317. *Benziminazole Analogues of Biologically Active Indole Derivatives.*

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The benziminazole analogue of 5-hydroxytryptamine, *viz.*, 1-2′-aminoethyl-6-hydroxybenziminazole, has been prepared. 6-Amino-1-ethyl-2-methylbenziminazole and its N^6-methyl derivative have been synthesised as possible antagonists of 5-hydroxytryptamine.

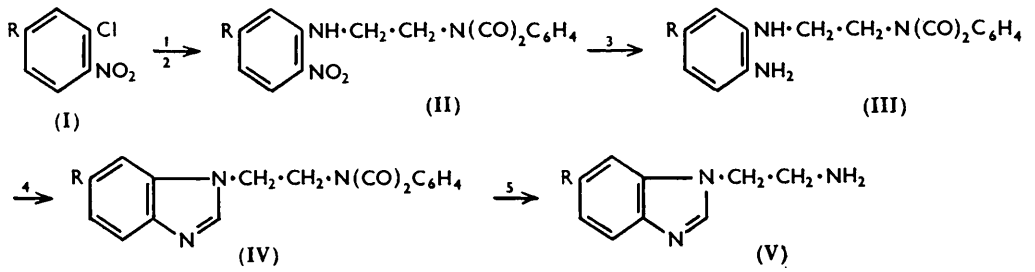
Considerable interest has been taken in recent years in the effect on biological activity of replacing an aryl nucleus in an active compound by a different nucleus. Sometimes this replacement does not alter the type of biological activity, or even change the potency greatly; *e.g.*, α-thienylalkylamines resemble the analogous phenylalkylamines closely in hypertensive activity,[1] and 2-thenoic esters of alkamines resemble the corresponding benzoic esters as local anæsthetics (cf. 2-thenoylecgonine methyl ester and cocaine [2]). On the other hand, pyrithiamine is a powerful antagonist of thiamine.[3] We have been interested in the replacement of the indole by the benziminazole nucleus. Mamalis, Petrow, and Sturgeon [4] prepared β-1-benziminazolylalanine but it had a negligible effect upon the growth of a variety of micro-organisms and presumably does not inhibit the utilization of tryptophan. We have prepared the benziminazole analogue (V; R = OH) of 5-hydroxytryptamine (serotonin) in order to discover whether it resembles or differs from serotonin in its pharmacological action.

As a model reaction sequence 1-2′-aminoethylbenziminazole (V; R = H) was first prepared by the series of reactions (I—V). This analogue of tryptamine had already been made by Mamalis *et al.*[4] who used a different route to the diamine (III; R = H), devised by Karrer and Naef.[5] When 3-chloro-4-nitroanisole (I; R = OMe) was used as a starting material, reduction of the nitroamine (II; R = OMe) and cyclisation of the product (III; R = OMe) were achieved in one operation by using formic acid as solvent; this device obviated the difficulty of isolating the very unstable *o*-diamine (III; R = OMe). The compound (IV; R = OMe) gave 1-2′-aminoethyl-6-methoxybenziminazole (V; R = OMe) with hydrazine and 1-2′-aminoethyl-6-hydroxybenziminazole (V; R = OH) with hot hydrobromic acid. Both bases were isolated as dipicrates.

Acetylation of the diamine (III; R = H) gave a diacetyl derivative which was cyclised

[1] Blicke and Burckhalter, *J. Amer. Chem. Soc.*, 1942, **64**, 477.
[2] Steinkopf and Ohse, *Annalen*, 1924, **437**, 14.
[3] Woolley and White, *J. Biol. Chem.*, 1943, **149**, 285.
[4] Mamalis, Petrow, and Sturgeon, *J.*, 1950, 1600.
[5] Karrer and Naef, *Helv. Chim. Acta*, 1936, **19**, 1029.

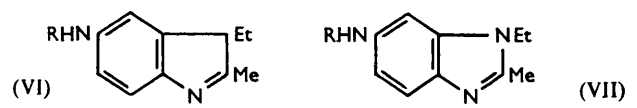
with phosphorus oxychloride; treatment of the product with hydrazine gave 1-2′-aminoethyl-2-methylbenziminazole which was isolated as its dihydrochloride. 1-2′-Aminoethyl-2-phenylbenziminazole (isolated as its dihydrochloride) was obtained directly when the dibenzoyl derivative of the diamine (III; R = H) was treated with hydrazine. A similar cyclisation did not occur with the diacetyl derivative.



(I) (II) (III) (IV) (V)

Reagents: 1, $H_2N{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$; 2, $C_6H_4(CO)_2O$; 3, Fe–HCl; 4, $H{\cdot}CO_2H$; 5, N_2H_4

Woolley and Shaw [6] have shown that 5-amino-3-ethyl-2-methylindole (VI; R = H) inhibits the stimulant action of serotonin on isolated segments of sheep carotid artery, and that this inhibitory action is increased 150-fold by methylation of the 5-amino-group, *i.e.*, in (VI; R = Me). We have therefore prepared the benziminazole analogues (VII; R = H and Me) of these two indole derivatives. In making these compounds we relied



(VI) (VII)

upon Philips's observation [7] that methylation of 2-methyl-5(6)-nitrobenziminazole with dimethyl sulphate in the absence of alkali gives mainly 1 : 2-dimethyl-6-nitrobenziminazole, and have assumed that ethylation with diethyl sulphate under the same conditions will also occur mainly at the nitrogen atom *meta* to the nitro-group. Philips proved the structure of his main methylation product by synthesis of 1 : 2-dimethyl-6-nitrobenziminazole from 2-chloro-*N*-methyl-5-nitroaniline, but we were unable to replace the chlorine atom in 2-chloro-*N*-ethyl-5-nitroethylaniline by an amino-group, even under more drastic conditions than Philips used; not could we replace the chlorine atom in 2-chloro-5-nitroaniline by ethylamino.

Ethylation of 2-methyl-5(6)-nitrobenziminazole gave two products in the proportion of 8 : 1 by weight. The more abundant isomer was assumed to be 1-ethyl-2-methyl-6-nitrobenziminazole. Catalytic reduction of the nitro-group gave 6-amino-1-ethyl-2-methylbenziminazole; reduction of the formyl derivative of this base with lithium aluminium hydride gave the 6-methylamino-compound, which was isolated as its dipicrate.

Experimental

1-2′-*Aminoethyl-6-hydroxybenziminazole*.—A mixture of 3-chloro-4-nitroanisole [8] (15 g.), ethylenediamine (24 g.), and anhydrous cupric chloride (1·5 g.) was heated to 50° with stirring. After a few minutes the mixture began to boil and heating was discontinued until the vigorous reaction subsided, then the mixture was heated for 1 hr. on the steam-bath. Excess of ethylene diamine was removed *in vacuo* (steam-bath) and N-(3-*methoxy*-6-*nitrophenyl*)*ethylenediamine hydrochloride* obtained from the residue by crystallisation from 0·5N-hydrochloric acid (yield 76%) (Found: C, 43·3; H, 5·6. $C_9H_{14}O_3N_3Cl$ requires C, 43·6; H, 5·7%). This product (14·5 g.) was heated with phthalic anhydride (21 g.) in pyridine (40 ml.) at 100° for 6 hr. The mixture was diluted with water, and the solid 5-*methoxy*-2-*nitro*-N-2′-*phthalimidoethylaniline* (II;

[6] Woolley and Shaw, *J. Pharmacol.*, 1950, **111**, 43.
[7] Philips, *J.*, 1931, 1143.
[8] Hodgson and Hanley, *J.*, 1926, 543.

R = OMe) recrystallised from dioxan, as yellow needles, m. p. 208° (96%) (Found: C, 59·7; H, 4·4; N, 12·3. $C_{17}H_{15}O_5N_3$ requires C, 59·8; H, 4·4; N, 12·3%). The phthalimido-compound (21 g.) in 98—100% formic acid (70 ml.) and water (250 ml.) was reduced by iron powder (35 g.) and hydrochloric acid (30 ml.), the acid being added dropwise to the hot (steam-bath) stirred mixture during 2 hr. The product, obtained as a gum from the cooled mixture by extraction with chloroform, crystallised from aqueous alcohol. *6-Methoxy-1-2′-phthalimidoethylbenziminazole* (IV; R = OMe) had m. p. 174° (yield 37%) (Found: C, 67·2; H, 4·8; N, 13·2. $C_{18}H_{15}O_3N_3$ requires C, 67·3; H, 4·7; N, 13·1%). The phthaloyl group was removed by hydrazine and *1-2′-aminoethyl-6-methoxybenziminazole dipicrate* isolated as yellow needles, m. p. 214—218° (decomp.) (from aqueous alcohol) (Found: C, 40·7; H, 3·1; N, 19·8. $C_{10}H_{13}ON_3,2C_6H_3O_7N_3$ requires C, 40·7; H, 2·9; N, 19·4%). Both the *O*-methyl and the phthaloyl group were removed by boiling the methoxyphthalimidoethylbenziminazole (6 g.) with 46—48% hydrobromic acid (100 ml.) for 5 hr. The mixture was diluted with water (100 ml.), phthalic acid removed by filtration, and the filtrate evaporated *in vacuo* at 100°. The dark violet residue was dissolved in dilute aqueous ammonia, and the solution left until excess of ammonia had evaporated. Addition of saturated aqueous picric acid precipitated crude *1-2′-aminoethyl-6-hydroxybenziminazole dipicrate* (30%). Four crystallisations from aqueous alcohol (50% v/v) gave red prisms, which decomposed above 140° (Found: C, 39·0; H, 2·8; N, 19·8. $C_9H_{11}ON_3,2C_6H_3O_7N_3$ requires C, 39·7; H, 2·7; N, 19·8%).

1-2′-Aminoethyl-2-methylbenziminazole.—*N-o*-Nitrophenylethylenediamine [9] was converted into its phthaloyl derivative which, crystallised from acetone, had m. p. 176° (Karrer and Naef [5] record m. p. 184°). This crude product (25 g.) was reduced by stirring it for 6 hr. with iron powder (25 g.) in refluxing ethanol, 2N-hydrochloric acid being added at the rate of 1 ml. per ½ hr. The hot mixture was filtered and the filtrate diluted with a large volume of water; *N*-2′-phthalimidoethyl-*o*-phenylenediamine (II; R = H) crystallised slowly; it had m. p. 124—125° after two crystallisations from alcohol (Karrer and Naef [5] record m. p. 124°). Acetylation with acetic anhydride gave *NN′-diacetyl-N-2′-phthalimidoethyl-o-phenylenediamine*, m. p. 192—193° after crystallisation from chloroform–acetone (Found: N, 11·6. $C_{20}H_{19}O_4N_3$ requires N, 11·5%). The diacetyl compound (3 g.) was cyclised by boiling phosphorus oxychloride (15 ml.) for 3 hr. The solution was diluted with water and extracted with chloroform. *2-Methyl-1-2′-phthalimidoethylbenziminazole* so obtained, and crystallised from acetone–ether, had m. p. 170° (Found: C, 70·4; H, 5·3; N, 13·7. $C_{18}H_{15}O_2N_3$ requires C, 70·8; H, 4·9; N, 13·8%). This phthalimido-compound was treated with an equal weight of hydrazine hydrate in boiling alcohol for 10 hr. The mixture was acidified and filtered and the base extracted with chloroform. The residue after removal of the chloroform was dissolved in dilute hydrochloric acid and the acid solution evaporated *in vacuo*. *1-2′-Aminoethyl-2-methylbenziminazole dihydrochloride* was crystallised twice from methanol–acetone; it did not melt below 250° (Found: N, 16·7. $C_{10}H_{15}N_3Cl_2$ requires N, 17·0%).

1-2′-Aminoethyl-2-phenylbenziminazole.—*N*-2-Phthalimidoethyl-*o*-phenylenediamine (10 g.) was heated with benzoic anhydride (40 g.) for 4 hr. at 100°. *NN′-Dibenzoyl-N-2′-phthalimidoethyl-o-phenylenediamine*, recrystallised from chloroform–acetone, had m. p. 197—198° (Found: N, 8·5. $C_{30}H_{23}O_4N_3$ requires N, 8·8%). Hydrazinolysis of this product as described above for the 2-methylbenziminazole compound gave *1-2′-aminoethyl-2-phenylbenziminazole dihydrochloride*; recrystallised from methanol–acetone, it did not melt below 250° (Found: N, 13·8. $C_{15}H_{17}N_3Cl_2$ requires N, 13·6%).

6-Amino-1-ethyl-2-methyl- and 1-Ethyl-2-methyl-6-methylamino-benziminoazole.—2-Methyl-5(6)-nitrobenziminazole (10 g.), obtained by nitration [10] of 2-methylbenziminazole,[11] was heated with diethyl sulphate (7·5 ml.) at 140° for 7 hr. The mixture was basified with 4N-sodium hydroxide, and the solid collected. Some 40% of unchanged starting material was recovered from the filtrate by acidification with acetic acid and this amount was not decreased by prolonging the reaction time. The ethylated product (yield, 30—40%) was crystallised first from aqueous alcohol or water and then from benzene. The latter solvent revealed the presence of two isomers. The less soluble isomer, m. p. 176°, constituting one-ninth of the total product, was assumed to be *1-ethyl-2-methyl-5-nitrobenziminazole* (Found: C, 58·7; H, 5·5. $C_{10}H_{11}O_2N_3$ requires C, 58·5; H, 5·4%). The more soluble isomer, m. p. 142° after

[9] Linsker and Evans, *J. Org. Chem.*, 1945, **10**, 283.
[10] Fisher and Hess, *Ber.*, 1903, **36**, 3967.
[11] Philips, *J.*, 1928, 2393.

crystallisation from benzene and finally from water or aqueous alcohol, was assumed to be 1-*ethyl*-2-*methyl*-6-*nitrobenziminazole* on the basis of Philips's methylation of 2-methyl-5(6)-nitrobenziminazole [7] (Found : C, 58·5; H, 5·6%). It was reduced catalytically in alcoholic suspension over Raney nickel at 3 atm. for 3 hr. 6-*Amino*-1-*ethyl*-2-*methylbenziminazole*, crystallised from benzene–light petroleum (b. p. 60—80°), had m. p. 174° (Found : C, 68·4; H, 7·4; N, 24·4. $C_{10}H_{13}N_3$ requires C, 68·6; H, 7·4; N, 24·0%). The *monopicrate* (from water) had m. p. 205° (Found : C, 47·5; H, 4·0; N, 20·7. $C_{10}H_{13}N_3,C_6H_3O_7N_3$ requires C, 47·5; H, 4·0; N, 20·8%). A solution of the free base in 98—100% formic acid was distilled slowly for 6 hr., toluene being added dropwise; water and toluene distilled over through a Dufton column. The mixture was diluted with water, and the aqueous layer separated and evaporated to dryness *in vacuo*. The residue was taken up in water, basified with sodium hydrogen carbonate, and extracted with chloroform. The dried extract (Na_2SO_4) gave on evaporation 1-*ethyl*-6-*formamido*-2-*methylbenziminazole* which, crystallised from ethyl methyl ketone, had m. p. 170° (yield 40%) (Found : C, 64·7; H, 6·5; N, 20·3. $C_{11}H_{13}ON_3$ requires C, 65·0; H, 6·4; N, 20·7%). The formyl compound (0·25 g.) in tetrahydrofuran (20 ml.) was added slowly to a suspension of lithium aluminium hydride (1 g.) in tetrahydrofuran (20 ml.) and the mixture then boiled with stirring for 1½ hr. The product, extracted with ether after decomposition of excess of lithium aluminium hydride, did not crystallise; it was converted into 1-*ethyl*-2-*methyl*-6-*methylaminobenziminazole dipicrate* which crystallised from aqueous alcohol and decomposed above 140° (yield 80%) (Found : C, 42·5; H, 3·2; N, 19·7. $C_{11}H_{15}N_3,2C_6H_3O_7N_3$ requires C, 42·6; H, 3·2; N, 19·5%).

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