200. *Contributions to the Chemistry of Synthetic Antimalarials. Part I. Some δ-Diethylamino-α-methylbutylamino-derivatives of Pyridine and Thiazole.*

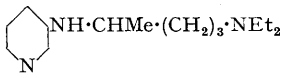
By J. N. Ashley and J. F. Grove.

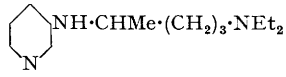
Syntheses of some *δ-diethylamino-α-methylbutylamino-derivatives* of pyridine and thiazole are described. The compounds exhibit no antimalarial, bactericidal, or trypanocidal activity.

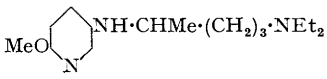
Most of the very large number of compounds prepared as possible antimalarials consist essentially of a heterocyclic nucleus—usually quinoline or acridine, and frequently containing a methoxyl group, with and without other substituents—attached to a side chain carrying one or more basic groups. Although the effect of varying the length and nature of the side-chain attached to the quinoline nucleus (usually in the 4 or 8 position) and to the 5 position in acridine has been very fully investigated, little attention has been directed towards attempts to simplify the heterocyclic nucleus. Relatively few compounds of this type in the pyridine and thiazole series have been described and, of these, only a small number have been tested for antimalarial activity; and frequently the results are unrecorded. In view of the known therapeutic effect of the pyridine and thiazole rings in combination with other groupings it was decided to prepare some derivatives of pyridine and thiazole containing the δ-diethylamino-α-methylbutylamino grouping (present in Pamaquin and Mepacrine) so that these could be tested for antimalarial activity.

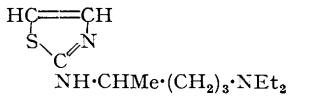
The following compounds of the type mentioned above are reported in the literature : 2-di*cyclo*hexylaminoethylaminopyridine (Bockmühl, Krohs, and Ehrhart, U.S.P. **1,936,547**), 2-diethylaminoethylaminopyridine, 2-γ-diethylaminopropylaminopyridine, and 2-γ-piperidino-ββ-dimethylpropylaminopyridine (Rothman and Fricker, G.P. 602,049), 3-diethylaminoethylamino-6-phenoxypyridine and 3-δ-diethylamino-α-methylbutylamino-6-phenoxypyridine (E.P. 373,624). Whether or not these compounds are active as antimalarial agents is unrecorded. 2-*p*-Aminobenzenesulphonamidothiazole is reported (Coggeshall, Maier, and Best, *J. Amer. Med. Assoc.*, **1941**, **117**, 1077) to be active against *P. knowlesi* and to have some effect against *P. inui* and *P. cynomolgi* in rhesus monkeys, but to be inactive against *P. cathemerium* in canaries; whilst Walker and Van Dyke (*Proc. Soc. Exp. Biol. Med.*, **1941**, **48**, 368) state that it is active against *P. lophuræ* in ducks. Since the completion of the present work we have become acquainted with the work of Mosher and of Goldsmith * (Ph.D. Theses, Penn. State Coll., 1942) who have prepared a series of 2-ω-dialkylaminoalkylaminopyridines, but in no case was the side chain, present in Pamaquin or Mepacrine, introduced into the pyridine ring. Whether these compounds exhibited antimalarial activity is unrecorded.

Subsequent papers in this series will describe synthetic work, mainly, but not entirely, concerned with the simplification or modification of known active antimalarials.

(I.) 

 (II.)

(III.) 

 (IV.)

Two methods have been employed for the synthesis of compounds (I), (II), (III), and (IV) : (*a*) condensation of the heterocyclic primary amine with ε-diethylamino-β-pentanone diethylacetal followed by hydrogenation

* This work has been published recently by Whitmore, Mosher, Goldsmith, and Rytina (*J. Amer. Chem. Soc.*, 1945, **67**, 393).

of the resulting anil, and (*b*) condensation of the heterocyclic bromo-compound with δ-diethylamino-α-methylbutylamine. Method (*a*) was used for the synthesis of (II) and (III), and (*b*) for (I) and (IV). An attempt was first made to prepare (I) by method (*a*); condensation appeared to proceed normally, but the only product which was isolated before or after hydrogenation was a very high boiling viscous oil. Nothing definite was obtained from this and it was considered probable that condensation of the acetal with 2-aminopyridine was complex due to the tautomeric character of the amine. Support for this was found in the case of 3-amino- and 3-amino-6-methoxy-pyridine in which there is no possibility of tautomerism, and both these amines condensed quite normally with the acetal. In view of the anomalous behaviour of 2-aminopyridine no attempt was made to synthesise (IV) by method (*a*).

Each of the four bases (I), (II), (III), and (IV) formed salts which were hygroscopic and very soluble in water and none was obtained solid. Aqueous solutions of the monohydrochlorides were prepared by dissolving the pure base in the requisite amount of dilute hydrochloric acid and these solutions were used in the biological tests. No activity was exhibited by any of the four hydrochlorides against *P. gallinaceum* infection in chicks, *Staph. aureus* in presence of blood, or *T. equiperdum* infection in mice.

Experimental.

Intermediate Compounds.—3-Aminopyridine was prepared (*a*) in 40% yield by reduction of 6-chloro-3-nitropyridine with zinc and sulphuric acid (Binz and Schickh, *Ber.*, 1935, **68**, 315) and (*b*) in 60% yield by catalytic reduction of 6-chloro-3-nitropyridine in the presence of palladised calcium carbonate (Binz and Schickh, *loc. cit.*). 3-Nitro-6-methoxypyridine was obtained in theoretical yield by reaction of sodium methoxide with 6-chloro-3-nitropyridine (cf. preparation of 4-methoxypyridine by Haitinger and Lieben, *Ber.*, 1885, **18**, 930). 3-Amino-6-methoxypyridine was obtained in theoretical yield by catalytic reduction of the nitro compound (*cf.* Binz and Schickh, *loc. cit.*). 2-*Bromothiazole.* 2-Aminothiazole was diazotised in the presence of 30% aqueous hydrobromic acid (Wibaut and Jansen, *Rec. trav. chim.*, 1934, **53**, 77); the yield of bromo-compound was 45%. ε-Diethylamino-β-pentanone diethylacetal, b. p. 116—118°/16 mm., was prepared as indicated by Kühn (*J. pr. Chem.*, 1940, **156**, 129).

2-δ-*Diethylamino-α-methylbutylaminopyridine* (I).—2-Bromopyridine (64 g.), δ-diethylamino-α-methylbutylamine (100 g.), anhydrous potassium carbonate (56 g.) and copper bronze (1 g.) were heated under reflux at 180° for 20 hours. After cooling and dilution with water, extraction with ether yielded a pale yellow oil (27 g.), b.p. 194—203°/25 mm., which could not be purified by further distillation. It was converted into the *di-picrate*, m. p. 149°, which crystallised in flat yellow prisms when alcohol was added to its solution in acetone (Found: C, 45·1, 44·9; H, 4·4, 4·35; N, 17·8, 18·2. $C_{14}H_{25}N_3,2C_6H_3O_7N_3$ requires C, 45·0; H, 4·5; N, 18·1%). The free *base* (I) regenerated from this di-picrate was a colourless slightly hygroscopic liquid, b. p. 182°/14 mm. (Found: N, 17·85. $C_{14}H_{25}N_3$ requires N, 17·9%). Attempts to prepare the hydrochloride, hydrobromide, sulphate, phosphate, tartrate, succinate, oxalate, and salicylate as crystalline solids were unsuccessful. The tartrate was obtained solid after precipitation and washing with acetone but could be kept in this condition only in a desiccator. The methylene bis-oxynaphthoate was an amorphous solid.

3-δ-*Diethylamino-α-methylbutylaminopyridine* (II).—A mixture of 3-aminopyridine (13 g.), ε-diethylamino-β-pentanone diethylacetal (35 g.) and ammonium chloride (0·07 g.) was heated and the bath-temperature raised from 140° to 220° during 2 hours. The residue (28·5 g.), left after removal of unchanged 3-aminopyridine and acetal, was dissolved in ethyl acetate (310 c.c.) and hydrogenated at 60°/30 atm. in presence of 11% of platinised charcoal. The uptake of hydrogen was 82% after 93 minutes. This yielded a pale yellow oil (19 g.) which was purified by treatment with hot dilute hydrochloric acid (to decompose any unchanged anil) and subsequent conversion to the picrate. The *base* (15·2 g.) was obtained as a colourless liquid, b. p. 175—178°/0·5 mm. (Found: N, 17·75. $C_{14}H_{25}N_3$ requires N, 17·9%).

3-δ-*Diethylamino-α-methylbutylamino-6-methoxypyridine* (III).—A mixture of 3-amino-6-methoxypyridine (15·7 g.), ε-diethylamino-β-pentanone diethylacetal (32·3 g.) and ammonium chloride (0·07 g.) was heated and the product worked up as described for (II). Hydrogenation of the anil resulted in 75% uptake of hydrogen in 1 hour. The base (12·8 g.), b. p. 218—220°/20 mm., slowly darkened on keeping. It had a pronounced green fluorescence, particularly when dissolved in organic solvents (Found: N, 15·6; OMe, 11·6. $C_{15}H_{27}ON_3$ requires N, 15·8; OMe, 11·7%). The oily picrate could not be obtained crystalline.

2-δ-*Diethylamino-α-methylbutylaminothiazole* (IV).—A mixture of 2-bromothiazole (44·2 g.), δ-diethylamino-α-methylbutylamine (42·5 g.), anhydrous potassium carbonate (37·5 g.) and copper bronze (0·5 g.) was heated under reflux at 165° for 5 hours. Heating at a higher temperature for a longer time caused a considerable decrease in yield. The product obtained by extraction with ether had b. p. 145°/0·3 mm. The liquid was converted into the *di-picrate*, m. p. 137·5° which crystallised in heavy prisms by addition of alcohol to an acetone solution (Found: C, 41·1; H, 4·5; N, 17·8. $C_{12}H_{23}N_3S,2C_6H_3O_7N_3$ requires C, 41·3; H, 4·15; N, 18·1%). The free *base* (18% yield) obtained from the di-picrate was a colourless liquid, b. p. 150°/1 mm. (Found: C, 59·7; H, 9·45; N, 17·2. $C_{12}H_{23}N_3S$ requires C, 59·75; H, 9·5; N, 17·4%).

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