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Substituted Diethylaminoalkylthioalkylamines. II. 4-Aminoquinoline Derivatives

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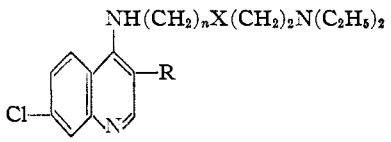
In a previous communication[1] there has been reported the preparation of a series of diethylaminoalkylthioalkyl derivatives of 8-amino-6-methoxyquinoline and 9-amino-6-chloro-2-methoxyacridine.

The present report deals with the preparation of some diethylaminoethylthioalkyl derivatives of substituted 4-aminoquinolines and a few of their corresponding sulfinyl and sulfonyl analogs. The quinoline derivatives are of the type



where R is methyl or hydrogen, X is thio, sulfinyl or sulfonyl, and n is 2 or 3. Only one compound of this type, namely, 7-chloro-4-(2-(2-diethylaminoethylthio)-ethylamino)-quinoline[2] has been reported in the literature.

In the present work the quinoline derivatives with a diethylaminoethylthioalkylamino side chain in the 4-position were prepared by condensing either 4,7-dichloroquinoline[2] or 4,7-dichloro-3-methylquinoline[2] with an excess of diethylaminoethylthioalkylamine at 160°. These condensations were also carried out with comparable yields using phenol as a solvent. The diethylaminoethylthioalkylamines were prepared by the condensation of diethylaminoethylisothiouronium chlorides with the appropriate phthalimidoalkyl bromide in the presence of sodium ethoxide, followed by hydrolysis of the intermediate diethylaminoethylthioalkylphthalimides.[3] The condensation products after purification were converted into their crystalline phosphates. The 7-chloro-4-substituted-quinoline bases were crystalline solids but the corresponding 3-methylquinoline bases were viscous, yellow oils. In contrast to the 8-aminoquinoline derivatives[1] the substituted 4-aminoquinolines were stable toward air. The yields varied from 48–68%.

Two 7-chloro-4-(diethylaminoethylsulfonylalkylamino)-quinolines were prepared by oxidation of the sulfides with acid permanganate at 6–8°. Similar treatment of 7-chloro-4-(2-diethylaminoethylthio)-alkylamino-3-methylquinoline yielded a viscous, oily product that decomposed on attempted vacuum distillation.

One sulfoxide was prepared during the present investigation; 7-chloro-4-(2-(2-diethylaminoethylsulfinyl)-ethylamino)-quinoline was obtained by treatment of an acetone solution of the corresponding sulfide with 30% hydrogen peroxide solution at room temperature.

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

7-Chloro-4-(2-(2-diethylaminoethylthio)-ethylamino)-quinoline.—A mixture of 19.8 g. (0.10 mole) of 4,7-dichloroquinoline,[2] 35.4 g. (0.20 mole) of 2-(2-diethylaminoethylthio)-ethylamine[3] and 0.1 g. of sodium iodide was stirred for one hour at an inside temperature of 160–165° (initial exothermic reaction). The reaction mixture was allowed to cool to 90–100° and poured, with stirring, into cold 10% hydrochloric acid. The acidic solution was made neutral to congo red with sodium acetate and extracted with ether (extract discarded). The aqueous layer was made alkaline with cold 30% sodium hydroxide solution and extracted with ether. This ether extract (dried with potassium carbonate) was then evaporated to dryness *in vacuo*, leaving 46.1 g. of a solid, which was subjected to vacuum distillation. The main fraction distilled at 188–192° at 16–19μ (bath temperature 221–235°) as an orange, viscous liquid which solidified on cooling; 24.8 g. of product was obtained. This crude material was purified by recrystallization from ether-petroleum ether (ether solution charcoaled), and then had a melting point of 80–82° (13.2 g. or 39%). For analysis a sample was recrystallized again; the white platelets melted at 82–83°.[4]

7-Chloro-4-(2-(2-diethylaminoethylsulfinyl)-ethylamino)-quinoline.—A solution of 1.0 g. (3.0 millimoles) of 7-chloro-4-(2-(2-diethylaminoethylthio)-ethylamino)-quinoline and 0.36 g. (3.2 millimoles) of 30% hydrogen peroxide solution in 9 ml. of acetone was allowed to stand at room temperature for twenty-four hours. The solvent was removed *in vacuo;* the residue solidified when triturated with hot petroleum ether. The crude product, after drying, weighed 0.83 g. Two recrystallizations from benzene–petroleum ether gave 0.40 g. (38%) of product melting at 134–136°. Another recrystallization raised the melting point to 135–137°.

7-Chloro-4-(2-(2-diethylaminoethylsulfonyl)-ethylamino)-quinoline.—A solution of 40.5 g. (0.12 mole) of 7-chloro-4-(2-(2-diethylaminoethylthio)-ethylamino)-quinoline (m. p. 94–96°[4]) in 800 ml. of water containing 20.7 ml. (0.25 mole) of 12 N hydrochloric acid was chilled in an ice-bath while a solution of 23.7 g. (0.15 mole) of potassium permanganate in 950 ml. of water containing 12.5 ml. (0.15 mole) of 12 N hydrochloric acid was added dropwise with stirring over a period of one and one-half hours (inside temperature of 6–8°). The manganese dioxide was removed by filtration and washed with hot

(1) Huber, Bair, Boehme, Laskowski, Jackman and Clinton, THIS JOURNAL, **67**, 1849 (1945).

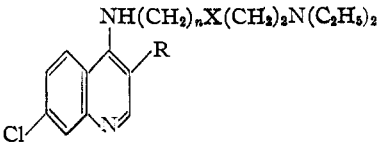
(2) U. S. Patent 2,233,970.

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

(4) In another experiment a higher-melting isomer (94–96°) was obtained when the crude base was recrystallized from benzene-petroleum ether. When dissolved in petroleum ether and seeded with the low-melting isomer, this high-melting form gave crystals melting at 80–82.5°. Furthermore, both isomers produced the same sulfone on oxidation.

TABLE I

QUINOLINE DERIVATIVES



R	Substituent groups X	n	B. p.,[a] °C.	u	M. p.,[a] °C.	Yield,[b] %	Formula	Percentage composition[c] C Calcd.	C Found	H Calcd.	H Found	N or S or Cl El.	N or S or Cl Calcd.	N or S or Cl Found
H	S	2	.....	..	82–83[d]	68	$C_{17}H_{24}ClN_3S$	60.50	60.71	7.12	6.92	N[j]	12.45	12.62
H	S	3	192–197[e]	65	71–73	48[f]	$C_{18}H_{26}ClN_3S$	61.45	61.08	7.39	7.36	S[k]	9.16	9.14
H	SO	2	.....	..	135–137	38	$C_{17}H_{24}ClN_3OS$	57.70	57.98	6.79	6.97	N	11.88	11.45
H	SO_2	2	.....	..	145–147	42	$C_{17}H_{24}ClN_3O_2S$	55.20	54.98	6.54	6.84	N	8.67	8.63
H	SO_2	3	.....	..	94–96	19[g]	$C_{18}H_{26}ClN_3O_2S$	56.31	56.02	6.83	6.63	..	...	...
CH_3	S	2	165–166[h]	3–4	.....	53	$C_{18}H_{26}ClN_3S$	61.48	61.24	7.39	7.30	S	9.11	9.38
CH_3	S	3	191–193[i]	20	.....	61	$C_{19}H_{28}ClN_3S$	62.38	62.20	7.66	7.64	Cl	10.08	10.00

[a] All melting and boiling points are uncorrected. [b] Purified products (yield based on quinoline). [c] We are indebted to the Misses Alice Rainey and Patricia Curran for the microanalyses. [d] Also 94–96° (see reference 4). [e] Bath temperature, 230°. [f] Yield based on unrecovered quinoline, 61. [g] Yield of crude product, 47. [h] Bath temperature, 194–201°. [i] Bath temperature, 214–223°. [j] Also S: calcd., 9.51; found, 9.68. [k] Also Cl: calcd., 9.70; found, 9.14.

TABLE II

DIPHOSPHATES[a,b] OF QUINOLINE DERIVATIVES

	Formula	Analyses, %[c] Calcd. Base	Calcd. Acid	Found[d] Base	Found[d] Acid
1	$C_{17}H_{24}ClN_3S\cdot 2H_3PO_4$	63.3	36.7	63.6	36.7
2	$C_{18}H_{26}ClN_3S\cdot 2H_3PO_4$	64.2	35.8	65.1	35.2
4	$C_{17}H_{24}ClN_3O_2S\cdot 2H_3PO_4$	65.3	34.7	66.1	34.9
6	$C_{18}H_{26}ClN_3S\cdot 2H_3PO_4$	64.2	35.8	64.6	35.7
7	$C_{19}H_{28}ClN_3S\cdot 2H_3PO_4$	65.1	34.9	65.5	35.8

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

water, and the filtrate, plus washings, was made alkaline with cold 30% sodium hydroxide solution. About one-third the volume of chloroform was added and the mixture was shaken in a separatory funnel and allowed to stand from five to ten minutes. Decolorizing carbon was added; the mixture was shaken again and filtered, and the layers separated. The aqueous layer was then extracted two additional times with chloroform. The combined extracts were shaken with anhydrous potassium carbonate, the mixture was filtered, and the filtrate was concentrated *in vacuo* on a steam-bath. This solution was decolorized, shaken with activated alumina, filtered, and then evaporated *in vacuo* on a steam-bath to yield 32.5 g. of light-colored solid. Recrystallization from benzene–petroleum ether (6 to 1; benzene solution digested with charcoal and activated alumina) produced 22.3 g. (50.3%) of needles, m. p. 140–146° (softening at 137°). A sample recrystallized two additional times melted at 145–147° (90–95% recovery on each recrystallization).

7-Chloro-4-(3-(2-diethylaminoethylthio)-propylamino)-3-methylquinoline.—A mixture of 21.2 g. (0.10 mole) of 4,7-dichloro-3-methylquinoline,[2] 38.0 g. (0.20 mole) of 3-(2-diethylaminoethylthio)-propylamine,[3] 21.2 g. (0.23 mole) of phenol, and 0.1 g. of sodium iodide was heated with stirring at an inside temperature of 160° for eight hours. The cooled melt was taken up in cold 30% sodium hydroxide solution and extracted with ether. The ethereal extract was extracted with cold dilute hydrochloric acid; the acidic solution was made neutral to congo red with sodium acetate and extracted with ether (extract discarded). The aqueous solution was made strongly alkaline with cold 30% sodium hydroxide solution and extracted with ether. This extract was dried over anhydrous potassium carbonate and evaporated *in vacuo*, yielding an oily residue (42.9 g.), which was subjected to fractional distillation *in vacuo*. The main fraction, 24.6 g. of dark reddish-brown oil, boiled at 162–188° at 65–105 μ (bath temperature 205–240°). Redistillation gave 22.2 g. (60.5%) of an orange oil with a boiling temperature of 191–193° at 20 μ (bath temperature 214–223°).

7-Chloro-4-(2-(2-diethylaminoethylthio)-ethylamino)-3-methylquinoline Diphosphate.—To a solution of 15.9 g. (0.045 mole) of 7-chloro-4-(2-(2-diethylaminoethylthio)-ethylamino)-3-methylquinoline dissolved in 50 ml. of methanol was added dropwise with stirring and cooling a cold solution of 10.1 g. (0.091 mole) of 85% phosphoric acid in 40 ml. of methanol. (At this point in some preparations an oily salt separated; solidification resulted upon trituration with ethanol.) The resulting solution was allowed to stand at room temperature for three days; the product, which crystallized as pale yellow rosets, was filtered and washed with acetone or ether (weight 22.3 g.). When powdered and washed with ether or acetone, a salt was obtained that gave satisfactory analyses. These phosphates can be recrystallized from a water–methanol–isopropanol mixture.

Summary

The preparation of a series of diethylaminoethylthioalkyl derivatives of some substituted 4-aminoquinolines, of two of the corresponding sulfones, and of one sulfoxide is described. The bases readily yielded well-defined crystalline phosphates.

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