Quaternary Ammonium Salts of 8-(Dialkylaminoalkoxy)-theobromines and -caffeines as Curariform Agents*

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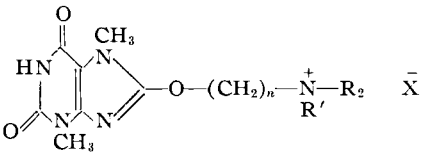
Three 8-(dialkylaminoalkoxy)-theobromine compounds were prepared by reacting the appropriate sodium dialkylamino alcoholate with 8-chlorotheobromine. Nine quaternary salts were prepared from the above three compounds by reacting each with methyl iodide, ethyl iodide, and benzyl chloride. The nine quaternary compounds along with nine corresponding caffeine quaternary compounds, previously reported, were tested for their curariform activity.

CONTEMPORARY STUDIES with synthetic curariform compounds began with Bovet's working from a model of (+)-tubocurarine (1). This was followed by the synthesis and testing of a large number of quaternary ammonium compounds. Choline derivatives were among these (2). Included among the curariform agents studied by Bovet was tris-(β-triethylammoniumethoxy)-1,2,3-benzene triiodide (Flaxedil), which was found to be most active (3). The present study was instituted with the view of preparing a group of compounds related to phenylcholine ethers and carrying out a very preliminary testing for possible curariform activity. Consequently a number of aminoalkyl ethers and their quaternary ammonium salts having the following general formula have been prepared from 8-chlorotheobromine.



The present syntheses represent an extension of the work with the corresponding derivatives of caffeine (4).

EXPERIMENTAL

8-Chlorotheobromine.—This was prepared according to Biltz and Beck (5). Fifty grams of theobromine, suspended in 500 ml. of dry chloroform was refluxed at room temperature while a stream of dried chlorine was bubbled through it for six hours. The 8-chlorotheobromine was separated from the reaction mixture and recrystallized from glacial acetic acid. Yield—98%, m. p. 297°.

8 - (Dialkylaminoalkoxy) - theobromines.—The sodium amino alkoxides were prepared in a 500-ml., three-necked flask fitted for refluxing by allowing 2.6 Gm. (0.12 mole) of sodium metal, cut into small pieces, to react with 0.18 mole of the appropriate alcohol (dimethylaminoethanol, diethylaminoethanol, or diethylaminopropanol) in 50 ml. of dry benzene. The mixture was warmed over a water bath to complete the reaction as indicated by the absence of sodium particles. 8-Chlorotheobromine (0.12 mole) was added and refluxing with stirring was continued for two hours, by which time the reaction was complete. The solution was filtered while hot. The filtrate was transferred to a separatory funnel, washed three times with 50-ml. portions of water, dried over anhydrous sodium sulfate, and refiltered. Benzene was then removed under reduced pressure. Another 50-ml. portion of benzene was added and subsequently removed as above. The damp material was dried in an oven at 60° and recrystallized from benzene solution. The melting points and analyses are shown in Table I.

Quaternary Salts of 8-(Dialkylaminoalkoxy)-theobromines.—The aminoalkyl ether (0.01 mole) was dissolved in 50 ml. of absolute ethanol, and 0.015 mole of methyl iodide, ethyl iodide, or benzyl chloride was added with thorough stirring. The solution was placed in a refrigerator until the quaternary salt crystallized out. The salt was filtered out while cold, redissolved in absolute ethanol, and precipitated with ether. This process was repeated for each salt until a constant melting point was obtained. The melting points, analyses, and yields of the quaternary salts are given in Table II.

Pharmacological Studies.—These studies were only preliminary in scope to determine whether or not the compounds exhibited sufficient curariform activity to justify a complete activity study. They were carried out by the method used primarily for testing the curariform activity. A modification of the screen-drop test described by Cavillito, *et al.* (6), and the head-drop test (7) were used to determine the relative potencies of the compounds. In the mouse screen-drop test, groups of twelve white mice were used at each dosage level. The ED_{50} was determined using the method of probit analysis described by Burn (8). The agents were administered intraperitoneally in 0.25 ml. of solution.

TABLE I.—8-(DIALKYLAMINOALKOXY)-THEOBROMINES

R	n	M. p.	Yield, %	—Nitrogen, %— Calcd.	Found
CH_3	2	149–150	26	26.2	26.1
CH_3CH_2	2	172–173	25	23.7	23.7
CH_3CH_2	3	161–162	23	22.6	22.6

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TABLE II.—QUATERNARY SALTS OF 8-(DIALKYLAMINOALKOXY)-THEOBROMINES

R	n	R′	X	Yield, %	M. p.	—Nitrogen, %— Calcd.	Found
CH_3	2	CH_3	I	23	87– 88	17.1	17.1
		CH_3CH_2	I	20	126–128	16.5	16.5
		$C_6H_5CH_2$	Cl	12	131–133	17.5	17.5
CH_3CH_2	2	CH_3	I	20	106–107	16.0	16.0
		CH_3CH_2	I	25	96– 98	15.5	15.5
		$C_6H_5CH_2$	Cl	10	111–112	16.6	16.6
CH_3CH_2	3	CH_3	I	25	56– 57	15.5	15.4
		CH_3CH_2	I	24	76– 78	15.0	15.1
		$C_6H_5CH_2$	Cl	13	102–103	16.1	16.1

In the head-drop tests, groups of two rabbits were used. The concentrations of the solutions were adjusted to give a head-drop within a volume of 1–2 ml. The list of the compounds tested along with the results are included in Table III. The series of quaternary salts previously synthesised by these authors (4) were included in these tests.

DISCUSSION

The same procedure was satisfactory for preparing the methiodides, ethiodides, and benzchlorides of the dialkylaminoalkoxy derivatives of theobromine, which was not true for preparing the corresponding caffeine-substituted quaternaries (4). As indicated in Table III, the relative activities of the compounds differ in the mouse and the rabbit which may be ascribed to species variation, as previously reported (9). The theory that more than one quaternary ammonium group is essential for curare-like activity, as in (+)-tubocurarine, does not hold here. The distance-activity relationship theory, which has been criticized by later investigators, proposes that the distance between onium heads has a direct relationship to the attainment of maximum activity. This theory is also without support in this study, since the compounds have only one onium head. No conclusion is drawn as to why only one theobromine derivative exhibited activity while seven caffeine derivatives were active.

The degree of activity exhibited by the compounds did not warrant further pharmacological investigations.

TABLE III.—PARALYZING DOSES IN THE PRELIMINARY MOUSE SLOPING-SCREEN AND RABBIT HEAD-DROP TESTS

R	n	R′	X	Mouse Tests, Dose, 50 mg./Kg.	Rabbit Tests, mg./Kg.
Theobromine Derivatives					
CH_3	2	CH_3	I	0[a]	0
		CH_3CH_2	I	0	0
		$C_6H_5CH_2$	Cl	0	0
CH_3CH_2	2	CH_3	I	0	0
		CH_3CH_2	I	0	0
		$C_6H_5CH_2$	Cl	0	0
CH_3CH_2	3	CH_3	I	72.5	17.4
		CH_3CH_2	I	0	0
		$C_6H_5CH_2$	Cl	0	0
Caffeine Derivatives					
CH_3	2	CH_3	I	168.3	50.9
		CH_3CH_2	I	37.6	10.8
		$C_6H_5CH_2$	Cl	57.3	5.6
CH_3CH_2	2	CH_3	I	38.1	12.8
		CH_3CH_2	I	39.3	15.4
		$C_6H_5CH_2$	Cl	124.6	42.1
CH_3CH_2	3	CH_3	I	38.2	13.3
		CH_3CH_2	I	0	0
		$C_6H_5CH_2$	Cl	0	0
Flaxedil		..	..	4.1	0.47

[a] Inactive.

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