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Substituted Diethylaminoalkylthioalkylamines. I. 8-Aminoquinoline and 9-Aminoacridine Derivatives

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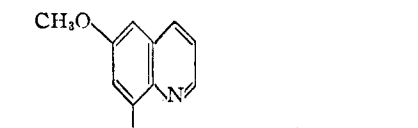
The preparation of some dialkylaminoalkylthioalkyl halides and dialkylaminoalkylthioalkylamines has recently been reported from these Laboratories.[1] The considerable pharmacological importance of compounds having a dialkylaminoalkylamino grouping as part of the molecule[2] made it seem of interest to introduce their analogs, in which the carbon chain is interrupted by thio or sulfonyl groups, into nuclei which are known to possess chemotherapeutic potentialities.

The present report deals with the preparation of some diethylaminoethylthioalkylamino-quinolines and -acridines, and one of the corresponding sulfonyl derivatives. The quinoline and acridine derivatives are of the types I–II.



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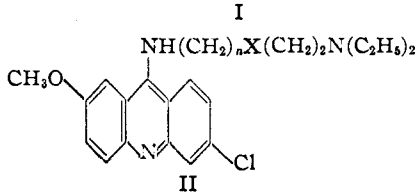

II

where X is thio or sulfonyl, and *n* is 2 or 3. Only a few compounds of the types I–II have been recorded in the literature. Thus the preparation of 8-(2-(2-diethylaminoethylthio)-ethylamino)-5,6-dimethoxyquinoline,[3] 6-chloro-9-(2-(2-diethylaminoethylthio)-ethylamino)-2-methylmercaptoacridine,[4] and 6-chloro-9-(2-(3-diethylaminoethylthio)-propylamino)-acridine[5] has been claimed. However, details of the syntheses of these compounds and of their physical properties are lacking.

In this work 8-(diethylaminoethylthioalkylamino)-6-methoxyquinolines were prepared by condensation of excess 8-amino-6-methoxyquinoline and diethylaminoethylthioalkyl chlorides in the presence of water. The diethylaminoethylthioalkyl chlorides were prepared by condensation of diethylaminoethylisothiouronium chloride with the appropriate haloalcohol and subsequent chlorination of the diethylaminoethylthioalkanol thus formed with thionyl chloride.[1] The yields of the condensation products varied from 37 to 49%. The free bases were viscous liquids which show the instability toward air typical of most 8-aminoquinoline derivatives. The pure compounds formed crystalline citrates which were considerably more stable than the parent bases.

In the acridine series condensation was effected by heating to 115° equimolecular amounts of 6,9-dichloro-2-methoxyacridine and the diethylaminoethylthioalkylamine in the presence of excess phenol for several hours. In this instance, the presence of phenol is necessary since the condensation has been shown[6] to proceed through the 9-phenoxyacridine compounds. The bright yellow crystalline dihydrochlorides were obtained in yields of 40–60%.

One of the above-mentioned sulfides was oxidized to the corresponding sulfone; 6-chloro-9-(2-(2-diethylaminoethylsulfonyl)-ethylamino)-methoxyacridine dihydrochloride was prepared by oxidation of the corresponding sulfide with hot permanganic acid. As anticipated, the oxidation of an 8-(2-diethylaminoethylthio)-alkylamino-6-methoxyquinoline with permanganic acid resulted in the formation of an intractable, tarry material.

The compounds prepared are listed in Tables I and II. Details of the preparation of typical compounds are given in the experimental section.

Most of these compounds are being tested for their pharmacological activity, particularly toward malaria-causing plasmodia. Results of these tests will be reported at a later date.

Experimental

8-(3-(2-Diethylaminoethylthio)-propylamino)-6-methoxyquinoline.—A mixture of 83.5 g. (0.48 mole) of 8-amino-6-methoxyquinoline, 50.3 g. (0.24 mole) of 3-(2-diethylaminoethylthio)-propyl chloride,[1] 21 ml. (0.25 mole) of 12 *N* hydrochloric acid, and 61 ml. of water was heated successively for four hours at 50–55°, two hours at 75° and sixteen and one-half hours at 102°. The cooled reaction mixture was dissolved in 600 ml. of water; 60 ml. of 12 *N* hydrochloric acid was added and the dark solution was cooled slowly to 15° with stirring. The recovered 8-amino-6-methoxyquinoline hydrochloride was filtered, washed twice with ice water, and dried; the yield was 43.7 g. The filtrate was made neutral to congo red with sodium acetate and extracted with ether (extract discarded), and the aqueous layer was made strongly alkaline with cold 30% sodium hydroxide solution and solid potassium carbonate. The liberated base was extracted with ether, and the ethereal solution, after drying with anhydrous potassium carbonate, was evaporated *in vacuo* under nitrogen to yield an oily residue (64.2 g.), which was fractionated *in vacuo* under nitrogen. The main fraction, 44.6 g. of orange-yellow oil, distilled at 168–173° at 0.5–1.0 μ (bath temperature 193–215°). A second distillation

(1) Clinton, Suter, Laskowski, Jackman and Huber, THIS JOURNAL, **67**, 594 (1945).

(2) Goodman and Gilman, "The Pharmacological Basis of Therapeutics," The Macmillan Co., New York, N. Y., 1941, pp. 286, 460, 903.

(3) U. S. Patent 1,938,047.

(4) U. S. Patent 2,082,171.

(5) U. S. Patent 2,077,249.

(6) Sherndal, *Ind. Eng. Chem., News Ed.*, **21**, 1154 (1943).

TABLE I

	Substituent groups	B. p.[a] °C.	B. p.[a] μ	B. p.[a] Bath temp., °C.	M. p., °C.[a]	Yield,[b] %	Formula	Analyses, %[c] Calcd.	Found
	8-AMINOQUINOLINE DERIVATIVES								
1	8-(2-(2-Diethylaminoethylthio)-ethylamino)-6-methoxy-	161–163[d]	2	192–196	.....	38	$C_{18}H_{27}N_3OS$	C, 64.9	64.92
								H, 8.10	7.81
2	8-(3-(2-Diethylaminoethylthio)-propylamino)-6-methoxy-	168–171[d]	1	198–209	.....	49	$C_{19}H_{29}N_3OS$	C, 65.7	65.53
								H, 8.35	8.32
3	8-(2-(2-Diethylaminoethylthio-2-ethylthio)ethylamino)-6-methoxy-	188–192[d]	2	211–214	.....	37	$C_{20}H_{31}N_3OS$	C, 61.03	60.47
								H, 7.94	8.42
								S, 16.30	16.90
	ACRIDINE DERIVATIVES (DIHYDROCHLORIDES)								
4	6-Chloro-9-(2-(2-diethylamino-ethylthio)-ethylamino)-2-methoxy-	.....	..	.....	253–256 (dec.)	42 (87[e])	$C_{22}H_{28}Cl_4N_3OS\cdot 2HCl$	C, 53.82	53.88
								H, 6.12	6.41
								S, 6.52	5.92
5	6-Chloro-9-(2-(2-diethylamino-ethylsulfonyl)-ethylamino)-2-methoxy-	.....	..	.....	235–237 (dec.)	31	$C_{22}H_{28}ClN_3O_3S\cdot 2HCl$	C 50.51	50.30
								H, 5.78	5.78
6	6-Chloro-9-(3-(2-diethylamino-ethylthio)-propylamino)-2-methoxy-	.....	..	.....	251–254 (dec.)	39 (80[e])	$C_{23}H_{30}ClN_3OS\cdot 2HCl$	C, 54.81	55.03
								H, 6.35	6.28
								S, 6.35	6.06

[a] All melting and boiling points are uncorrected. [b] Purified products (yield based on side chain (1–3) and acridine (4–6)). [c] We are indebted to the Misses Alice Rainey and Patricia Curran for the microanalyses. [d] Distilled under nitrogen. [e] Yield of crude products.

TABLE II

CITRATES[a] OF 8-AMINOQUINOLINE DERIVATIVES[b]

	Formula	Analyses, %[c] Calcd. Base	Calcd. Acid	Found[d] Base	Found[d] Acid
1	$C_{18}H_{27}N_3OS\cdot C_6H_8O_7$	63.4	36.4	63.5	36.4
2	$C_{19}H_{29}N_3OS\cdot C_6H_8O_7$	64.4	35.6	64.2	35.8
3	$C_{20}H_{31}N_3OS\cdot C_6H_8O_7$	67.4	32.6	67.4	29.3

[a] All salts had no true melting point but decomposed slowly over a wide temperature range. [b] Same numbering as in Table I. [c] We are indebted to Mr. George Bronell for the acid and base analyses. [d] All precipitated as hydrates; results here given on anhydrous basis.

gave 40.5 g. (48.7%) of yellow oil distilling at 168–171° at 1.0 μ (bath temperature 198–209°).

6-Chloro-9-(2-(2-diethylaminoethylthio)-ethylamino)-2-methoxyacridine Dihydrochloride.—A mixture of 25.0 g. (0.14 mole) of 2-(2-diethylaminoethylthio)-ethylamine,[1] 37.5 g. (0.14 mole) of 6,9-dichloro-2-methoxyacridine, and 100 g. of phenol was heated with stirring for three hours at an inside temperature of 113–115°. The amber melt was cooled to *ca.* 70° and poured into 1000 ml. of acetone; 40 ml. of 12 *N* hydrochloric acid was added. The resulting mixture was stirred for one hour and filtered, yielding 61 g. (87%) of orange-yellow crystals. A sample recrystallized from dry methanol-acetone melted at 253–255° (dec.).

6-Chloro-9-(2-(2-diethylaminoethylsulfonyl)-ethylamino)-2-methoxyacridine Dihydrochloride.—To a hot, stirred solution of 2.45 g. (5.0 millimoles) of 6-chloro-9-(2-(2-diethylaminoethylthio)ethylamino)-2-methoxyacridine dihydrochloride and 0.68 g. (5.0 millimoles) of sodium acetate trihydrate in 85 ml. of water was added dropwise a hot solution of 1.05 g. (6.7 millimoles) of potassium permanganate in 30 ml. of water containing 0.56 ml. (6.7 millimoles) of 12 *N* hydrochloric acid. The hot solution was filtered through Filtercel and the residue was washed well with hot water. The combined filtrate and washings were concentrated *in vacuo* to *ca.* 120 ml., and then 100 ml. of acetone and 12 ml. of 12 *N* hydrochloric acid were added; on cooling there was obtained 1.28 g. of orange crystals. Several recrystallizations from dry methanol–acetone with decolorization gave 0.82 g. (31%) of orange needles melting at 235–237° (dec.).

8-(3-(2-Diethylaminoethylthio)-propylamino)-6-methoxyquinoline Monocitrate.—To a solution of 31.9 g. (0.092 mole) of twice-distilled 8-(3-(2-diethylaminoethylthio)-propylamino-6-methoxyquinoline dissolved in 45 ml. of absolute alcohol was added a warm solution of 19.3 g. (0.092 mole) of citric acid monohydrate in 30 ml. of absolute alcohol. An additional 60 ml. of absolute alcohol was added and the solution was kept slightly above room temperature until crystallization had started. After standing overnight, the citrate was filtered, washed with cold absolute alcohol and then with ether. This product was powdered, slurried with ether and cold absolute alcohol, filtered, and washed with ether. While still moist the salt was removed from the funnel (when sucked dry in the funnel these citrates colored slightly, presumably due to hydration) and dried *in vacuo* at room temperature. A yield of 48.2 g. (97.2%) was obtained. This product analyzed satisfactorily without further purification.

Summary

The preparation of a series of diethylaminoethylthioalkylamino-quinoline and -acridine derivatives and one of the corresponding sulfones is described. The bases readily yielded well-defined crystalline citrates or hydrochlorides.

RENSSELAER, N. Y. RECEIVED JULY 5, 1945