Crystallization from ethyl alcohol gave 36 g., m.p. 166–167°.

The bromide IV was converted successively to V, VI and VIII by procedures that require no further description.[1]

The xanthoethyl derivative VII was also made by an unmodified procedure.[6]

(6) G. S. Skinner and J. B. Bicking, THIS JOURNAL, **72**, 1140 (1950).

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Alkylene Bis-(2-thenylquaternaryammonium) Salts[1]

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During the past few years, bis-quaternary-ammonium salts of a wide variety of types have been prepared and studied for curarimimetic and autonomic drug activity. Peak curarimimetic activity usually is associated with bis-quaternary salts in which ten carbon atoms or equivalent distance separates the quaternary nitrogen atoms and autonomic blockade is maximal in homologs with a five or six carbon atom separation. In the present series of compounds, 2-thenyl substituted quaternary salts of various size were prepared for comparison with one another and with some corresponding isosteric phenyl substituted analogs.

Muscle paralytic activity, as measured in mice according to published procedures,[3] followed the expected sequence. In the bis-thenyldimethylammonium series, activity increased in the following sequence with ED_{50} values of approximately 8 mg. per kg. for the C_6, 2 for C_9 and 1 for the C_{10} homologs; corresponding bis-benzyldimethylammonium derivatives were of the same order of activity as the thenyl analogs. In the C_{10} bis-thenylammonium series, activity decreased with degree of steric hindrance about the nitrogen atoms in the order: dimethyl (1 mg. per kg.), diethyl (2 mg. per kg.) and cyclohexamethylene (10 mg. per kg.). Tests for autonomic activity (in anesthetized dogs) revealed that all of the compounds markedly reduced blood pressure, but for only from five to thirty minutes after intravenous administration of 2 mg. per kg. Mechanism of action varied within the series.[4]

Experimental[5]

2-Thenylamines.—Tertiary 2-thenylamines were prepared by the Leuckart reaction from 2-thienylaldehyde[6] (0.1 mole), formic acid (0.25 mole) and appropriate secondary amine (0.2 mole). The procedure was similar to that of Smith and Macdonald[7]; refluxing was for ten hours or with volatile amines, heating was carried out in a pressure bomb. From dimethylamine, N,N-dimethyl-2-thenylamine[8] was obtained in better than 70% yield and its physical properties agreed with those published. Treatment with methyl iodide yielded a crystalline methiodide, m.p. 167–168°.

Anal. Calcd. for $C_8H_{14}INS$: C, 33.93; H, 4.98; I, 44.82. Found: C, 34.09; H, 5.09; I, 44.20.

N,N-Diethylthenylamine was prepared in similar manner in 65% yield; b.p. 40° at 1.5 mm., $n^{20}D$ 1.5095.

Anal. Calcd. for $C_9H_{15}NS$: N, 8.27. Found: N, 8.18.

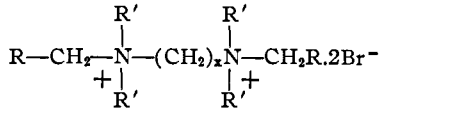
Methiodide, m.p. 156°. *Anal.* Calcd. for $C_{10}H_{18}INS$: C, 38.59; H, 5.79. Found: C, 38.64; H, 5.89.

From hexamethyleneimine there was obtained a 44% yield of N-(2-thenyl)-hexamethyleneimine, b.p., 72–73° at 1.5 mm., $n^{23}D$ 1.5375.

Anal. Calcd. for $C_{11}H_{17}NS$: N, 7.17. Found: N, 6.77.

TABLE I

α,ω-ALKYLENE BIS-QUATERNARYAMMONIUM SALTS



R	R′	x	M.p., °C. (cor.)	Reflux, hr.	Yield, %	Analyses, % Calcd. Carbon	Calcd. Hydrogen	Calcd. Bromine	Found Carbon	Found Hydrogen	Found Bromine
2-C_4H_3S	CH_3	3	219	23	60	42.15	5.83	33.33	42.42	5.98	32.75
2-C_4H_3S	CH_3	4	223	8	85	43.37	6.07	32.07	43.71	6.28	31.65
2-C_4H_3S	CH_3	5	111–114	8	75	44.53	5.70	31.19	44.65	6.26	30.65
2-C_4H_3S	CH_3	6	218–220	3[a]	70	S, 12.18		30.36	S, 11.75		29.90
2-C_4H_3S	CH_3	9	226	35	50	48.59	7.09	28.11	48.40	7.14	28.29
2-C_4H_3S	CH_3	10	200	7[a]	60	49.47	7.26	27.47	49.56	7.23	26.96
2-C_4H_3S	C_2H_5	10	176–180	50	40	52.65	7.87	25.03	52.85	8.04	24.45
2-C_4H_3S	Cyclo(—CH_2—)$_6$[b]	10	201–204	24	45	55.64	7.88	23.14	55.76	8.08	23.36
C_4H_5	CH_3	5	218–220	8	85	55.20	7.25	31.94	55.27	7.26	31.64
C_6H_5	CH_3	6	226	8	90	56.03	7.45	31.07	56.20	7.43	30.72
C_6H_5	CH_3	10	208	8	70	58.94	8.14	28.01	59.08	8.08	27.75

[a] 90 lb. pressure in bomb. [b] Hexamethyleneimonium derivative.

Reaction of Thenylamines with Alkylene Dibromides.—The bis-quaternaryammonium bromide salts were prepared by heating the reagents in *n*-propanol solution in the proportions: 0.05 mole of α,ω-alkylene dibromide, 0.15 mole of tertiary thenylamine, 50 ml. of propanol. Heating time, yields and analyses are summarized in Table I. The bis-quaternary salts were recrystallized from *n*-propanol.

Reaction of Benzyldimethylamine with Alkylene Dibromides.—Benzyldimethylamine (15 g. or 0.11 mole) was re-

(1) Contribution from the Department of Chemistry, James Millikin University, and from the Research Laboratories of Irwin, Neisler & Company.

(2) (a) Phillips Petroleum Co., Waco, Texas; (b) Irwin, Neisler & Company.

(3) C. J. Cavallito, A. E. Soria and J. O. Hoppe, THIS JOURNAL, **72**, 2661 (1950).

(4) Curarimimetic tests by Dr. T. B. O'Dell, autonomic activity measurements by Dr. F. J. Macri, of Irwin, Neisler & Company.

(5) Halogen analyses by Mr. C. F. Duewer of Irwin, Neisler & Company. Microanalyses by Clark Microanalytical Laboratory, Urbana, Illinois.

(6) W. J. King and F. F. Nord, *J. Org. Chem.*, **13**, 635 (1948).

(7) P. A. S. Smith and A. J. Macdonald, THIS JOURNAL, **72**, 1037 (1950).

(8) L. P. Kyrides, F. C. Meyer, F. B. Zienty, J. Harvey and L. W. Bannister, *ibid.*, **72**, 745 (1950).

TABLE I

REPLACEMENT OF AMINO GROUP BY HYDROGEN

Compound deaminated	Product: Structure	Product: B.p., °C.	Product: $n^{25}D$	Product: d^{25}_4	Yield, %: Using C_2H_5OH	Yield, %: Using H_3PO_2
3-H_2N-$C_6H_4CF_3$	$C_6H_5CF_3$	98–101			37	47.4
3-H_2N-4-Br-$C_6H_3CF_3$	4-Br-$C_6H_4CF_3$	154–155	1.4705	1.607	40	67
5-H_2N2-Br-$C_6H_3CF_3$	2-Br-$C_6H_4CF_3$	165–168			60	
3-H_2N-2,4-Br-$C_6H_2CF_3$ or 5-H_2N-2,4-Br-$C_6H_2CF_3$	2,4-Br-$C_6H_3CF_3$[a]	97–102.5[b]	1.5279	2.006		53
Unfractionated reaction mixture	.....[c]				49.3	65.7

[a] Calcd. for $C_7H_3Br_2F_3$: Br, 52.56. Found: Br, 52.51. [b] At 20.5 mm. [c] The products consisted of benzotrifluoride, *p*-bromo-, *o*-bromo- and 2,4-dibromobenzotrifluoride. They were obtained in 4.8, 21, 12 and 11.5% yield, respectively, using ethanol; in 12.5, 20, 22 and 11.2% yield using H_3PO_2.

fluxed for 8 hours in 100 ml. of *n*-propanol with 0.04 mole of alkylene dibromide. The solution was cooled, diluted with ethyl ether, the precipitate filtered off and recrystallized from hot *n*-propanol–benzene solution.

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The Formation and Deamination of Brominated *m*-Aminobenzotrifluorides[1]

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m-Bromobenzotrifluoride is a useful starting material for the synthesis of a number of compounds since it readily forms a Grignard reagent.[2] Although *m*-bromobenzotrifluoride can be made in a straightforward reaction from benzotrifluoride, the ortho and para isomers must be made indirectly. Jones[3] has prepared *p*-bromobenzotrifluoride in an over-all yield of about 40% from *p*-nitrotoluene; however, the process required the use of two bromination steps, a fluorination, a reduction and, finally, the replacement of the amino group by bromine. Jones was also able to prepare *o*-bromobenzotrifluoride, but again a lengthy procedure was used. Since the completion of this research, Benkeser and Severson[4] have described a two-step synthesis of *o*-bromobenzotrifluoride involving the metallation and subsequent bromination of benzotrifluoride with 28% yields.

Since *m*-aminobenzotrifluoride is commercially available, it seemed probable that it might serve as a starting point for a convenient synthesis of *o*- and *p*-bromobenzotrifluoride. This paper reports a study of the bromination of *m*-aminobenzotrifluoride and the deamination of the resulting aminobromo compounds to form various bromobenzotrifluorides.

m-Aminobenzotrifluoride was brominated under a variety of conditions. The best yields of monobromobenzotrifluorides resulted when the reaction was carried out at 5–10° in an excess of the amine when no catalyst was employed. Both 3-amino-4-bromo- and 5-amino-2-bromobenzotrifluoride were obtained under these conditions but no 3-amino-2-bromobenzotrifluoride was isolated during any experiments. When larger amounts of bromine were used, a compound believed to be 5-amino-2,4-dibromobenzotrifluoride was formed. When the brominations were conducted at 50° or when *m*-acetaminobenzotrifluoride served as the starting material, a considerable amount of unidentified high boiling material resulted.

The structure of the 3-amino-4-bromobenzotrifluoride was established by deamination to a bromobenzotrifluoride which, when hydrolyzed with sulfuric acid, was converted to *p*-bromobenzoic acid. The amine was also diazotized and treated with hydrobromic acid to give the known 3,4-dibromobenzotrifluoride. The 5-amino-2-bromobenzotrifluoride was diazotized and reduced to *o*-bromobenzotrifluoride thus establishing the position of the bromine as being adjacent to the trifluoromethyl group. Final confirmation resulted when the replacement of the amino group by chlorine gave the known 2-bromo-5-chlorobenzotrifluoride.[5]

The aminodibromobenzotrifluoride was deaminated and hydrolyzed to 2,4-dibromobenzoic acid indicating that its structure was either 3-amino-2,4-dibromo- or 5-amino-2,4-dibromobenzotrifluoride. Since no 3-amino-2-bromobenzotrifluoride was ever isolated, it seems likely that 5-amino-2,4-dibromobenzotrifluoride was formed.

Deaminations were carried out using either hypophosphorus acid or ethanol as the reducing agent. Better yields were obtained with hypophosphorus acid as indicated in Table I.

Experimental

The Bromination of *m*-Aminobenzotrifluoride.—The bromination of *m*-aminobenzotrifluoride and the corresponding acetamino compound were carried out under a variety of conditions. The latter compound was treated with bromine at 100° without catalyst and at 50° with a small amount of iron powder but most of the starting material was recovered. Essentially these same results have recently been reported.[6] The bromination of *m*-aminobenzotrifluoride at 10° without catalyst produced 21% conversions each of 3-amino-4-bromo- and 5-amino-2-bromobenzotrifluoride. At 5–10° using iron a 40% conversion to 3-amino-4-bromobenzotrifluoride was obtained but no other isomeric products were isolated; at 50°, a 31% yield was obtained with no other monobromo compound isolated.

A typical procedure follows. *m*-Aminobenzotrifluoride (1 mole) was added to 300 ml. of glacial acetic acid in a one-liter flask equipped with stirrer, addition funnel and thermometer. The contents were cooled to 10° and bromine (1 mole) added dropwise; about 2.5 hours were required for the addition. After another hour of stirring, 500 ml. of concentrated ammonia solution was added slowly and the

(1) Presented at the 118th Meeting of the American Chemical Society, Chicago, 1950.

(2) J. H. Simons and E. O. Ramler, THIS JOURNAL, **65**, 389 (1943).

(3) R. G. Jones, *ibid.*, **69**, 2346 (1947).

(4) R. A. Benkeser and R. G. Severson, *ibid.*, **73**, 1424 (1951).

(5) E. T. McBee, R. A. Sanford and P. J. Graham, *ibid.*, **72**, 1651 (1950).

(6) E. T. McBee, O. R. Pierce, R. D. Lowry and E. Rapkin, *ibid.*, **73**, 2022 (1951).