25. *New Potential Chemotherapeutic Agents. Part IV. Derivatives of Benziminazole.*

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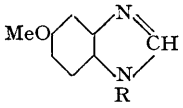
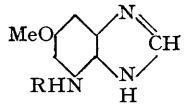
5-Methoxy-1-β-diethylaminoethylbenziminazole (I; R = $-CH_2 \cdot CH_2 \cdot NEt_2$) has been synthesised from 3-amino-4-β-diethylaminoethylanisole. A projected synthesis of a benziminazole analogue of pamaquin failed at the final stage owing to unexpected difficulties in the hydrolysis of 7-p-*toluenesulphon-(β-diethylaminoethyl)amido-5-methoxybenziminazole*. Two examples are given of the preparation of 2-chloro-5-hydroxyalkylamino-7-methoxyacridines.

SYNTHESES of methoxylated 1-diethylaminoalkylbenziminazoles have been described by Ochiai and Katada (*J. Pharm. Soc. Japan*, 1940, **60**, 543), Simonov (*J. Gen. Chem. Russia*, 1940, **10**, 1588), and Clemo and Swan (*J.*, 1944, 274), and a synthesis of a 2-β-aminoethylethoxybenziminazole has been described by Chatterjee (*J.*, 1929, 2965). Where any biological data have been reported, these have shown that these compounds are without action on avian malaria; but at the time the following experiments were begun it was not clear whether this was also true for the benziminazoles (I, R = diethylaminoalkyl) unsubstituted at the 2-position. Evidence on this point was obtained by the preparation of 5-*methoxy*-1-β-*diethylaminoethylbenziminazole* (I; R = $-CH_2 \cdot CH_2 \cdot NEt_2$) which proved to be without effect on trophozoite infections due to *P. relictum* in canaries

(I.) 

 (II.)

and *P. gallinaceum* in chicks. This was confirmed when Clemo and Swan (*loc. cit.*) published their work on a number of benziminazoles substituted at the 1-position by the group $-CHMe \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot NEt_2$—among them a homologue of the base (I; R = $-CH_2 \cdot CH_2 \cdot NEt_2$)—all of which were biologically inactive.

The method used for the preparation of (I; R = $-CH_2 \cdot CH_2 \cdot NEt_2$) differs from the procedure of Clemo and Swan and started from 3-nitro-4-*p*-toluenesulphonamidoanisole. As in the synthesis of the corresponding 4-p-*toluenesulphon*-(β-*diethylaminoethyl*)*amidoanisole*, the sodium salt of the nitrosulphonamide was alkylated by β-chloroethyldiethylamine in alcoholic solution to give 3-*nitro*-4-p-*toluenesulphon*-(β-*diethylaminoethyl*)-*amidoanisole*. From this the toluenesulphonyl group was removed with cold 90% sulphuric acid leaving 3-*nitro*-4-β-*diethylaminoethylaminoanisole*. Hydrogenation over Raney nickel gave the corresponding 3-amino-compound which, without purification, was acidified and converted by heating with formic acid to the benziminazole (I; R = $-CH_2 \cdot CH_2 \cdot NEt_2$), a reddish oil yielding a colourless crystalline hydrochloride.

Experiments were also made to prepare a benziminazole having substituents similar in character and orientation to those of pamaquin, *e.g.* (II; R = $-CH_2 \cdot CH_2 \cdot NEt_2$). These began with the reduction, by hydrogen sulphide in aqueous ammonia, of 3 : 5-dinitro-4-aminoanisole to 5-nitro-3 : 4-diaminoanisole, characterised by a 2 : 3-*diphenylquinoxaline*. By the action on the nitro-diamine of formic and hydrochloric acids, 7-*nitro*-5-*methoxybenziminazole* was obtained and catalytically reduced to the 7-*amino-derivative*. For the purpose of alkylation, a p-*toluenesulphonamide* was prepared which, from its solubility in alkali, appears to be the desired product (II; R = p-$SO_2 \cdot C_6H_4 \cdot Me$) rather than the 1- or the 3-toluenesulphonamide. Heating with β-chloroethyldiethylamine in alcoholic sodium ethoxide gave a mono-β-diethylaminoethyl derivative (m. p. 179—181°) accompanied, when the reaction was prolonged, by a di-β-diethylaminoethyl compound, probably 7-p-*toluenesulphon*-(β-*diethylaminoethyl*)*amido*-5-*methoxy*-1(or 3)-β-*diethylaminoethylbenziminazole*. From its method of formation the product, m. p. 179—181°, is regarded as the 7-p-*toluenesulphonamide* of (II; R = $-CH_2 \cdot CH_2 \cdot NEt_2$), although the possibility that alkylation has occurred in the 1- or 3-position rather than at the sulphonamido group cannot be entirely excluded. Hydrolysis of the protective group with cold 90% sulphuric acid yielded a basic oil; this was apparently heterogeneous, and the desired benziminazole could not be isolated from it. In view of its unsatisfactory features this work was discontinued.

In the experimental section two examples are given of the preparation of 2-chloro-5-hydroxyalkylamino-7-methoxyacridines. Investigations in this series were suspended when these compounds were shown to be without effect on avian malaria.

EXPERIMENTAL.

4-p-*Toluenesulphon*-(β-*diethylaminoethyl*)*amidoanisole*.—The addition of sodium hydroxide (45 g.) in water (120 c.c.) to a solution of 4-*p*-toluenesulphonamidoanisole (30 g.) in the 3% aqueous alkaline solution (150 c.c.) precipitated the sodium salt (30 g.), which was dried and heated with β-chloroethyldiethylamine hydrochloride (20 g., 1·15 mol.) in a solution of sodium (2·7 g., 1·15 mol.) in absolute alcohol (50 c.c.) under reflux for 32 hours. The filtered liquid was evaporated and, after ether extraction, a light brown oil (22 g.) was obtained and this was converted into 4-p-*toluenesulphon*-(β-*diethylaminoethyl*)*amidoanisole hydrochloride*, colourless prisms, m. p. 169°, from alcohol–ether (Found: C, 57·5; H, 7·2; N, 6·5. $C_{20}H_{28}O_3N_2S,HCl$ requires C, 58·1; H, 7·1; N, 6·8%). The *picrolonate* separated in pale yellow aggregates, m. p. 131—132° (Found: C, 56·1; H, 5·6. $C_{30}H_{36}O_8N_6S$ requires C, 56·2; H, 5·6%).

3-*Nitro*-4-p-*toluenesulphon*-(β-*diethylaminoethyl*)*amidoanisole*.—The sodium derivative of 3-nitro-4-*p*-toluenesulphonamidoanisole was prepared by adding a solution of sodium (3·45 g., 1 mol.) in alcohol (100 c.c.) to the amide (48 g., 1 mol.) also dissolved in hot alcohol (300 c.c.). β-Chloroethyldiethylamine (27·5 g., 1·25 mol.) was then introduced and the solution refluxed on a steam-bath for 48 hours. Alcohol was removed from the filtered solution, and the syrupy residue shaken with 2N-sodium hydroxide and ether. The product obtained by evaporating the ether layer, when triturated with light petroleum, gave yellow microcrystalline plates (65 g., 91%), m. p. 44·5—46·5°, and was identified as 3-nitro-4-*p*-toluenesulphon-(β-diethylaminoethyl)amidoanisole by means of the *picrate*, which crystallised from ethanol in yellow needles, m. p. 154° (Found: C, 48·0; H, 4·7. $C_{26}H_{30}O_{12}N_6S$ requires C, 48·0; H, 4·6%).

3-*Nitro*-4-β-*diethylaminoethylaminoanisole*.—The above sulphonamide (10 g.) was dissolved in sulphuric acid (40 c.c. of 90%) at 0° and left overnight. The product obtained by pouring on to ice (100 g.) and basifying with ammonia was extracted with ether. Evaporation of the dried solution gave 3-nitro-4-β-diethylaminoethylanisole which formed blood-red needles, m. p. 42° (5·6 g., 88%), characterised by the *picrate*, crystallising from acetone in long, thin, orange-red prisms, m. p. 181° (decomp.) (Found: C, 45·5; H, 4·6. $C_{19}H_{24}O_{10}N_6$ requires C, 46·0; H, 4·8%).

5-*Methoxy*-1-β-*diethylaminoethylbenziminazole*.—The alkylated nitroanisidine (1·87 g.) dissolved in alcohol was hydrogenated over Raney nickel at normal temperature and pressure; a colourless liquid was obtained from which the crude diamine hydrochloride was isolated by evaporation of the filtered and acidified solution. The free base was refluxed with formic acid (2 g., 6 mol.) in an oil-bath at 120° for 6 hours. Aqueous sodium hydroxide (10 c.c., 40%) liberated the *benziminazole* which distilled at 145—165° (air-bath temp.)/0·1 mm. as a red oil (Found: C, 67·6; H, 8·6. $C_{14}H_{21}ON_3$

requires C, 68·0; H, 8·5%). The hydrochloride (0·65 g., 30%) precipitated from a solution of the base in dry ether, after 3 crystallisations from ethanol–ethyl acetate consisted of colourless needles, m. p. 203° (evacuated capillary).

5-Nitro-3 : 4-diaminoanisole.—A suspension of powdered 3 : 5-dinitro-4-aminoanisole (10 g.) in ethanol (200 c.c.) and aqueous ammonia (4 c.c., *d* 0·88) was repeatedly saturated with hydrogen sulphide and heated to boiling until the red nitro-compound was no longer visible. Finally the boiling liquid was filtered from sulphur and the product, which separated on standing, was washed with carbon disulphide leaving the 5-nitro-3 : 4-diaminoanisole as dark red needles (6·6 g., 63%), which, after crystallisation from ethanol, had m. p. 181—182°. When heated in ethanol with benzil and sodium acetate, the sparingly soluble *8-nitro-6-methoxy-2 : 3-diphenylquinoxaline* separated as green–yellow needles, m. p. 239—241°, after recrystallisation from ethanol (Found : C, 70·2; H, 4·3. $C_{21}H_{15}O_3N_3$ requires C, 70·6; H, 4·2%).

7-Nitro-5-methoxybenziminazole.—5-Nitro-3 : 4-diaminoanisole (2 g.), formic acid (1 c.c.) and 4N-hydrochloric acid (20 c.c.) were heated under reflux, and in 30 minutes more formic acid (1 c.c.) was added. After 1 hour's refluxing the cooled solution was neutralised with ammonia, and the precipitated *benziminazole* crystallised from ethanol, giving yellow rectangular plates (1 g., *ca.* 50%) subliming > 250° (Found : C, 49·7; H, 3·6. $C_8H_7O_3N_3$ requires C, 49·7; H, 3·6%). Owing to the insolubility of the base larger quantities were more easily purified by recrystallisation of the hydrochloride, which separated from dilute hydrochloric acid in a felted mass of yellow needles, decomp. 100°. The salt lost hydrogen chloride on drying or heating and was hydrolysed by hot water.

7-Amino-5-methoxybenziminazole.—The nitro-iminazole (0·2 g.) suspended in methanol was hydrogenated at 50°/30 atms. over Raney nickel. Difficulties, sometimes encountered in the reductions, were overcome by first refluxing a suspension of the nitro compound in methanol with Raney nickel for 1 hour. After reduction, evaporation of the filtered solution left a brown oil which did not crystallise but gave the amino-iminazole *monopicrate* crystallising from ethanol as an orange powder, m. p. *ca.* 240° (decomp.) (Found : C, 43·3; H, 2·9. $C_{14}H_{12}O_8N_6$ requires C, 42·9; H, 3·1%).

The product obtained by heating the amino-iminazole with *p*-toluenesulphonyl chloride and pyridine at 100° for 1 hour, treated with water and crystallised from ethanol, gave *7-p-toluenesulphonamido-5-methoxybenziminazole* as a grey crystalline powder, m. p. 244—246° (decomp.). When pure, it separated in tiny colourless needles, m. p. 248° (decomp.) (Found : C, 56·7; H, 5·0; N, 13·4; S, 9·9. $C_{15}H_{15}O_3N_3S$ requires C, 56·8; H, 4·7; N, 13·2; S, 10·1%).

7-p-Toluenesulphon-(β-diethylaminoethyl)amido-5-methoxybenziminazole.—The sulphonamidobenziminazole (0·92 g.) and β-chloroethyldiethylamine hydrochloride (0·5 g.) were added to a solution of sodium (0·13 g., 2 mol.) in ethanol, and the mixture refluxed for 22 hours. By treatment with water and ether extraction, a pale brown oil (0·8 g.) was isolated which solidified on trituration with ligroin, in which the product, m. p. *ca.* 170°, was sparingly soluble. By recrystallisation from ethanol–ligroin the *sulphon-β-diethylaminoethyl-amide* gave colourless needles, m. p. 179—181° (decomp.) (Found : C, 60·8; H, 6·9; S, 7·7. $C_{21}H_{28}O_3N_4S$ requires C, 60·6; H, 6·7; S, 7·7%). A repetition of this experiment with the sulphonamide (2·85 g.) and refluxing for 48 hours gave a more resinous product from which extractions with warm ligroin gave colourless plates (0·2 g.), m. p. 120°, of the dialkylated sulphonamide, readily soluble in dilute mineral acid and insoluble in aqueous alkali (Found : C, 63·2; H, 7·7; N, 14·0. $C_{27}H_{41}O_3N_5S$ requires C, 62·9; H, 8·0; N, 13·6%). Crystallisation of the insoluble (in ligroin) fraction gave a pale brown solid (0·3 g.), m. p. 170—177° which, after further crystallisation from ethanol–ligroin, had m. p. 179—181°, alone or mixed with the mono-alkylated sulphonamide.

7-*p*-Toluenesulphon-(β-diethylaminoethyl)amido-5-methoxybenziminazole (0·13 g.) was dissolved in 90% sulphuric acid (1 c.c.) and set aside for some hours. The dark liquid was poured on ice and the solution basified. By ether extraction a brown oil was isolated and this with alcoholic picric acid gave a sparingly soluble orange solid. Crystallisation from acetone gave an inseparable mixture of yellow rhombs and red prisms, the proportions of which were not affected by varying the amount of picric acid used.

2-Chloro-5-amino-7-methoxyacridine Hydrochloride.—This aminoacridine was prepared by the general method of Albert and Ritchie (*Org. Synth.*, 1942, **22**, 5), a solution of 2 : 5-dichloro-7-methoxyacridine (2·8 g.) in phenol (15 g.) at 70° being treated with ammonium carbonate (0·9 g.) and heated at 120—130° for 10 minutes. The cooled mixture was treated with ethanol (5 c.c.) and concentrated hydrochloric acid (2 c.c.) and then diluted with ether (50 c.c.), the *amino-acridine hydrochloride* separating as slender yellow needles (3·2 g., 95% yield), m. p. 260°. It was sparingly soluble and was purified by continuous extraction with methanol (Found : C, 56·8; H, 4·3. $C_{14}H_{11}ON_2Cl,HCl$ requires C, 56·95; H, 4·1%).

2-Chloro-5-β-hydroxyethylamino-7-methoxyacridine.—Ethanolamine (2·4 g.), 2 : 5-dichloro-7-methoxyacridine (5·6 g.) and phenol (15 g.) were heated together on the steam-bath for 2 hours. The reaction mixture was diluted with ethanol (20 c.c.), concentrated hydrochloric acid (2 c.c.) and ether (20 c.c.), and the precipitated solid purified by extraction with methanol. The *acridine hydrochloride* formed golden prisms, m. p. 235—237° (decomp.) (Found : C, 56·9; H, 4·8; N, 7·8. $C_{16}H_{15}O_2N_2Cl,HCl$ requires C, 56·6; H, 4·7; N, 8·3%). Treatment of the hydrochloride dissolved in phenol with aqueous sodium hydroxide gave the free base which crystallised from aqueous ethanol in orange needles, m. p. 189—192° (Mietzsch and Mauss, *Chem. Abstr.*, 1932, **26**, 4684, give m. p. 191—192°).

γ-Hydroxy-n-propylamine.—2-Cyanoethanol (*Org. Synth.*, 1923, **3**, 57) (10 g.) in alcoholic ammonia (100 c.c.) was hydrogenated at high pressure over Raney nickel, the temperature rising to 90° during 2 hours. The filtered solution was distilled to give the propanolamine (7 g., 67%), b. p. 185—189° (Putochin, *Ber.*, 1926, **59**, 605, gives b. p. 185—186°) (Found : C, 48·0; H, 12·0. Calc. for C_3H_9ON : C, 48·0; H, 12·0%).

2-Chloro-5-γ-hydroxy-n-propylamino-7-methoxyacridine Hydrochloride.—The propanolamine (3 g.), 2 : 5-dichloro-7-methoxyacridine (5·6 g.) and phenol (20 g.) were heated at 120—130° for 2 hours, and the *hydrochloride* (9·5 g.) isolated as in the case of the lower homologue. After purification by repeated digestion with acetone it had m. p. 241—243° (decomp.) (Found : C, 57·7; H, 5·4. $C_{17}H_{17}O_2N_2Cl,HCl$ requires C, 57·8; H, 5·1%).

The two hydroxyalkylaminoacridines proved inactive when tested against *P. relictum* in canaries and *P. gallinaceum* in chicks. For the biological tests we thank Miss A. Bishop, Molteno Institute, Cambridge, and Miss I. M. Tonkin, National Institute of Medical Research, London.

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