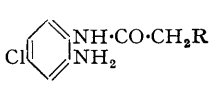
385. *Structure and Antimalarial Activity. Part III. Some Benziminazoles.*

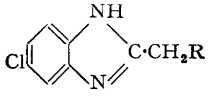
By D. Muriel Hall and E. E. Turner.

5(or 6)-*Chloro*-2-*diethylamino*- and 5(or 6)-*chloro*-2-*piperidino-methylbenziminazoles* have been prepared by ring-closure of the corresponding o-*aminoacetanilides*. Cyclisation of p-*chloro*-o-*amino*-β-*piperidinobutyranilide* gave only the unsaturated 5(or 6)-*chloro*-2-*propenylbenziminazole* by elimination of piperidine.

In Parts I and II (*J.*, 1945, 694, 699) a number of basic derivatives of various heterocyclic systems was described. The investigation has now been extended to the benziminazole series.

p-*Chloro*-o-*nitro*-ω-*chloroacetanilide* was heated with diethylamine or piperidine under pressure and the resulting p-*chloro*-o-*nitro*-ω-*diethylamino*(or *piperidino*)*acetanilide* reduced to

(I.) 

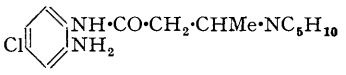


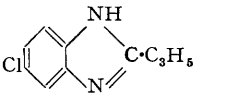
(II.)

the o-*amino*-compound (I; R = NEt_2 or NC_5H_{10}). The latter readily underwent ring closure in boiling glacial acetic acid solution in the presence of sodium acetate to give 5(or 6)-*chloro*-2-

diethylamino(or *piperidino*)*methylbenziminazole* (II; R = NEt_2 or NC_5H_{10}). The *hydrochlorides* of (I) and (II) showed no antimalarial activity when tested against *Plasmodium relictum* and *P. gallinaceum*.

p-*Chloro*-o-*nitro*-β-*bromobutyranilide* reacted with piperidine at 120° to give a mixture of *p*-chloro-*o*-nitroaniline, p-*chloro*-o-*nitrocrotonanilide* and p-*chloro*-o-*nitro*-β-*piperidinobutyranilide*. In a subsequent preparation with only a slight change in the experimental conditions no unsaturated compound was formed, but the crotonanilide was formed slowly by the elimination of piperidine from the butyranilide when the latter was heated at 120°. Catalytic hydrogenation of *p*-chloro-*o*-nitro-β-piperidinobutyranilide gave the o-*amino*-compound (III) with some *azoxy*-5-*chloro*-2-β-*piperidinobutyramidobenzene*. Attempted ring closure of (III) in boiling glacial acetic acid containing sodium acetate gave a resin but, at the higher temperature made possible by using propionic acid and sodium propionate and boiling for not more than 10 minutes, unpolymerised 5(or 6)-*chloro*-2-*propenylbenziminazole* (IV) was obtained. It was not found

(III.) 



(IV.)

possible to induce ring closure without the elimination of piperidine. In (IV) C_3H_5 is either $\cdot CH{:}CH\cdot CH_3$ or $\cdot CH_2\cdot CH{:}CH_2$, the former being preferred on grounds of conjugative stabilisation.

Ahmed, Narang, and Ray (*J. Indian Chem. Soc.*, 1938, **15**, 152) prepared 2-diethylaminomethyl- and 2-piperidinomethyl-benziminazole but in attempts to prepare the corresponding ethyl compounds they obtained only a polymer of 2-vinylbenziminazole.

The pharmacological tests were done by Dr. Ann Bishop of the Molteno Institute and Miss I. Tonkin of the National Institute for Medical Research.

Experimental.

p-*Chloro*-o-*nitro*-ω-*chloroacetanilide*.—(For the nitration of *p*-chloroacetanilide see *J.*, 1945, 699.) Chloroacetyl chloride (50 g.) was added to *p*-chloro-*o*-nitroaniline (50 g.) in the presence of dry benzene, and the mixture heated under reflux for 1 hour. p-*Chloro*-o-*nitro*-ω-*chloroacetanilide* crystallised from the cooled benzene solution in yellow needles, m. p. 141—142° (Found: Cl, 28·6. $C_8H_6O_3N_2Cl_2$ requires Cl, 28·5%); yield, 69·5 g., 97%.

p-*Chloro*-o-*nitro*-ω-*diethylaminoacetanilide*.—*p*-Chloro-*o*-nitro-ω-chloroacetanilide (25 g., 1 mol.) and diethylamine (16·5 g., 2·2 mols.) were heated together in benzene solution for 3 hours on a water-bath. Diethylamine hydrochloride was filtered off, and the benzene solution evaporated. The residue contained a considerable amount of unchanged chloro-compound which could not be removed by fractional crystallisation; the fractions were therefore collected and heated in a sealed tube with excess of diethylamine for 5 hours in a bath kept at 112°. The product was poured into water and p-*chloro*-o-*nitro*-ω-*diethylaminoacetanilide* separated as an oil which soon solidified, and crystallised from alcohol in light yellow needles, m. p. 58—59° (Found: N, 14·7. $C_{12}H_{16}O_3N_3Cl$ requires N, 14·7%). Traces of unchanged chloro-compound were removed by dissolving the base in dilute hydrochloric acid, filtering, and reprecipitating with ammonia.

p-*Chloro*-o-*amino*-ω-*diethylaminoacetanilide*.—Reduction of the above nitro-compound (10 g.) in alcoholic solution with hydrogen in the presence of Raney nickel catalyst gave p-*chloro*-o-*amino*-ω-*diethylaminoacetanilide*, which crystallised from light petroleum (b. p. 80—100°) in flat rods, m. p. 75—76° (Found: N, 16·9. $C_{12}H_{18}ON_3Cl$ requires N, 16·4%); yield, 7·7 g., 86%. The *dihydrochloride* was obtained by passing hydrogen chloride into a solution of the base in dry benzene. It crystallised from alcohol–light petroleum (b. p. 40—60°) in fine needles, m. p. 188° (decomp.) (Found: N, 12·4. $C_{12}H_{20}ON_3Cl_3$ requires N, 12·8%).

5(or 6)-*Chloro*-2-*diethylaminomethylbenziminazole*.—*p*-Chloro-*o*-amino-ω-diethylaminoacetanilide (3·3 g.) and fused sodium acetate (2 g., 2 mols.) in glacial acetic acid (15 c.c.) were heated at the boiling point for 1 hour. The cooled solution was made alkaline with 10% sodium hydroxide solution and extracted with benzene. The benzene solution was dried (K_2CO_3) and evaporated, giving a residue of 2·5 g. (80%) of 5(or 6)-*chloro*-2-*diethylaminomethylbenziminazole*, which crystallised from light petroleum (b. p. 80—100°) in needles, m. p. 150—151° (Found: N, 17·9. $C_{12}H_{16}N_3Cl$ requires N, 17·7%). The *dihydrochloride* was obtained by passing hydrogen chloride into a solution of the benziminazole in dry benzene. It crystallised from alcohol–light petroleum (b. p. 40—60°) in prisms, m. p. indefinite (Found: N, 13·55. $C_{12}H_{18}N_3Cl_3$ requires N, 13·5%).

p-*Chloro*-o-*nitro*-ω-*piperidinoacetanilide*.—*p*-Chloro-*o*-nitro-ω-chloroacetanilide (20 g., 1 mol.) and piperidine (13·6 g., 2 mols.) were heated in a bath kept at 140° for 4 hours. The product was cooled, ground with water, and crystallised from alcohol; yield of p-*chloro*-o-*nitro*-ω-*piperidinoacetanilide* 18 g., 75%; pale yellow needles, m. p. 99°, from alcohol or light petroleum (b. p. 80—100°) (Found: N, 13·8. $C_{13}H_{16}O_3N_3Cl$ requires N, 14·1%).

p-*Chloro*-o-*amino*-ω-*piperidinoacetanilide*.—The above nitro-compound (18 g.) was reduced in alcoholic solution with hydrogen in the presence of Raney nickel catalyst. p-*Chloro*-o-*amino*-ω-*piperidinoacetanilide* separated after evaporation of most of the alcohol; yield 13·5 g., 83%. It crystallised from slightly aqueous alcohol in almost colourless, thin plates, m. p. 121—122·5° (Found:

N, 15·7. $C_{13}H_{18}ON_3Cl$ requires N, 15·7%). The *monohydrochloride* was obtained by passing hydrogen chloride into a solution of the base in acetone. It crystallised from alcohol in plates, m. p. 217° (decomp.) (Found : N, 13·5. $C_{13}H_{19}ON_3Cl_2$ requires N, 13·8%).

5(or 6)-*Chloro*-2-*piperidinomethylbenziminazole.*—*p*-Chloro-*o*-amino-ω-piperidinoacetanilide (6·5 g.) and fused sodium acetate (4 g., 2 mols.) in glacial acetic acid (30 c.c.) were heated at the boiling point for 1 hour. 5(or 6)-*Chloro*-2-*piperidinomethylbenziminazole* was precipitated from the solution by 10% sodium hydroxide solution, and crystallised from light petroleum (b. p. 100—120°) in plates, m. p. 163—164° (Found : N, 16·9. $C_{13}H_{16}N_3Cl$ requires N, 16·8%); yield 5 g. (82%). The *monohydrochloride*, obtained by passing hydrogen chloride into a solution of the benziminazole in acetone, crystallised from alcohol in needles, m. p. 249—251° (decomp.) (Found : N, 14·1. $C_{13}H_{17}N_3Cl$ requires N, 14·7%).

β-Bromobutyryl Chloride.—β-Bromobutyric acid (87 g.) was added to thionyl chloride (79 g.) with cooling, and the mixture heated for 2 hours on a water-bath. The product was distilled under reduced pressure; yield 81 g., 83%; b. p. 61°/16 mm.

p-*Chloro*-o-*nitro*-β-*bromobutyranilide.*—β-Bromobutyryl chloride (16 g.) was added to *p*-chloro-*o*-nitroaniline (10 g.) in the presence of dry benzene (about 50 c.c.), and the mixture heated under reflux for 1 hour. p-*Chloro*-o-*nitro*-β-*bromobutyranilide* crystallised from the benzene solution on cooling and was recrystallised from alcohol; yield 16 g., 86%; yellow flat needles, m. p. 99° (Found : 5·148 mg. gave 5·250 mg. of AgCl + AgBr. $C_{10}H_{10}O_3N_2ClBr$ requires 5·300 mg.). (It resembles 5-chloroacridine in its irritant action on the skin.)

p-*Chloro*-o-*nitro*-β-*piperidinobutyranilide.*—(a) *p*-Chloro-*o*-nitro-β-bromobutyranilide (20 g.) and piperidine (12 g., 2·2 mols.) were heated for 5 hours in a bath kept at 120°. The product was poured into water and, when the gum had become solid, treated with dilute hydrochloric acid. The insoluble residue was crystallised from aqueous alcohol giving *ca.* 2 g. of *p*-chloro-*o*-nitroaniline, m. p. and mixed m. p. 116°. The acid solution on treatment with ammonia gave a yellow solid, which after crystallisation from aqueous alcohol still had an indefinite m. p. Repeated fractional crystallisations from light petroleum gave (1) a little more *p*-chloro-*o*-nitroaniline, m. p. 115—117°; (2) p-*chloro*-o-*nitrocrotonanilide*, brown-yellow, flat rods, m. p. 157—158°, from light petroleum (b. p. 80—100°) (Found : C, 50·0; H, 3·8; N, 11·65. $C_{10}H_9O_3N_2Cl$ requires C, 49·9; H, 3·8; N, 11·65%); (3) p-*chloro*-o-*nitro*-β-*piperidinobutyranilide*, yellow rods, m. p. 65—66°, from light petroleum (b. p. 60—80°) (Found : C, 55·1; H, 6·2; N, 12·65. $C_{15}H_{20}O_3N_3Cl$ requires C, 55·3; H, 6·2; N, 12·9%).

(b) *p*-Chloro-*o*-nitro-β-bromobutyranilide (32 g.) and piperidine (19 g.) were heated for 3 hours in a bath kept at 125°. The product was dissolved in benzene, and washed with water and then with dilute hydrochloric acid. Evaporation of the benzene solution gave *ca.* 3 g. of *p*-chloro-*o*-nitroaniline, m. p. 114—116°. The acid solution was treated with ammonia, and the precipitate crystallised from light petroleum (b. p. 60—80°); yield of *p*-chloro-*o*-nitro-β-piperidinobutyranilide, m. p. 63—65°, 19 g., 58%. In this experiment no *p*-chloro-*o*-nitrocrotonanilide could be detected.

p-*Chloro*-o-*amino*-β-*piperidinobutyranilide.*—*p*-Chloro-*o*-nitro-β-piperidinobutyranilide (6·5 g.) was reduced in alcoholic solution with hydrogen in the presence of Raney nickel catalyst. During the reduction the product separated as a white solid; this was redissolved with hot alcohol, and the nickel filtered from the hot solution. p-*Chloro*-o-*amino*-β-*piperidinobutyranilide* crystallised from the solution after evaporation of most of the alcohol. It was readily soluble in hot alcohol or hot benzene but sparingly soluble in the cold. It crystallised from benzene in needles, m. p. 141·5° (Found : C, 60·8; H, 7·2; N, 14·2. $C_{15}H_{22}ON_3Cl$ requires C, 60·9; H, 7·5; N, 14·2%); yield 2·5 g., 42%. The amine was readily soluble in the cold in a mixture of piperidine and alcohol, but it was not possible to carry out the reduction in this solvent since piperidine poisoned the catalyst.

The reduction was repeated on 10·5 g. of the nitro-compound and, after filtration of the nickel, hot water was added to the hot alcoholic solution. On cooling, yellow crystals (3·5 g.; 18%) were deposited. This substance crystallised from light petroleum (b. p. 100—120°) in yellow rectangular prisms, m. p. 156—157°, and proved to be *azoxy*-5-*chloro*-2-β-*piperidinobutyramidobenzene* (Found : C, 59·6; H, 6·7; N, 13·7. $C_{30}H_{40}O_3N_6Cl_2$ requires C, 59·7; H, 6·7; N, 13·9%). The mother-liquors after removal of the azoxy-compound were treated with more water and extracted with chloroform. Evaporation of the chloroform gave a residue which on crystallisation from benzene yielded 1·4 g. (15%) of the normal amine, m. p. 141·5°.

Benziminazole Formation from p-*Chloro*-o-*amino*-β-*piperidinobutyranilide.*—(1) The amine (0·5 g.) with fused sodium acetate (0·3 g.) in glacial acetic acid (3 c.c.) was heated at the boiling point for 45 mins. A gum separated which was insoluble in water, and more gum was precipitated on addition of 10% sodium hydroxide solution. The gum was readily soluble in alcohol and benzene but would not crystallise. It was presumably polymerised 5(or 6)-chloro-2-propenylbenziminazole (cf. Ahmed, Narang, and Ray, *loc. cit.*).

(2) The above amine (0·5 g.) with fused sodium propionate (0·32 g.) in propionic acid (5 c.c.) was heated at the boiling point for 10 mins. Dilute sodium hydroxide solution was added, and the precipitate (0·3 g., 90%) crystallised from benzene. 5(or 6)-*Chloro*-2-*propenylbenziminazole* was obtained as a white microcrystalline powder, m. p. 184—187° (Found : C, 62·5; H, 4·7; N, 14·8. $C_{10}H_9N_2Cl$ requires C, 62·3; H, 4·7; N, 14·6%).

Microanalyses are by Drs. Weiler and Strauss, Oxford.

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