[CONTRIBUTION FROM THE LABORATORIES OF THE UNIVERSITY OF MARYLAND]

Synthetic Antimalarials. Some 1-(4-Diethylamino-1-methylbutylamino)-isoquinolines[1]

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An investigation of dialkylaminoalkylaminoisoquinolines was a natural consequence of the high degree of activity found in the 4-dialkylaminoalkylaminoquinolines. The present paper describes the preparation of three such substances and the phosphates of two of them. The necessary 1-chloroisoquinolines were obtained from another laboratory.[2]

The arylation of noval diamine by a 1-chloroisoquinoline takes place readily under conditions approximating those necessary in the 4-chloroquinoline series.[3] The products are readily distillable, but offer some difficulty in the preparation of salts of definite composition.

Table I shows the compounds prepared. One typical preparation is given in detail in the Experimental Part together with the preparations of phosphates of two of the bases.

TABLE I

Product	SN[b]	Reaction Temp., °C.[a]	Reaction Time, hr.	B. p., °C.	Mm.	Yield, %
4-Chloro-1-(4-diethylamino-1-methylbutylamino)-isoquinoline	14,038	160 165	1 0.5	167–169	0.2	61
5-Chloro-1-(4-diethylamino-1-methylbutylamino)-isoquinoline	11,447	155 160	1 4.5	200–218	0.4	65
8-Chloro-1-(4-diethylamino-1-methylbutylamino)-isoquinoline	13,806	160–170	1	162–167	0.2	69

[a] Temperatures given are those of the reaction mixture. [b] These numbers identify the drugs in the forthcoming monograph, "A Survey of Antimalarial Drugs 1941–1945," F. Y. Wiselogle, Editor, in press.

Experimental

4-Chloro-1-(4-diethylamino-1-methylbutylamino)-isoquinoline (SN-14,038).—A mixture of 22.1 g. of 1,4-dichloroisoquinoline and 39.0 g. of noval diamine was stirred and heated at 160° for one hour and at 165° for one-half hour. At the end of the heating period, a test portion of the reaction mixture was completely soluble in 5% nitric acid. Inasmuch as dichloroisoquinolines are insoluble in this medium, it was assumed that the reaction was complete.

The mixture was dissolved in 10% acetic acid[4] and extracted with ether. The ether extracts were discarded and the aqueous layer was made strongly basic and extracted again with ether. The residue from the dried ethereal extracts was distilled *in vacuo* after removal of the ether by distillation; yield, 21.5 g. (61%); b. p. 167–169° (0.2 mm.). *Anal.* Calcd. for $C_{18}H_{26}N_3Cl$: C, 67.58; H, 8.18. Found: C, 66.75, 66.87; H, 7.89, 8.33.

5-Chloro-1-(4-diethylamino-1-methylbutylamino)-isoquinoline Diphosphate (SN-11,447-5).—The base for this salt was prepared in the usual way. The diphosphate, formed from 12.72 g. of base and 9.2 g. of 85% phosphoric acid in 25 ml. of water, was precipitated by 50 ml. of 2-propanol after prolonged cooling; 16.5 g. of salt was obtained. The salt was reconverted to base and the latter was taken up in benzene and washed with water whereupon the solvent was removed *in vacuo*. The residual oil was dissolved in ethanol and stirred while the appropriate amount of 85% phosphoric acid was added. The resulting suspension was stirred for several days at room temperature before filtration; yield, 10.1 g. (49%) of salt dried to constant weight; m. p. 107–115°. *Anal.* Calcd. for $C_{18}H_{26}N_3Cl \cdot 2H_3PO_4$: P, 12.01. Found: P, 12.35, 12.37.

8-Chloro-1-(4-diethylamino-1-methylbutylamino)-isoquinoline Triphosphate (SN-13,806-5).—The base for this salt was prepared in the usual way. The triphosphate was precipitated twice from a stirred solution of the base in ethanol; the impure salt first obtained was reconverted to base, extracted with ether, washed, and freed from ether *in vacuo*. This product was converted to pure triphosphate in the same way. The crude salt (38 g., 91%, from 21.7 g. of base) melted at 153–155°. The purified product (17.6 g., 90%, from 10.2 g. of base) melted at 154.0–155.9°. *Anal.* Calcd. for $C_{18}H_{26}N_3Cl \cdot 3H_3PO_4$: C, 35.22; H, 5.75; P, 15.15. Found: C, 35.49, 35.71; H, 5.60, 5.83; P, 15.08, 15.04.

Summary

The preparation of three 1-(4-diethylamino-1-methylbutylamino)-isoquinolines and the phosphates of two of them is described.

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(2) Supplied by Dr. R. L. Shriner, University of Indiana, see THIS JOURNAL, **68**, in press (1946).

(3) See Drake, *et al.*, *ibid.*, **68**, 1208 (1946).

(4) Alternately, the product may be isolated by making the mixture strongly alkaline directly.