taken to dryness under vacuum on a steam bath. The residue was crystallized from ethanol to give 6.7 g. (62.5%) of 3-methyl-5-ethyl-6-phenyl-*meta*-thiazane-2,4-dione, m.p. 99–100°.

Anal. Calcd. for $C_{13}H_{15}NO_2S$: C, 62.62; H, 6.07; N, 5.62. Found: C, 63.33; H, 6.33; N, 5.28.

Action of Hydrogen Peroxide on the Dione.—A mixture of 10.0 g. (0.043 mole) of the dione, 100 ml. of glacial acetic acid and 15 ml. of 30% hydrogen peroxide was stirred for 19 hr. at room temperature. All of the solvents were then removed under vacuum while heating on a steam bath. A glassy residue was obtained which when refluxed with chloroform gave a white solid. The chloroform solution was cooled and filtered to give 9.6 g. (88% yield) of 2-ethyl-3-phenyl-3-sulfopropionamide monohydrate. The product was very soluble in water forming strongly acidic solutions. A portion was crystallized from ethanol and chloroform to give an analytically pure sample, m.p. 201–203°.

Anal. Calcd. for $C_{11}H_{17}NO_5S$: C, 47.98; H, 6.22; N, 5.09; S, 11.64. Found: C, 48.08; H, 5.79; N, 5.06; S, 11.44.

Acetylenic Amines. III. The Haloethynyl Derivatives

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The preparation of some haloethynyl analogs of acetylenic amines and their pharmacological evaluation in hypertensive rats is reported. The bromo analogs are more potent than the corresponding chloro compounds. The most potent compound in this series is 3-*t*-butylamino-3-methyl-1-bromo-1-butyne hydrochloride, and this material is about as potent as the nonhalogenated analog (XVI).

The availability of a large number of acetylenic amines by the Hennion synthesis[1,2,3] and the antihypertensive activity[4] of some of these amines prompted us to prepare the haloethynyl derivatives of selected members of these series.

Since the reaction of the aminoacetylenes with N-bromosuccinimide (used to prepare 1-bromo-3-*t*-butylamino-3-methyl-1-butyne) proved

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to be of limited applicability, the more general method of treating the sodium salt of the acetylene with the appropriate *p*-toluenesulfonyl halide[5] was used to obtain the other haloethynyl derivatives. In the preparation of the haloethynyl derivative of the N-β-hydroxyethyl compound, it was necessary to protect the hydroxyl group by conversion to the tetrahydropyranyl derivative.

The compounds were tested in renal hypertensive rats prepared by the procedure described by Kempf and Page.[6] Systolic blood pressure was determined by the microphonic manometric method of Friedman and Freed.[7] Following the control blood pressure determination the compounds were administered by mouth to groups of three rats. Blood pressure readings were recorded hourly for 7 hr. The results are reported in the table as the average percentage change in blood pressure from control over the 7 hr. observation period. Each figure represents the mean change in blood pressure for three animals.

In general, the bromo derivatives were more potent hypotensive agents than the corresponding chloro compounds. For example, X was more potent than V. The *t*-butyl group on the nitrogen appears to promote activity, and methyl groups for the R^1, R^2 seem to be most advantageous.

Compound IV is of interest since it appears to show a hypertensive effect.

Experimental[8]

3-(*t*-Butylamino)-1-chloro-3-methyl-1-butyne Hydrochloride (I).—A suspension of sodamide was prepared by adding 2.5 g. (0.11 g.-at.) of sodium to about 300 ml. of liquid ammonia (to which a small amount of ferric nitrate had been added). One-tenth of a mole, 13.9 g., of 3-(*t*-Butylamino)-3-methyl-1-butyne was added dropwise and the solution was stirred for 1 hr. Dry ether (250 ml.) was added, and the mixture was warmed to drive out the ammonia and then heated under reflux for 1 hr. A solution of 20 g. (0.105 mole) of *p*-toluenesulfonyl chloride in 150 ml. of dry ether was then added over a 5 min. period. The mixture was stirred and refluxed for 2 hr., then allowed to stand overnight. After cautiously adding 200 ml. of water, the ether layer was separated, dried with potassium carbonate and concentrated under reduced pressure. The concentrate was distilled to yield 9.5 g. of crude product, b.p. 45–50° (9 mm.). It was redistilled to give 7.0 g. of an oil, b.p. 55° (10 mm.), n_D^{25} 1.4510. The hydrochloride salt was prepared by adding excess ethanolic hydrogen chloride to an

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(8) The melting points were determined with a Fisher–Johns assembly and are reported as read.

TABLE I

AMINO ACETYLENIC HALIDE HYDROCHLORIDES

$R^1R^2C(NR^3R^4)C{\equiv}CX \cdot HCl$

Compound	R^1	R^2	R^3	R^4	X	M.p. °C.	Yield, %	Antihypertensive activity Blood pressure change[a]/dose, mg./kg.
I	CH_3	CH_3	t-C_4H_9	H	Cl	158–159	29	8.6/40
II	CH_3	CH_3	t-C_5H_{11}	H	Cl	123–124	23	0/20
III	CH_3	i-C_3H_7	i-C_3H_7	H	Cl	174–176	33	0/20
IV	CH_3	n-C_4H_9	t-C_4H_9	H	Cl	122–124	11	+8.8/20
V	CH_3	CH_3	t-C_4H_9	CH_3	Cl	138–139	13	+3/20
VI	—$(CH_2)_5$—		C_2H_5	H	Cl	210–212	16	5/20
VII	—$(CH_2)_5$—		t-C_4H_9	H	Cl	208–210	40	3/20
VIII	CH_3	CH_3	CH_2CH_2OH	C_2H_5	Cl	102–105	27	0/20
IX	CH_3	CH_3	t-C_4H_9	H	Br	182–183	11	14/20
X	CH_3	CH_3	t-C_4H_9	CH_3	Br	208–210	33	8.4/20
XI	CH_3	CH_3	i-C_3H_7	H	Br	219–220	33	0/20
XII	i-C_3H_7	i-C_3H_7	H	H	Br	225	12	0/20
XIII	CH_3	CH_3	CH_3	C_2H_5	Br	196–197	49	4/20
XIV	—$(CH_2)_6$—		C_2H_5	H	Br	248	16	5/20
XV	—$(CH_2)_5$—		t-C_4H_9	H	Br	241–242	52	7.7/20
XVI[c]	CH_3	CH_3	t-C_4H_9	H	H			12.6/20

Compound	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found
I	$C_9H_{17}Cl_2N$	51.43	51.93	8.16	8.14	6.67	6.41	—	—
II	$C_{10}H_{19}Cl_2N$	—	—	—	—	6.25	5.97	31.63	31.63
III	$C_{10}H_{19}Cl_2N$	—	—	—	—	6.25	5.99	31.63	31.39
IV	$C_{12}H_{23}Cl_2N$	—	—	—	—	5.55	5.45	28.11	28.31
V	$C_{10}H_{19}Cl_2N$	—	—	—	—	6.25	6.20	31.63	31.82
VI	$C_{9}H_{17}Cl_2N$	—	—	—	—	6.31	6.20	15.96	16.22[b]
VII	$C_{12}H_{21}Cl_2N$	—	—	—	—	5.60	5.80	28.34	28.19
VIII	$C_9H_{17}Cl_2NO$	—	—	—	—	6.20	6.06	31.36	30.91
IX	$C_9H_{17}BrClN$	42.45	42.38	6.73	6.74	—	—	—	—
X	$C_{10}H_{19}BrClN$	44.70	44.78	7.13	7.10	5.22	5.28	—	—
XI	$C_8H_{15}BrClN$	39.94	39.97	6.28	6.50	5.82	5.54	—	—
XII	$C_9H_{17}BrClN$	42.45	42.60	6.73	6.62	5.50	5.62	—	—
XIII	$C_8H_{15}BrClN$	39.94	40.62	6.28	6.15	5.82	5.53	—	—
XIV	$C_{10}H_{17}BrClN$	45.04	45.56	6.43	6.61	5.25	5.10	—	—
XV	$C_{12}H_{21}BrClN$	48.91	49.06	7.18	7.32	4.75	4.81	—	—
XVI[c]									

[a] The numerator is the average percentage drop over the seven-hour period. A plus indicates a rise in pressure. [b] Ionic chlorine only. [c] See reference (1).

ether solution containing 4.0 g. of the base. The salt was collected and recrystallized from ethyl acetate; yield 3.5 g.

3-(2-Hydroxydiethylamino)-3-methyl-1-butyne.—A solution of 30 g. (0.27 mole) of 3-ethylamino-3-methyl-1-butyne, 15 g. (0.34 mole) of ethylene oxide, aud 500 ml. of ethanol was stirred at room temperature for 14 hr. and then refluxed for 2 hr. After cooling, alcoholic hydrogen chloride (10%) was added until the mixture was acidic to litmus, and then all solvents were removed at reduced pressure. The residue was dissolved in water, made basic to litmus with 50%

sodium hydroxide solution and extracted with ether. The ether solution was separated, dried, and distilled. The residue was distilled at 89–90° (10 mm.) giving 9.5 g. of colorless oil, n_D^{25} 1.4529. The hydrochloride was prepared and after crystallizing from ethyl acetate melted at 124–126°.

Anal. Calcd. for $C_9H_{18}ClNO$: C, 56.38; H, 9.46; N, 7.31; Cl, 18.50. Found: C, 56.23; H, 9.43; N, 7.27; Cl, 19.15.

3-Methyl-3-[2-(2-tetrahydropyranoxy)-diethylamino]-1-butyne.—To a solution of 38.1 g. (0.2 mole) of 3-(2-hydroxydiethylamino)-3-methyl-1-butyne hydrochloride in 100 ml. of chloroform was added 40 ml. of dihydropyran and five drops of sulfuric acid. After stirring for 4 hr., 100 ml. of 20% sodium hydroxide solution was added. The chloroform layer was separated, dried with anhydrous potassium carbonate and concentrated on a steam bath. The residue was distilled, collecting 44.2 g. (92% yield) of product, b.p. 82° (1 mm.), n_D^{25} 1.4652.

Anal. Calcd. for $C_{14}H_{25}NO_2$: N, 5.85. Found: N, 5.76.

1-Chloro-3-(2-hydroxydiethylamino)-3-methyl-1-butyne Hydrochloride (VIII).—A suspension of sodamide in *ca.* 400 ml. of liquid ammonia was prepared from 4.4 g. (0.19 g.-at.) of sodium; 3-methyl-3-[2-(2-tetrahydropyranoxy)-diethylamino]-1-butyne (44 g., 0.18 mole) was added dropwise, and the solution was stirred for 2 hr., then diluted with 200 ml. of dry ether, and refluxed for 3 hr. The solution then was cooled to −10° in a dry nitrogen atmosphere, and a solution of 40 g. (0.2 mole) of *p*-toluenesulfonyl chloride in 300 ml. of dry ether was added dropwise, holding the temperature below 10°. The reaction mixture was then refluxed for 30 min. After standing overnight, 200 ml. of water was added. The ether layer was separated and shaken with 200 ml. of 1 *N* HCl. The acid solution was stirred at room temperature for 30 min., then made strongly basic with 50% sodium hydroxide solution and extracted with two 50 ml. portions of ether. The ether was dried with anhydrous potassium carbonate and concentrated under reduced pressure. The concentrate was distilled, collecting 12.3 g. of product, of b.p. 73–75° (1 mm.), n_D^{25} 1.4793–1.4800. The hydrochloride salt was prepared in ethyl acetate in a yield of 11.0 g.

3-*t*-Butylamino-3-methyl-1-bromo-1-butyne.—A mixture of 27.8 g. (0.2 mole) of 3-*t*-butylamino-3-methyl-1-butyne, 35.8 g. (0.2 mole) of N-bromosuccinimide and 250 ml. of carbon tetrachloride was refluxed overnight. The reaction mixture then was filtered and the filtrate concentrated at reduced pressure. The residue was distilled yielding 5 g. of product boiling at 70–80° (10 mm.) The solid distillate after recrystallizing from low boiling petroleum ether melted at 41–42°.

Anal. Calcd. for $C_9H_{16}BrN$: C, 49.55; H, 7.39. Found: C, 49.74; H, 7.66.

1-Bromoethynyl-1-(*t*-butylamino)-cyclohexane Hydrochloride (XV).—To a suspension of sodamide prepared from 2.5 g. (0.11 g.-at.) of sodium in 100 ml. of liquid ammonia there was added 18.0 g. (0.1 mole) of 1-(*t*-butylamino)-1-ethynylcyclohexane. After stirring for 1 hr., 200 ml. of dry ether was added, and the solution was refluxed for 2 hr. A solution of 24 g. (0.1 mole) of *p*-toluenesulfonyl bromide in 200 ml. of dry ether was added in a 5 min. period. After the mixture was refluxed for 1 hr., it was allowed to stand overnight. After adding 200 ml. of water, the ether layer was separated and shaken with 200 ml. of 1 *N* HCl. The solid which crystallized from solution was collected and dried, yielding 19.5 g. of crude hydrochloride, m.p. 232–234°. Recrystallization from isopropyl alcohol gave 15.4 g.

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Synthesis and Hypotensive Activity of Unsymmetrically Substituted Acetylenic Bis-Quaternary Ammonium Compounds and Certain of Their Reduction Products[1]

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A series of acetylenic bis-quaternary compounds derived from quinoline has been prepared as a part of a structure-activity study of steric requirements for ganglionic blockade. Certain of the products have been reduced stereospecifically to the *cis*- and *trans*-olefins, and further to alkanes. Biological studies have shown several of the compounds to possess marked hypotensive effects.

The synthesis by Biel and DiPierro[3] and the biological evaluation by Buckley and co-workers[4] of a series of potent ganglionic blocking agents possessing an acetylenic group between two quaternary nitrogen atoms stimulated a continued study by us, with the aim of investigating steric requirements of the two quaternary nitrogens for maximum ganglionic blockade. Gill[5,6] stated that the blocking action of bis-quaternary ammonium alkanes depends on the length of the

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