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SOME BIS- AND TRIS-AMINO AND AMMONIUM DERIVATIVES OF *SYMMETRICAL*-TRIAZINE

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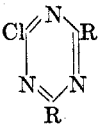
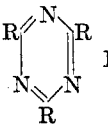
Most of the highly active curarimimetic compounds which have been prepared are di-quaternary ammonium derivatives. Flaxedil,® or 1,2,3-tris(diethylaminoethoxy)benzene triethiodide, is of interest in that its activity, although less than that of *d*-tubocurarine, is equal to or greater than that of some analogous bis-substituted derivatives (1). One explanation for the somewhat greater activity of Flaxedil® than the 1,3-bis-quaternary analog is that the substituent in the 2-position of the benzene ring tends to keep apart the onium functions in the 1,3-substituted positions, at a distance from each other more nearly optimal for high activity (2).

In the present communication, bis- and tris-quaternary ammonium substituted derivatives of 1,3,5-triazine are described which show some interesting structure-activity variations. Benzene and triazine are both rigid ring systems of approximately the same size. The side chains were attached to the 2,4- or 2,4,6-positions by controlled reaction of dialkylaminoalkyl-amines, -alcohols, or -thiols with the readily available cyanuric chloride.[1] Substituted amino-*s*-triazines (3) and some aminoalkylamino-*s*-triazines (4) previously have been prepared by reaction of cyanuric chloride with ammonia or amines under controlled conditions. Of these, 2-amino-4,6-bis(piperidylaminopropylamino)-1,3,5-triazine (3) is the closest approach to the present series.

The compounds prepared, their properties, and comparable biological activities are outlined in Table I. The salts of these compounds were usually very hygroscopic. Preliminary tests for neuromuscular blockade were run using mice and active compounds were also tested in rabbits. The results show: slight reduction of activity with increased chain length (II *vs.* IV); much greater activity of bis- than tris- derivatives (I *vs.* VIII, II *vs.* IX); no significant difference between imino and ether linkage of side chain (IX *vs.* XI); very marked increase in activity in compounds formed by quaternization with benzyl chloride (IX *vs.* X; also XIII); loss of activity with increased steric hindrance about the quaternary nitrogen (IV *vs.* VI); surprising activity of bis-hydrochloride III as compared with quaternary IV but not present in tris- derivatives VII or XII. The greater activity of the bis- than tris- derivatives is not incompatible with the explanation of Pelikan and Unna for greater activity of Flaxedil® than its 1,3-bis-analog (2), since the present series compares 1,3,5-tris *vs.* 1,3-bis derivatives rather than 1,2,3 *vs.* 1,3 analogs. In the symmetrical triazine series, the third quaternary group may be in a position which repels approach of the molecule to the receptor site or else enables it to be more readily displaced from its site of action after adsorption. The data available suggest that high curarimimetic

[1] American Cyanamid Company, New York, N. Y.

TABLE I

sym-TRIAZINE  and  DERIVATIVES

COMPOUND	R	M.P., °C. (Corr.)	YIELD,[b] %	ANALYSES[d] Calc'd X⁻	Calc'd N (or C, H)	Found X⁻	Found N (or C, H)	CURARIMIMETIC DOSE MG./KG., INCLINED SCREEN, MOUSE, S.C.[c] LD_{50}	ED_{50}
I	bis-$NH(CH_2)_2N(C_2H_5)_2CH_2I$	200	26	40.43	15.62	40.33	15.09	1.5	1.4
II	bis-$NH(CH_2)_2N(C_2H_5)_2I$	94 dec.	22	38.70	14.95	38.26	14.88	2.7	1.0
III	bis-$NH(CH_2)_2N(C_2H_5)_2$·HCl	159[a]	81	15.94		15.64		6.0	4.0
IV	bis-$NH(CH_2)_2N(C_2H_5)_2I$	172[a]	—	37.11	C 38.63 H 6.50	37.80	C 38.0 H 6.83	4.4	2.0
V	bis-$NH(CH_2)_2N(C_3H_7)_2$·HCl	117[a] dec.	82	14.15		14.81		—	—
VI	bis-$NH(CH_2)_2N(C_3H_7)_2I$	79[a]	23	33.05	C 42.22 H 7.35	33.48	C 42.89 H 7.56	>20	>20
VII	tris-$NH(CH_2)_2N(C_2H_5)_2$·HCl	256 dec.	70	19.96	23.65	19.37	22.94	25–30	16
VIII	tris-$NH(CH_2)_2N(C_2H_5)_2CH_2I$	214 dec.	10	44.82	14.83	44.70	14.53	35	17
IX	tris-$NH(CH_2)_2N(C_2H_5)_2I$	236 dec.	37	42.70	14.13	42.77	13.91	40	20
X	tris-$NH(CH_2)_2N(C_2H_5)_2C_6H_5CH_2Cl$	90	—	13.24	15.69	13.69	15.42	6.3	2.7
XI	tris-O-$(CH_2)_2N(C_2H_5)_2I$	175[a]	—	42.56	9.40	42.01	9.17	>20	20
XII	tris-S-$(CH_2)_2N(C_2H_5)_2$·HCl	187[a]	35	16.99		16.45		>20	>20
XIII	tris-S-$(CH_2)_2N(C_2H_5)_2C_6H_5CH_2Cl$	127	63	11.87	C 60.28 H 7.77	11.71	C 59.76 H 8.11	0.8	0.7

[a] Sinters or softens below this melting point. [b] Yield of analytically satisfactory product from preceding intermediate. [c] Rabbit HD_{50} mg. per kg. I.V. values were for I, 0.8; II, 0.5; X, 0.5; XIII, 0.07. [d] Microanalyses by Clark Microanalytical Laboratory, Urbana, Illinois.

activity of bis- and tris-quaternary ammonium salts is associated with the presence of two quaternary groups properly arranged in space, and that a third quaternary group may increase or decrease activity by possibly altering the relative position of any two quaternary functions to a more or less optimum configuration for adsorption to or displacement from the receptor site. The high activity of quaternaries containing one benzyl group and two smaller substituents on each nitrogen may result from ease of approach to an anionic receptor by the nitrogen face containing a small substituent and subsequent protection by the relatively large benzyl group against displacement of the adsorbed ion by another cation. The surprising activity of the bis tertiary amine salt III may be related to a high degree of ionization of both basic groups of this molecule at physiological *p*H values. A peculiar property of the free base of VII is its high solubility in cold water and insolubility in hot water. The tris amine may be in a hydrated and ionized state in cool solutions; heating could dehydrate the ion and yield undissociated tertiary amine of lower aqueous solubility. A hydrated, ionized form would be expected to resemble a quaternary salt in biological activity.

In addition to neuromuscular blockade, most of these compounds also elicited a transitory reduction of blood pressure in dogs.

EXPERIMENTAL

2,4,6-tris-(Diethylaminoethylamino)-1,3,5-triazine trihydrochloride (VII). A clear solution of 9.2 g. (0.05 mole) of cyanuric chloride in 50 ml. of dry toluene was added slowly, with stirring and cooling, to a solution of 25 g. (0.21 mole) of diethylaminoethylamine in 150 ml. of dry toluene. The mixture was refluxed for six hours and cooled; the white crystalline product was filtered off, washed with benzene, and dried at 80°.

2,4,6-tris-(Diethylaminoethylamino)-1,3,5-triazine tris-quaternary derivatives (VIII, IX, X). The trihydrochloride (VII) was dissolved in water, made strongly alkaline with sodium hydroxide, and extracted with ether. The ether extract was dried over sodium hydroxide pellets, filtered, and evaporated. The residue was taken up in ethanol, five molar equivalents of alkyl or other quaternizing halide were added, and the solution was refluxed for eight hours. The solution was concentrated if necessary, diluted with ether, and the precipitate filtered off. The compounds were dissolved in alcohol and re-precipitated with ether at least twice, then dried *in vacuo*, finally over P_2O_5.

2-Chloro-4,6-bis-(3-diethylaminopropylamino)-1,3,5-triazine salts (III, IV). A clear solution of 18.5 g. (0.1 mole) of cyanuric chloride in 150 ml. of dry toluene was cooled to 0° and to it was added slowly (1–2 hours) with stirring and cooling to 0–5°, a solution of 28.6 g. (0.22 mole) of diethylaminopropylamine in 100 ml. of propanol-2. The solution was stirred with cooling for an additional hour, then allowed to warm to room temperature. Precipitation of the product (III) was completed by addition of ether. The product was purified by dissolving it in alcohol and reprecipitating it by addition of ether. The salt was dried *in vacuo*, finally over P_2O_5.

The above dihydrochloride was converted to its free base as with VII. To 7.4 g. (0.02 mole) of base dissolved in 20 ml. of *tert*-butanol, was added 12.5 g. (0.08 mole) of ethyl iodide and the mixture was refluxed for 3 hours. The cooled reaction mixture was filtered, the solid was treated with hot propanol-1, cooled, filtered, and this filtrate was diluted with ether to precipitate the desired product. Precipitation from propanol-1 by addition of ether was repeated and the product (IV) was dried *in vacuo*.

2-Chloro-4,6-bis-(diethylaminoethylamino)-1,3,5-triazine salts (I, II). The free base was prepared as in the preceding procedure except that diethylaminoethylamine was used in place of diethylaminopropylamine. Aliquots of the base were treated in ethanol with four equivalents of methyl iodide and ethyl iodide, respectively, to yield I and II, which were precipitated with ether and dried.

2-Chloro-4,6-bis-(3-dipropylaminopropylamino)-1,3,5-triazine salts (V, VI). Cyanuric chloride and dipropylaminopropylamine were allowed to react according to the procedure used for the preparation of III, except that the ingredients, after mixing, were stirred for an additional two hours at room temperature. The dihydrochloride (V) was converted to the free base and refluxed in propanol-2 for six hours with *n*-propyl iodide to yield VI.

2,4,6-tris-(Triethylammoniumethoxy)-1,3,5-triazine triiodide (XI). To a solution of 47 g. (0.4 mole) of diethylaminoethanol in 250 ml. of dry toluene was added 9.6 g. (0.4 mole) of sodium hydride and the mixture was refluxed under nitrogen until the sodium hydride was all consumed (approximately 15 hours). To the cooled reaction mixture was added dropwise, with stirring, a solution of 18.4 g. (0.1 mole) of cyanuric chloride in 50 ml. of toluene. The mixture was refluxed for six hours, cooled, extracted four times with water in a separatory-funnel, and the resulting toluene solution was concentrated under reduced pressure to yield the viscous tris-base. The base was dissolved in 100 ml. of ethanol, 78 g. (0.5 mole) of ethyl iodide was added, and the solution was refluxed for three hours. The solution was concentrated and the residue was diluted with *tert*-butanol to precipitate the product. The precipitate was dissolved in hot propanol-1 and precipitated by addition of *tert*-butanol. The product was washed with ether and dried at 80° *in vacuo*.

2,4,6-tris-(3-Diethylaminopropanethio)-1,3,5-triazine salts (XII and XIII). To a cooled solution of 3.7 g. (0.02 mole) of cyanuric chloride in 75 ml. of *tert*-butanol was added, with cooling and stirring under nitrogen, a solution of 10.3 g. (0.07 mole) of diethylaminopro-

panethiol in 75 ml. of *tert*-butanol. The solution was refluxed for two hours then cooled to precipitate the product which was recrystallized twice again from *tert*-butanol. The product was washed with ether and dried at 80°, finally over P_2O_5, to yield XII.

The trihydrochloride XII was converted to the free base in the usual way. The base, together with five equivalents of benzyl chloride, was dissolved in propanol-2 and the solution was refluxed for four hours. The mixture was concentrated and diluted with ether. The solvent was decanted from the settled product which was reprecipitated twice more from a propanol-2 solution by the addition of ether. Drying of the product *in vacuo* over P_2O_5 gave XIII.

Biological tests. The mouse screening tests were carried out according to literature procedures (5).

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SUMMARY

Cyanuric chloride has been treated with dialkylaminoalkylamines to yield 2,4-bis- and 2,4,6-tris substituted dialkylaminoalkylamino-1,3,5-triazines. A tris-derivative of a dialkylaminoalkanol and of a thiol also were prepared. Quaternary salts of some of these show curarimimetic activity. Some structure-activity relationships are discussed.

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