mixed m. p. 186°. When cold solutions of the diamine (2·16 g., 1 mol.) and of the imino-ether hydrochloride (3·71 g., 1 mol.) in methanol (8 c.c. and 4 c.c., respectively) were mixed, the liquid boiled and ammonium chloride separated. Pouring into water (100 c.c.) gave 2-benzylbenziminazole (3·5 g., 84%), crystallising from aqueous alcohol in colourless needles, m. p. 191° (Found after drying at 100° in a vacuum: C, 80·6; H, 5·8. Calc. for $C_{14}H_{12}N_2$: C, 80·8; H, 5·8%).

(iii) A mixture of the diamine (1·08 g., 1 mol.), imino-ether hydrochloride (1·86 g., 1 mol.), and hydrogen chloride (0·37 g., 1 mol.) in methanol (6 c.c.), heated under reflux for 1 hour, poured into water, and basified, gave the benziminazole (1·65 g., 79%), m. p. 190°. A similar experiment in which a further equivalent of hydrogen chloride was added gave, after boiling for 1 hour, 53% of the benziminazole, m. p. 188—189°, and further heating failed to increase the yield.

(iv) Solutions of *o*-phenylenediamine (2·16 g., 1 mol.) and phenacetimino benzyl thioether hydrochloride (5·56 g., 1 mol.) in methanol (8 c.c. and 8 c.c., respectively) developed a strong odour of toluene-ω-thiol on mixing. After 20 minutes the solution was poured into water (350 c.c.) containing concentrated hydrochloric acid (20 c.c.). The thiol was removed by ether, the aqueous solution basified, and the benzylbenziminazole (3 g., 72%), m. p. 187—188°, collected. When a methyl-alcoholic solution of the imino-thioether hydrochloride and *o*-phenylenediamine dihydrochloride was set aside for 16 hours, the yield of benziminazole, m. p. 187°, was 42%.

2-Methylbenziminazole (I; R = Me).—A mixture of *o*-phenylenediamine (1·08 g.) and acetimino methyl ether hydrochloride (1·1 g.) in methanol (5 c.c.) was warmed on a steam-bath for 10 minutes, and the colourless 2-methylbenziminazole (1·2 g., 91%), m. p. 175—176°, precipitated with water. Phillips (*J.*, 1928, 2393) gives m. p. 176°. The benziminazole picrate separated from ethanol in long thin yellow prisms, m. p. 211—212° (Phillips, *J.*, 1929, 2820, gives m. p. 207—208°) (Found: C, 46·6; H, 3·0. Calc. for $C_8H_8N_2$,$C_6H_3O_7N_3$: C, 46·5; H, 3·0%).

1 : 2-*Dimethylbenziminazole.*—When acetimino methyl ether hydrochloride (0·65 g., 1 mol.) was added to a solution of *N*-methyl-*o*-phenylenediamine (0·73 g., 1 mol.) in dry methanol (2 c.c.), a vigorous reaction took place, the liquid boiling and a yellow solid being precipitated. After a few minutes the mixture was poured into water (30 c.c.), giving a buff-coloured precipitate (m. p. 66—69°) which, when dried, had m. p. 111—112° (0·52 g., 60%). Phillips (*loc. cit.*, 1929) gives for the trihydrate m. p. 65°, and for the anhydrous compound m. p. 112°. The picrate separated from aqueous ethanol in short yellow needles, m. p. 243° (decomp.) (Found: C, 48·4; H, 3·4. Calc. for $C_9H_{10}N_2$,$C_6H_3O_7N_3$: C, 48·0; H, 3·5%).

2-Benzyl-1-methylbenziminazole.—(i) Similarly prepared from phenylacetimino methyl ether hydrochloride (0·36 g., 1 mol.) and *N*-methyl-*o*-phenylenediamine (0·24 g., 1 mol.) in methanol (2 c.c.), 2-benzyl-1-methylbenziminazole separated as a pale yellow oil when the reaction mixture was poured into water. This was collected with ether and identified as a *picrate*, which separated from aqueous dioxan in yellowish-brown dodecahedra, m. p. 249° (decomp.) (Found: C, 55·7; H, 3·7; N, 15·9. $C_{15}H_{14}N_2$,$C_6H_3O_7N_3$ requires C, 55·9; H, 3·8; N, 15·5%).

(ii) The addition of phenacetimino benzyl thioether hydrochloride (6·4 g., 1 mol.) to a solution of the diamine from the catalytic hydrogenation (Raney nickel) of 2-nitromethylaniline (3·5 g., 1 mol.) in methanol (21 c.c.) was instantly followed by the liberation of toluene-ω-thiol. After 2 hours the mixture was diluted with water (200 c.c.) and strongly acidified, and the thiol removed with ether. The aqueous solution was basified with sodium carbonate, and the precipitated *benziminazole* isolated by ether extraction as a straw-coloured oil which on distillation (244—248°/18 mm.) was obtained as a solid (3·4 g., 66%), m. p. 69—70°. After several recrystallisations from *cyclo*hexane it separated in colourless prisms, m. p. 77—78° (Found: C, 80·8; H, 6·2. $C_{15}H_{14}N_2$ requires C, 81·1; H, 6·3%).

2-Methylbenzoxazole.—(i) A mixture of *o*-aminophenol (2·5 g., 1 mol.) and acetimino methyl ether hydrochloride (2·5 g., 1 mol.) in dry methanol (10 c.c.) were heated on a steam-bath for 30 minutes. After the addition of water containing a little sodium carbonate to the semi-solid sludge, the product was collected with ether and distilled. The benzoxazole was obtained as a colourless oil (2·38 g., 78%), b. p. 203—208°, turning red on standing; the *picrate* crystallised from ethanol in yellow prisms, m. p.

117—118° (Found : C, 46·5; H, 2·7; N, 15·2. $C_8H_7ON,C_6H_3O_7N_3$ requires C, 46·4; H, 2·8; N, 15·5%). Wager (*J. Org. Chem.*, 1940, **5**, 133) records m. p. 117—118° but gives no analysis.

(ii) A small rise in temperature was noted when the imino-ether hydrochloride (1·95 g.) and *o*-aminophenol (1·95 g.) were mixed in dry methanol (5 c.c.). After 2 hours at room temperature the mixture was worked up as before, giving 0·7 g. (30%) of benzoxazole, b. p. 200—210°.

(iii) A solution of acetimino benzyl thioether hydrochloride (1 mol.) and *o*-aminophenol (1 mol.) in ethanol was heated on a steam-bath for 20 minutes, cooled, and filtered from the precipitated ammonium chloride. Picric acid was added to the heated filtrate, giving the benzoxazole picrate (51%), m. p. and mixed m. p. 117—118°.

6-*Chloro*-2-*methyl*-1-(3′-*diethylaminopropyl*)*benziminazole*.—(i) 5-Chloro-2-nitro-*N*-(γ-diethylaminopropyl)aniline (5·0 g.) (King, Acheson, and Yorke-Long, *loc. cit.*) was reduced catalytically over Raney nickel in methanol, and, after filtration and treatment with concentrated hydrochloric acid (5 c.c.), the solution was evaporated to dryness. The residue was heated under reflux with glacial acetic acid (1·1 c.c.) and 4N-hydrochloric acid (25 c.c.) for 90 minutes, and the deep red solution basified and extracted with ether. Distillation of the extract gave 6-chloro-2-methyl-1-(3′-diethylaminopropyl)-benziminazole (3·23 g., 66%) as a thick yellow oil, b. p. 140° (bath temperature)/0·14 mm. The *dipicrate* crystallised from aqueous ethanol in yellow needles, m. p. 217° (decomp.) (Found : C, 43·8; H, 4·1; N, 17·1. $C_{15}H_{22}N_3Cl,2C_6H_3O_7N_3$ requires C, 43·9; H, 3·8; N, 17·1%). The *dihydrochloride*, precipitated by passing hydrogen chloride into a solution of the free base in dry ether, separated in colourless deliquescent prisms, m. p. 100—110° (decomp.) (Found : Cl, 26·9. $C_{15}H_{22}N_3Cl,2HCl$ requires Cl, 30·2%).

(ii) The solution of 5-chloro-2-amino-(γ-diethylaminopropyl)aniline obtained from the nitro-amine (4·52 g.) by catalytic reduction in methanol (20 c.c.) was mixed with acetimino benzyl thioether hydrochloride (3·40 g.) dissolved in methanol (5 c.c.). Next day the solvent was evaporated, the residue treated with aqueous hydrochloric acid, and the benzyl mercaptan removed with ether. Addition of alkali to the aqueous solution and ether extraction gave the *benziminazole* as a pale yellow oil, b. p. 140° (bath temperature)/0·14 mm. (2·1 g., 47%) Found : C, 64·1; H, 8·0; N, 15·0. $C_{15}H_{22}N_3Cl$ requires C, 64·4; H, 7·9; N, 15·0%). The *dipicrolonate*, irregularly-shaped yellow prisms from aqueous ethanol, had m. p. 236° (decomp.) (Found : C, 52·2; H, 5·0; N, 19·3; Cl, 4·4. $C_{15}H_{22}N_3Cl,2C_{10}H_8O_5N_4$ requires C, 52·0; H, 4·7; N, 19·1; Cl, 4·4%). The dipicrate had m. p. and mixed m. p. with a sample prepared by method (i), 217° (decomp.).

5-*Chloro*-2-*methyl*-1-(3′-*diethylaminopropyl*)*benziminazole*.—4-Chloro-2-nitro-(3′-diethylaminopropyl)-aniline (2 g., 1 mol.) (King and Acheson, *loc. cit.*) was hydrogenated in methanol (15 c.c.) over Raney nickel, and the filtered solution acidified with concentrated hydrochloric acid (3 c.c.) and evaporated to dryness under diminished pressure. The residual oil was heated under reflux with glacial acetic acid (0·75 c.c., 1·9 mol.) in 4N-hydrochloric acid (12·5 c.c.) for 2 hours (cf. Phillips, *J.*, 1928, 2393), and the deep-red solution basified and extracted with ether. The *benziminazole* was a thick yellow oil, b. p. 160—164°(bath temperature)/0·14 mm., which solidified to long needles (1·55 g., 79%), m. p. 53—54° (Found : C, 64·1; H, 7·9; N, 15·3. $C_{15}H_{22}N_3Cl$ requires C, 64·4; H, 7·9; N, 15·0%).

The monopicrate crystallised from ethanol in very small yellow needles, m. p. 165°, but no satisfactory analyses were obtained for this compound owing to its tendency to disproportionate into the free base and the much less-soluble *dipicrate*. The latter salt separated from aqueous ethanol in brown diamond-shaped plates, m. p. 239° (decomp.), with a green lustre (Found : C, 43·6; H, 4·1; N, 17·3; Cl, 4·2. $C_{15}H_{22}N_3Cl,2C_6H_3O_7N_3$ requires C, 43·9; H, 3·8; N, 17·1; Cl, 4·8%).

N-(5-*Chloro*-2-3′-*diethylaminopropylaminophenyl*)*acetamidine* (II).—(i) The nitro-amine (1·27 g., 1 mol.) was catalytically hydrogenated in methanol (10 c.c.) and treated with acetimino methyl ether hydrochloride (0·5 g., 1 mol.). The mixture darkened, and a precipitate (0·84 g., 57%, m. p. 200°); soon formed which was collected after 4½ hours. (Similar results were obtained when the methanol solution was vigorously boiled for 90 minutes.) The filtrate, which gave no further precipitate when concentrated, was basified, and the resulting dark oil collected with ether and distilled. The pale-yellow product (0·25 g.) b. p. 165—170°(bath temperature)/0·15 mm., did not solidify on seeding with the 5-chlorobenziminazole and was evidently a mixture (Found : C, 62·2; H, 8·2%). Treatment with alcoholic picric acid gave a red semi-solid precipitate from which some benziminazole dipicrate, m. p. and mixed m. p. 237° (decomp.), was isolated by fractionation from alcohol. A further portion of the oil gave with alcoholic picrolonic acid the substituted 5-chlorobenziminazole *dipicrolonate*, yellow prisms (from ethanol), m. p. 235—236° (decomp.) (Found : C, 52·1; H, 4·7; Cl, 4·6. $C_{15}H_{22}N_3Cl,2C_{10}H_8O_5N_4$ requires C, 52·0; H, 4·7; Cl, 4·4%). The above precipitate of m. p. 200° crystallised from methanol in colourless prisms, m. p. 204°. It gave no ammonia with aqueous sodium hydroxide, even when heated, and apparently consisted of N-(5-*chloro*-2-3′-*diethylaminopropylaminophenyl*)*acetamidine hydrochloride* (Found : C, 53·8; H, 7·9; Cl, 21·6; N, 15·0. $C_{15}H_{25}N_4Cl,HCl$ requires C, 54·0; H, 7·8; Cl, 21·3; N, 16·8%). The base was a pale yellow oil, b. p. 160° (bath temperature)/0·2 mm. (Found : N, 17·7. $C_{15}H_{25}N_4Cl$ requires N, 18·9). A *monopicrate* obtained by the action of aqueous sodium picrate on the aqueous hydrochloride, separated from aqueous ethanol as the dihydrate in very deep-red prisms, m. p. 113—114° (Found : C, 45·2; H, 5·5; N, 16·8. $C_{15}H_{25}N_4Cl,C_6H_3O_7N_3,2H_2O$ requires C, 44·9; H, 5·7; N, 17·4%. Found, after drying over phosphoric anhydride in a vacuum at room temperature : C, 46·1; H, 5·4. $C_{15}H_{25}N_4Cl,C_6H_3O_7N_3,H_2O$ requires C, 46·4; H, 5·5%. Found, after drying at 100° in a vacuum : C, 46·9; H, 5·2; loss 1·9. $C_{15}H_{25}N_4Cl,C_6H_3O_7N_3,\frac{1}{2}H_2O$ requires C, 47·1; H, 5·2; loss 1·7%). The *dipicrate*, short yellow prisms from alcoholic picric acid, had m. p. 156° (decomp.) (Found : Cl, 5·1; $C_{15}H_{25}N_4Cl,2C_6H_3O_7N_3$ requires Cl, 4·7%).

In a further experiment the reduction product of the nitro-compound (2·1 g., 1 mol.) was treated with ethanolic hydrogen chloride (0·3 g. of HCl; 1·1 mols.) before addition to the imino-ether hydrochloride (0·8 g., 1 mol.). A rise of temperature occurred on mixing the reactants, and next day the precipitated hydrochloride of the acetamidine (m. p. 202°; 0·65 g., 27%) was collected, and the filtrate evaporated nearly to dryness. Ammonium chloride (0·2 g., 52%) then separated, and addition of alkali and extraction with ether gave a yellow oil, b. p. 165—170° (bath temperature)/0·2 mm. This failed to crystallise, but

gave, with picric acid, a salt from which benziminazole dipicrate was isolated having m. p. and mixed m. p. 237° (decomp.). When excess (2 mols.) of hydrogen chloride was used, no heating took place on mixing the reactants. Next day, on working up as before, a pale yellow oil, b. p. 160° (bath temperature)/0·2 mm. (1·47 g., 68%), was obtained, apparently the acetamidine (II) (Found : C, 60·9; H, 8·6; N, 17·5. $C_{15}H_{25}N_4Cl$ requires C, 60·7; H, 8·4; N, 18·9%); it was further characterised by the formation of the mono- and di-picrate and the hydrochloride, m. p.s and mixed m. p.s 113—114°, 156° (decomp.), and 202—203°, respectively. A solution of the amidine in hydrochloric acid became deep-cherry red on treatment with sodium nitrite; addition of this solution to alkaline β-naphthol produced a reddish-brown opalescence identical with that formed on making alkaline with sodium hydroxide alone.

Ring-closure of *N*-(5-chloro-2-3′-diethylaminopropylaminophenyl)acetamidine to 5-chloro-2-methyl-1-(3′-diethylaminopropyl)benziminazole was effected by heating the hydrochloride (0·3 g.) with acetyl chloride (3·5 c.c.) under reflux for 3 hours. The solid dissolved, and, after reaction, the mixture was cooled, diluted with water, basified, and extracted with ether. Evaporation of the dried extract gave a yellow oil solidifying to long needles (0·24 g., 92%), m. p. 52—54°, not depressed by addition of pure benziminazole prepared above. The dipicrate had m. p. and mixed m. p. 238° (decomp.) (Found : C, 44·0; H, 3·9; Cl, 5·3%).

4 : 5-*Dichloro*-2-*nitro*-N-(3′-*diethylaminopropyl*)*aniline*.—A mixture of 4 : 5-dichloro-1 : 2-dinitrobenzene (5 g.), freshly fused sodium acetate (6 g.), and 3-diethylaminopropylamine (5·2 c.c.) was heated, after the vigorous initial reaction had subsided, to 160° for 2 hours. The dark-coloured reaction mixture was then diluted with excess of dilute hydrochloric acid, unchanged nitro-compound removed with ether, the aqueous solution basified, and product extracted with ether. (Unless a large volume of water is used, the amine *hydrochloride* separates.) The amine was an orange-red oil (5·08 g., 75%), b. p. 185—190° (bath temperature)/0·02 mm.; its hydrochloride separated from aqueous hydrochloric acid as a microcrystalline yellow powder, m. p. 216—217° (Found : C, 43·5; H, 5·7. $C_{13}H_{19}O_2N_3Cl_2$,HCl requires C, 43·7; H, 5·6%). The *picrate*, fine yellow needles from aqueous ethanol, had m. p. 171—172° (Found, after drying at 116° in a vacuum : C, 41·6; H, 3·9; N, 15·5; Cl, 12·9. $C_{13}H_{19}O_2N_3Cl_2,C_6H_3O_7N_3$ requires C, 41·5; H, 4·0; N, 15·3; Cl, 12·9%).

5 : 6-*Dichloro*-2-*methyl*-1-(3′-*diethylaminopropyl*)*benziminazole*.—The above nitro-amine (3·82 g., 1 mol.) was reduced, acidified with concentrated hydrochloric acid (3·6 c.c.), and converted into the *benziminazole* as described for the monochloro-derivatives, using acetic acid (0·8 c.c., 1·2 mols.) and 4N-hydrochloric acid (25 c.c.). The product, a pale yellow oil (2·27 g., 61%), b. p. 175—180°(bath temperature)/0·02 mm. (Found : C, 57·1; H, 6·9; N, 13·4; Cl, 22·4. $C_{15}H_{21}N_3Cl_2$ requires C, 57·3; H, 6·7; N, 13·9; Cl, 22·6%), gave a *dipicrate*, long thin needles (from aqueous ethanol), m. p. 226—228° (decomp.) (Found : C, 42·3; H, 3·5; Cl, 8·7. $C_{15}H_{21}N_3Cl_2,2C_6H_3O_7N_3$ requires C, 41·9; H, 3·5; Cl, 9·2%).

When the *o*-diamine, dissolved in methanol containing 1 or 2 equivalents of hydrochloric acid, was treated with acetimino methyl ether hydrochloride in the manner of the previous experiments, the resulting base did not form purifiable salts with picric or picrolonic acid. From its composition the pale yellow oil, b. p. 180—185°(bath temperature)/0·2 mm., is probably N-(4 : 5-*dichloro*-2-3′-*diethylaminopropylaminophenyl*)*acetamidine* (Found : C, 54·6, 54·2; H, 7·4, 7·5; N, 15·0. $C_{15}H_{24}N_4Cl_2$ requires C, 54·4; H, 7·3; N, 16·1%).

5-*Methoxy*-2-*methyl*-1-(3′-*diethylaminopropyl*)*benziminazole*—2-Nitro-4-methoxy-*N*-(3′-diethylaminopropyl)aniline (7·0 g.) (King and Acheson, *J.*, 1946, 811) was hydrogenated in methanol over Raney nickel, the solution was filtered, and the filtrate and washings (54 c.c.) were divided into two parts. (i) To one half, concentrated hydrochloric acid (4 c.c.) was added, and the gum obtained on evaporation was heated under reflux with acetic acid (1 c.c.) and 4N-hydrochloric acid (15 c.c.). The methoxybenziminazole, isolated in the usual way, was a pale-yellow oil (2·2 g., 64%), b. p. 186—188°/0·8 mm., which formed long prisms, m. p. *ca.* 40° (Simonov, *Chem. Abs.*, 1941, **35**, 2870, gives b. p. 184—185°/2 mm. but no m. p.) (Found : C, 70·0; H, 9·2; N, 15·2. Calc. for $C_{16}H_{25}ON_3$: C, 69·8; H, 9·1; N, 15·3%). The dipicrate separated from aqueous *n*-propanol in clusters of short yellow prisms, m. p. 238—239° (decomp.) after sintering at *ca.* 225° (Simonov, *loc. cit.*, gives m. p. 236°) (Found : C, 46·1; H, 4·4. Calc. for $C_{16}H_{25}ON_3,2C_6H_3O_7N_3$: C, 45·8; H, 4·2%). (ii) Acetimino methyl ether hydrochloride (1·4 g.) was added to the other half of the triamine solution, which after 30 minutes was largely evaporated on a steam-bath. When alkali was added, ammonia was evolved, and extraction with ether gave an oily base (2·0 g.) distilling at 178—188°/0·8 mm. This base failed to solidify on seeding, but, when treated with alcoholic picric acid, gave the benziminazole dipicrate (2·8 g.), m. p. 229° (decomp.) (after one recrystallisation from *n*-propanol) (Found : C, 46·2; H, 4·5%).

5-Chloro-, 6-chloro-, and 5 : 6-dichloro-2-methyl-1-(3′-diethylaminopropyl) benziminazole proved to be inactive against *Plasmodium relictum* infection in chicks. For these tests we are indebted to Miss A. Bishop, Molteno Institute, University of Cambridge. We also thank the Medical Research Council for the award (to R. M. A.) of a Studentship.

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