modified by substituting 2-bromothiophene for 2-chlorothiophene and propionic anhydride for acetic anhydride. 3-Azabicyclo[3.2.2.]nonane was supplied through the courtesy of Eastman Chemical Products, Inc. All other ketones in this study were commercially available.

The Mannich reaction was carried out as previously described (8), utilizing procedure B. A solid usually appeared within 30–90 minutes and acetone was added to complete precipitation. It was observed that some of these compounds were only slightly soluble in ethanol, especially the ones of more complex structure. In such cases a few drops of water were added to help facilitate solution in the recrystallization processes. In general, the reactions proceeded smoothly to yield the expected product. It may be noted, however, that excellent yields are seldom obtained in the Mannich reaction due to the complexity of the products obtained which may be occasioned by by-product formation. The furan derivatives consistently produced low yields.

REFERENCES

(1) Mannich, C., and Lammering, D., *Ber.*, **55**, 3510 (1922).
(2) Blicke, F. F., and Blake, E. S., *J. Am. Chem. Soc.*, **52**, 235(1930).
(3) Levvy, G. A., and Nisbet, H. B., *J. Chem. Soc.*, **1938**, 1053.
(4) Denton, J. J., Turner, R. J., Neier, W. B., Lawson, V. A., and Schedl, H. P., *J. Am. Chem. Soc.*, **71**, 2048, 2050, 2053, 2054 (1949); **72**, 3279, 3792(1950).
(5) Weijlard, J., *et al.*, *ibid.*, **78**, 2342(1956).
(6) Fry, E. M., and Everette, L. M., *J. Org. Chem.*, **24**, 116(1959).
(7) Burckhalter, J. H., and Johnson, S. H., *J. Am. Chem. Soc.*, **73**, 4835(1951).
(8) Nobles, W. L., *et al.*, This Journal, **43**, 641(1954); **43**, 644(1954); **44**, 273(1955); **44**, 717(1955); **47**, 77(1958).
(9) Mercier, F., *et al.*, *J. physiol. Paris*, **45**, 186(1953).
(10) Da Re, P., *et al.*, *J. Org. Chem.*, **25**, 1097(1960).
(11) Hayes, K., *Chem. Abstr.*, **48**, 12809(1954); U. S. pat. 2,663,710.
(12) Blicke, F. F., "Organic Reactions," Vol. 1, John Wiley & Sons, New York, N. Y., 1942, p. 303.
(13) Karbe, H., *Arch. Pharm.*, **283**, 48(1950).
(14) Reichert, B., "Die Mannich-Reaktion," Springer-Verlag, Germany, 1959.
(15) Hellmann, H., and Opitz, G., "α-Aminoalkylierung," Verlag Chemie, Weinheim, Germany, 1960.
(16) Fuson, R. C., *Chem. Revs.*, **16**, 1(1935).
(17) Wright, H. B., and Freifelder, M., *J. Am. Chem. Soc.*, **71**, 1513(1949).
(18) Dodgen, D., and Nobles, W. L., This Journal, **46**, 437(1957).
(19) Bruson, H. A., and MacMullen, C. W., *J. Am. Chem. Soc.*, **63**, 270(1941).
(20) Kosak, A. I., and Hartough, H. D., "Organic Synthesis," Coll. Vol. 3, John Wiley & Sons, Inc., New York, N. Y., 1955, p. 14.
(21) Hartough, H. D., and Conley, L. G., *J. Am. Chem. Soc.*, **69**, 3096(1947).

Sympathetic Nervous System Blocking Agents

Investigation of Ethyl-, Hydroxyethyl-, Vinyloxyethyl-, and Propargyl-benzyldimethylammonium Halides and Related Compounds

By JAMES H. SHORT and URSULA BIERMACHER

A series of quaternary benzylamine derivatives has been prepared. They were examined for their ability to block the sympathetic nervous system without also blocking the parasympathetic system. The most active compounds were derivatives of benzyl(vinyloxyethyl)dimethylammonium halide. The *o*-bromo analog has activity of the same order of magnitude as bretylium. Pharmacological results and structure-activity relationships are discussed.

THROUGH routine screening of compounds for cardiovascular effects, it was observed that benzyl(vinyloxyethyl)dimethylammonium bromide (Table I, No. 1) had a blocking effect on the sympathetic nervous system, but apparently had little or no effect on the parasympathetic system. It appeared, therefore, to have activity of the same type as bretylium, which has recently been investigated in the clinic as an antihypertensive agent (1).

Interest in this type of pharmacological activity led us to synthesize a series of quaternary salts in order to investigate structure-activity relationships. Some of these compounds were prepared by the reaction of a benzyl halide with a tertiary amine. For those desired compounds which were not accessible by this route, the alternative procedure, reaction of an N,N-dimethylbenzylamine with an alkyl halide was employed.

The required intermediate amines and halides were prepared by standard methods and are described in the experimental section.

PHARMACOLOGICAL RESULTS[1]

The effectiveness of these compounds as sympathetic blocking agents was determined in unanesthetized cats. The candidate drugs were administered orally, and the degree and duration of the prolapse of the nictitating membrane were the criteria used to determine whether or not the desired activity was present. Since parasympatho-

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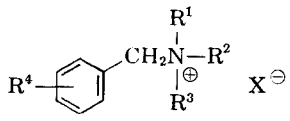
[1] The pharmacological activity of these compounds was investigated by Dr. John L. Schmidt, Mr. Charles Shannon, and Mr. Leo Wiemeler of the Division of Experimental Therapy, Abbott Laboratories. We are grateful to them for permission to use their data.

TABLE I.—QUATERNARY SALTS OF SUBSTITUTED BENZYLAMINES



No.	R^4	R^1	R^2	R^3	X	M.p., °C.	Method[a]	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	H	$CH_2CH_2OCH{=}CH_2$	CH_3	CH_3	Br	141–142	B[b]	$C_{13}H_{20}BrNO$	54.55	7.04	...	54.96	7.04	...
2	2-F	$CH_2CH_2OCH{=}CH_2$	CH_3	CH_3	Cl	149–149.5	B[b]	$C_{12}H_{19}ClFNO$	60.10	7.38	5.40	60.23	7.49	5.24
3	2-Cl	$CH_2CH_2OCH{=}CH_2$	CH_3	CH_3	I	128.5–129	[c]	$C_{13}H_{19}ClINO$	42.46	5.21	3.81	42.59	5.23	3.60
4	2-Br	$CH_2CH_2OCH{=}CH_2$	CH_3	CH_3	Br	117–118	B[d]	$C_{13}H_{19}Br_2NO$	42.76	5.25	3.84	43.01	5.07	3.61
5	2-CF_3	$CH_2CH_2OCH{=}CH_2$	CH_3	CH_3	Br	59.5–62	B	$C_{14}H_{19}BrF_3NO$[m]	...	...	3.95	...	...	3.78
6	2-Br	$CH_2CH_2OCH{=}CH_2$		 [e]	Br	105–106.5	B[f]	$C_{15}H_{23}Br_2NO$	47.43	5.72	3.45	47.52	5.62	3.39
7	H	C_2H_5	CH_3	CH_3	I	120–121	A[f]	$C_{11}H_{18}IN$	45.37	6.23	4.81	45.68	6.43	4.61
8	2-OCH_3	C_2H_5	CH_3	CH_3	I	108–109	A[f]	$C_{12}H_{20}INO$	44.87	6.27	4.36	44.88	6.43	4.22
9	2-Cl	C_2H_5	CH_3	CH_3	I	130.5–131.5	A[f]	$C_{11}H_{17}ClIN$	40.57	5.26	4.30	40.66	5.43	4.42
10	4-Cl	C_2H_5	CH_3	CH_3	I	160.5–161.5	A[f]	$C_{11}H_{17}ClIN$	40.57	5.26	4.30	40.70	5.10	4.21
11	2,4-Di-Cl	C_2H_5	CH_3	CH_3	I	166.5–167.5	A[f]	$C_{11}H_{16}Cl_2IN$	36.69	4.48	3.89	36.63	4.47	3.75
12	4-Br	C_2H_5	CH_3	CH_3	I	159.5–160.5	A[g]	$C_{11}H_{17}BrIN$	35.70	4.62	3.78	35.83	4.76	3.70
13	4-Cl	CH_3		 [l]	Cl	201.5–202	B[g]	$C_{12}H_{17}Cl_2NO$	54.98	6.53	5.34	54.75	6.24	5.16
14	2-Br	CH_2CH_2OH	C_2H_5	C_2H_5	Br	119.5–120.5	B[g]	$C_{13}H_{21}Br_2NO$	42.53	5.76	3.82	42.30	5.98	3.77
15	2-Br	C_2H_5	CH_2CH_2OH	CH_2CH_2OH	Br	110.5–112	B[g]	$C_{13}H_{21}Br_2NO_2$	40.75	5.53	3.65	40.45	5.56	3.70
16	2,4-Di-Cl	CH_3	CH_2CH_2OH	CH_2CH_2OH	Cl	113[h]	B[i]	$C_{12}H_{18}Cl_3NO_2$	45.81	5.77	4.45	45.68	5.68	4.43
17	2,4-Di-Cl	$CH_2CHOHCH_3$	CH_3	CH_3	Cl	90–92	B	$C_{12}H_{18}Cl_3NO$	48.27	6.07	4.69	48.05	6.26	4.49
18	4-Cl	CH_2CH_2OH	C_6H_{13}-*n*	C_6H_{13}-*n*	Cl	113.5–115	B	$C_{21}H_{37}Cl_2NO$	64.21	9.55	3.58	64.60	9.87	3.57
19	2-Cl	CH_2CH_2OH	CH_2CH_2OH	CH_2CH_2OH	Cl	134.5–136.5	B[g]	$C_{13}H_{21}Cl_2NO_3$	50.33	6.82	4.52	50.11	6.73	4.30
20	2-Cl	$CH_2CH_2CH_2OH$	C_2H_5	C_2H_5	Cl	144.5–145.5	B[i]	$C_{14}H_{23}Cl_2NO$	57.54	7.93	4.79	57.59	7.97	4.60
21	2-Cl	C_4H_9-*n*	CH_2CH_2OH	CH_2CH_2OH	Cl	103–106	B	$C_{15}H_{25}Cl_2NO_2$	55.91	7.82	4.34	55.71	7.50	4.45
22	H	$CH_2C{\equiv}CH$	CH_3	CH_3	Br	156–157	A[g]	$C_{12}H_{16}BrN$	56.71	6.34	5.50	56.63	6.53	5.54
23	3,4-Di-OCH_3	CH_3	$CH_2C{\equiv}CH$	$CH_2C{\equiv}CH$	Br	192.5–193.5	A[i]	$C_{16}H_{20}BrNO_2$	56.82	5.96	4.14	56.72	6.15	4.12
24	2-Br[k]	C_2H_5	CH_3	CH_3	I	119.5–120	A[f]	$C_{11}H_{17}BrIN$	35.69	4.63	3.78	35.94	4.69	3.60

[a] Method A is the reaction of a benzylamine with an alkyl halide; method B is the reaction of a benzyl halide with an alkylamine. [b] Recrystallized from methyl ethyl ketone containing a little methanol. [c] For method of preparation, see Experimental section. [d] Recrystallized from acetone. [e] NR^2R^3 = piperidino. [f] Recrystallized from methyl ethyl ketone. [g] Recrystallized from 2-propanol. [h] Melting point was not sharp. [i] Recrystallized from 2-propanol-ethyl ether. [j] Prepared by Miss Carol Christensen from N-methylveratrylamine and propargyl bromide, and recrystallized from ethanol-ether. [k] Bretylium iodide. [l] NR^2R^3 = morpholino. [m] Br: Calcd.: 22.57; Found: 22.56.

TABLE II.—MISCELLANEOUS COMPOUNDS

$$R^4\text{—}N^{\oplus}(R^1)(R^2)(R^3)\ X^{\ominus}$$

No.	R	R^2	R^3	R^4	X	M.p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
25	...	a	CH_3	CH_3	I	260–262[b]	$C_{11}H_{24}IN$	44.45	8.14	4.72	44.43	8.27	4.76
26	...	a	CH_3	$CH_2C_6H_5$	Br	171	$C_{17}H_{28}BrN$	62.57	8.65	4.29	62.41	8.39	4.30
27	1-Bromo-2-naphthylmethyl	CH_3	CH_3	C_2H_5	I	147.5–149	$C_{15}H_{19}BrIN$	42.89	4.55	3.33	42.61	4.83	3.34
28	2-Furylmethyl	CH_3	CH_3	C_2H_5	I	104–105[c]	$C_9H_{16}INO$	38.45	5.73	4.98	38.49	5.55	5.09
29	2-Furylmethyl	CH_3	CH_2	*o*-Bromobenzyl	Br	134–135.5	$C_{14}H_{17}Br_2NO$	44.82	4.57	3.73	44.80	4.76	3.63

[a] R^1R^2N = 2,2,4,6-tetramethylpiperidino. [b] Recrystallized from acetone. [c] Recorded m.p. is 103–104° (9).

lytic agents and ganglionic blocking agents alter the pupillary responses of the eye, normal responses were taken as indications that the parasympathetic nervous system was not also being blocked.

When the candidate drugs failed to cause a prolapse of the nictitating membrane at an initial low dose level, dosage was increased as high as 30 mg./Kg. Those substances which failed to show a response at such a high dose were classified as inactive. The active compounds are compared in Table III.

Several compounds related to bretylium, but bearing different substituents on the benzene ring, were examined. It was found that when the benzene ring carried a substituent in the *para* position (Table I, Nos. 10, 11, 12) the desired activity was not observed. However, when the bromine atom in the *ortho* position of the benzene ring was replaced by hydrogen, methoxy, or chloro (Nos. 7, 8, 9) these compounds were still active, but less so than bretylium (see Table III).

The compounds obtained by replacing the *o*-bromobenzyl moiety of bretylium with the 1-bromo-2-naphthylmethyl or 2-furylmethyl groups were inactive.

The quaternary salts prepared from various ethanol- and propanolamines were uniformly inactive (Table I, Nos. 14–21).

The most active group of compounds were those quaternary salts derived from (vinyloxyethyl)-dimethylamine (Table I, Nos. 1–5). Of this group, the *o*-bromo derivative (No. 4) was outstanding. It appears to be as potent as bretylium (No. 24), but with longer duration of activity. It is interesting to note that when the dimethylamino group of No. 4 is replaced by the piperidine group (No. 6), activity is lost.

The analogs of Nos. 4 and 24 containing no substituent on the benzene ring (Nos. 1 and 7) have comparable activity, as do the *o*-chloro analogs (Nos. 3 and 9).

Acute toxicity studies were carried out only with Nos. 1, 4, and 24. They were administered orally to mice, and all three failed to cause death at doses of 500 mg./Kg.

The activity shown by 1,1,2,2,4,6-hexamethylpiperidinium iodide (Table II, No. 25) appears to be due to ganglionic blockade rather than the desired activity.

EXPERIMENTAL[2]

***o*-Bromobenzyl Bromide.**—The procedure of DeTar and Carpino (2) was modified by running the reaction at 150° in the absence of benzoyl peroxide for 3 hours. The colorless oil boiled at 129–130° (15 mm.), n_D^{21} 1.6195.

1-Bromo-2-bromomethylnaphthalene.—A mixture of 53 Gm. (0.3 mole) of N-bromosuccinimide and 66.3 Gm. (0.3 mole) of 1-bromo-2-methylnaphthalene (Aldrich Chemical Co.) in 700 ml. of carbon tetrachloride was illuminated from below by a 150-watt light bulb. The light and flask were enclosed in a metal shield and the reaction was illuminated and stirred for 2 hours. The heat from the light bulb was sufficient to cause the carbon tetrachloride to reflux. The hot mixture was filtered, after which the product precipitated from the filtrate. The

[2] Microanalyses are due to Mr. Elmer F. Shelberg and staff of the Abbott Microanalytical Laboratory.

TABLE III.—COMPARATIVE PHARMACOLOGICAL ACTIVITIES

No.[a]	Relative Activity[b]	No.	Relative Activity
4	3.0	7	1.0
24[c]	2.5	1	1.0
3	2.25	5	1.0
9	2.0	25	0.5
2	1.5	8	0.1

[a] The numbers refer to the compounds in Tables I and II. [b] Activity is rated on a 0–3 scale, in which 3.0 is assigned as the relative activity of our most active compound. In arriving at these relative values, the dose and duration of effect have been given more weight than the actual degree of prolapse. The figures in this table represent approximate values, and are not to be considered definitive. [c] Bretylium iodide.

material was recrystallized once from Skelly B and weighed 63 Gm. (70%), m.p. 107.5–109°. The recorded m.p. is 107–108° (3).

o-Trifluoromethylbenzyl Alcohol.—Reduction of 36 Gm. (0.19 mole) of *o*-trifluoromethylbenzoic acid (4) with lithium aluminum hydride was accomplished in diethyl ether. The yield was 20.5 Gm. (61.4%) of material boiling at 124–126° (57 mm.), n_D^{25} 1.4661.

Anal.—Calcd. for $C_8H_7F_3O$: C, 54.56; H, 4.00. Found: C, 54.08; H, 3.88.

o-Trifluoromethylbenzyl Bromide.—A solution of 20.5 Gm. (0.12 mole) of *o*-trifluoromethylbenzyl alcohol and 4 ml. of pyridine was added, with stirring, dropwise over a period of 3 hours to 12.6 Gm. of phosphorus tribromide at −5 to −10°. After addition was complete, the reaction mixture was slowly allowed to come to room temperature overnight. It was poured onto ice. The white solid which formed was collected and washed well with ice water. On warming to room temperature the solid liquified; it was then distilled at 116–118° (60 mm.), n_D^{25} 1.4967. The yield was 21.5 Gm. (77.5%).

Anal.—Calcd. for $C_8H_6BrF_3$: C, 40.20; H, 2.53. Found: C, 40.11; H, 2.41.

Preparation of Substituted N,N-Dimethylbenzylamines.—The compounds listed below were prepared from dimethylamine and the appropriate benzyl halide according to the procedure of Eliel, Ferdinand, and Herrmann (5): 4-chloro-N,N-dimethylbenzylamine (5), b.p. 104–106° (19 mm.), n_D^{25} 1.5172; 2,4-dichloro-N,N-dimethylbenzylamine (5), b.p. 127–129° (20 mm.), n_D^{25} 1.5370; 2-chloro-N,N-dimethylbenzylamine (6), b.p. 103° (19 mm.), n_D^{25} 1.5212; 2-bromo-N,N-dimethylbenzylamine (7), b.p. 112–113° (17 mm.), n_D^{25} 1.5445; 4-bromo-N,N-dimethylbenzylamine (8), b.p. 98–102° (8 mm.), n_D^{26} 1.5401.

1-Bromo-2-dimethylaminomethylnaphthalene.—It was prepared from 1-bromo-2-bromomethylnaphthalene in the manner described above, b.p. 195–200° (2.5 mm.), n_D^{26} 1.6202.

Anal.—Calcd. for $C_{13}H_{14}BrN$: C, 59.10; H, 5.34; N, 5.30. Found: C, 59.04; H, 5.42; N, 5.15.

N,N-Dimethylfurfurylamine.—This compound was prepared by the Leuckart reaction as previously described (9), b.p. 142–144°, n_D^{25} 1.4592.

N,N-Dimethyl-*o*-methoxybenzylamine (10)—This compound was prepared from *o*-methoxy-N-methylbenzylamine[3] by methylation with formaldehyde and formic acid (11), b.p. 99–101° (10 mm.), n_D^{25} 1.5147.

1,2,2,4,6-Pentamethylpiperidine.—Methylation of 28 Gm. (0.2 mole) of 2,2,4,6-tetramethylpiperidine (Shell Development Co., Emeryville, Calif.) was accomplished with formaldehyde and formic acid (11). The yield of colorless liquid was 20.3 Gm. (65.5%), b.p. 60–61° (12 mm.), n_D^{25} 1.4508.

Anal.—Calcd. for $C_{10}H_{21}N$: C, 77.35; H, 13.63. Found: C, 77.29; H, 14.06.

A sulfate salt was prepared and recrystallized from a mixture of acetone and 2-propanol. It melted at 147–149°.

Anal.—Calcd. for $C_{10}H_{21}N \cdot H_2SO_4$: C, 47.41; H, 9.15; N, 5.53. Found: C, 47.54; H, 8.59; N, 5.52.

Preparation of the Quaternary Salts.—A solution of 0.1 mole of the amine and 0.1 mole of the halide[4] in 50 to 100 ml. of methyl ethyl ketone was allowed to stand at room temperature. The product precipitated after a few hours to several days. The less reactive combinations could be obtained more quickly by refluxing the reaction mixture. If the product precipitated as an oil, it was scratched and chilled until a solid formed. To purify the compounds, they were recrystallized from a suitable solvent such as acetone, methyl ethyl ketone, methanol, ethanol, or 2-propanol. These substances are described in Tables I and II.

(*o*-Chlorobenzyl)(vinyloxyethyl)dimethylammonium Iodide (Table I, No. 3).—A solution of 5.8 Gm. (0.05 mole) of (vinyloxyethyl)dimethylamine (Peninsular Chemresearch, Inc.) and 16 Gm. (0.1 mole) of *o*-chlorobenzyl chloride in 50 ml. of acetone was allowed to stand at room temperature for 3 days and then refluxed for 6 hours. To the solution was added a solution of 15 Gm. (0.1 mole) of sodium iodide in 100 ml. of acetone. After standing overnight at room temperature, the sodium chloride was collected, and the filtrate was concentrated and chilled to obtain 8.8 Gm. (48%) of white solid, m.p. 127–128.5°. One recrystallization from ethanol-acetone raised the melting point to 128.5–129°.

REFERENCES

(1) Boura, A. L. A., *et al.*, *Lancet*, **1959**, 17.
(2) DeTar, D. F., and Carpino, L. A., *J. Am. Chem. Soc.*, **78**, 477(1956).
(3) Bergmann, E. D., and Szmuszkovicz, J., *ibid.*, **73**, 5154(1951).
(4) Jones, R. G., *ibid.*, **69**, 2349(1947).
(5) Eliel, E. L., Ferdinand, T. N., and Herrmann, M. C., *J. Org. Chem.*, **19**, 1693(1954).
(6) v. Braun, J., Kühn, M., and Weismantel, J., *Ann.*, **449**, 275(1926).
(7) Thomson, T., and Stevens, T. S., *J. Chem. Soc.*, **135**, 63(1932).
(8) Dewhirst, K. C., and Cram, D. J., *J. Am. Chem. Soc.*, **80**, 3124(1958).
(9) Weilmuenster, E. A., and Jordan, C. N., *ibid.*, **67**, 416(1945); Moore, M. L., in Adams, R., "Organic Reactions," Vol. 5, John Wiley & Sons, Inc., New York, N. Y., 1949, p. 319.
(10) Stedman, E., *J. Chem. Soc.*, **130**, 1904(1927).
(11) Icke, R. N., Wisegarver, B. B., and Alles, G. A., in Horning, E. C., "Organic Syntheses," Coll. Vol. 3, John Wiley & Sons, Inc., New York, N. Y., 1955, p. 723.

[3] Prepared in this laboratory by Dr. W. B. Martin.
[4] If the halide was available in large quantities, such as methyl iodide and ethyl iodide, a two- to fourfold excess was used.