Brown, H. T. Hunter, G. M. Maciak, A. C. Brown, and D. Cline. The physical measurements were made by D. O. Woolf, Jr., and L. G. Howard. Many of the starting materials were prepared by Mr. L. A. White.

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

(1) Presented to the Division of Medicinal Chemistry of the American Chemical Society, Chicago, Illinois, September 3–8, 1961. Abstracted in part from a thesis submitted by John L. Neumeyer in partial fulfillment of the requirements for the degree of Doctor of Philosophy, University of Wisconsin, 1961.

(2) To whom correspondence should be addressed.

(3) J. H. Biel and F. DiPierro, *J. Am. Chem. Soc.*, **80**, 4609 (1958).

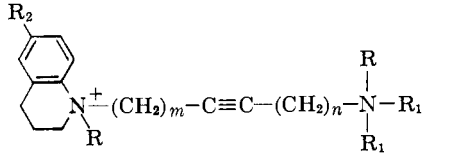
(4) F. M. Schalit, J. P. Buckley, W. J. Hudak, J. J. DeFeo, and E. C. Reif, *J. Am. Pharm. Assoc.*, **46**, 598 (1957); R. K. Bickerton, M. L. Jacquart, W. J. Kinnard, Jr., A. Bianculli, and J. P. Buckley, *ibid.*, **49**, 183 (1960).

(5) E. W. Gill, *Proc. Roy. Soc.* (London), **B150**, 381 (1959).

(6) E. W. Gill and H. R. Ing, *Il Farmaco*, **13**, 244 (1958).

chain linking the two cationic heads and he concluded that these compounds combine with the acetylcholine receptor and with an "anchoring site," the latter attachment preventing the depolarization which normally results from the combination of the acetylcholine receptor with a trimethylammonium group. Interquaternary distance/probability distributions were calculated by Gill for a series of polymethylene bis-quaternary compounds, maximum blocking activity being obtained when a distance of 6 to 7.8Å. separated the two cationic centers. One may conclude that optimum ganglionic blocking activity involves the coincidence of a narrow band of interreceptor distances with a small range of interionic distances in one of the favored configurations of the blocking molecule. This attractive theory is complicated by the fact that polymethylene chains are flexible and consequently interquaternary distance cannot be precisely defined. It was the purpose of our research to limit the degrees of rotational freedom of the polymethylene chain by introduction of an acetylenic bond, thus forcing the quaternary nitrogens to orient themselves in a more extended form. In this way it was hoped to achieve optimum "fit" on the receptor surface, producing a minimum of strain in the compound in question. By restriction of the internitrogen distance to closer tolerance, it was hoped that a more prolonged biological activity would be obtained. Structural requirements of the receptor sites of the sympathetic and the parasympathetic ganglia differ[7,8]; thus according to the two point attachment hypothesis, a more rigid molecule should produce activity of greater specificity. For comparison, certain acetylenic compounds were reduced to *cis* and *trans* olefins, and to completely saturated chains.

Cavallito and his co-workers[9] prepared numerous bis-quaternary ammonium compounds and concluded that optimum activity requires that one of the nitrogens should form a part of a small cationic group (the acetylcholine receptor site) and the second nitrogen should be a part of a bulky group (the "anchoring" site). On this basis we have prepared members of the series of compounds indicated:



m = 1-2
n = 1-3
R = CH_3
R^1 = CH_3 or C_2H_5
R^2 = H or OCH_3

(7) L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," The Macmillan Co., New York, N. Y., 1956, p. 618.

(8) U. Trendelenburg, *Ann. Rev. Pharmacol.*, **1**, 219 (1961).

(9) C. J. Cavallito in "Curare and Curare-like Agents," D. Bovet, F. Bovet-Nitti, and G. B. Marini-Bettolo, Editors, Elsevier Publishing Co., Amsterdam, 1959, p. 289.

TABLE

ACETYLENIC DIAMINES AND DERIVATIVES

No.	Am$_1$	m	n	Am$_2$	B.p. or m.p., °C.	mm.	n^{25}D	Yield, %	Method
1	$(C_2H_5)_2N$—	1	1	$(C_2H_5)_2N$—	120	14	1.4558	31, B	58, A
	Dihydrochloride				205–206[a]				
	Dimethiodide				203.5–205.5[a,b]				
2	THQ[c]	1	1	$(CH_3)_2N$—	108–110	0.01	1.5616	49	A
	Dihydrochloride				168–169[a]				
3	THQ[c]	1	2	$(C_2H_5)_2N$—	122–130	0.01	1.5472	35	C
	Dihydrochloride				198.5–199[d]				
	Dimethobromide				155–156[a,b]				
4	THQ[c]	1	2	$(CH_3)_2N$—	124–126	0.02	1.5605	52	C
	Dimethobromide				164–165.8[a,b,e]				
5	THQ[c]	1	3	$(CH_3)_2N$—	137–138	0.02	1.5499	40	D
	Dimethobromide				150–151[a,b]				
6	8-MethoxyTHQ[c]	1	1	$(CH_3)_2N$—	118–120	0.005	1.5552	75	A
	Dihydrochloride				160–163[f]				
7	8-MethoxyTHQ[c]	1	2	$(CH_3)_2N$—	116–126	0.02	1.5526	32	C
8	8-MethoxyTHQ[c]	1	3	$(CH_3)_2N$—	122–132	0.01	1.5455	35	D
9	6-MethoxyTHQ[c]	1	1	$(CH_3)_2N$—	142–144	0.03	1.5620	82	A
	Dihydrochloride				166–167[g]				
	Dimethobromide				160–162[a,b,h]				
10	6-MethoxyTHQ[c]	1	2	$(CH_3)_2N$—	126–134	0.005	1.5568	35	C
	Dimethobromide				179.5–180.5[a,b]				
11	6-MethoxyTHQ[c]	1	3	$(CH_3)_2N$—	122–128	0.005	1.5492	38	D
12		2	1	$(CH_3)_2N$—	27–28		..	38	A
	Dimethobromide				209–209.4[a,i]				

[a] Recrystallized from isopropyl alcohol. [b] Melts with decomposition. [c] 1,2,3,4-tetrahydro- from 1-butanol-ether. [g] Recrystallized from 1-butanol. [h] For monohydrate. [i] Recrystal-

In addition, one compound was prepared in which the acetylenic chain was attached to the 2-position of an N-methylquinolinium unit.

Acetylenic diamines of the 8-methoxy-1,2,3,4-tetrahydroquinoline series could not be converted to their bis-quaternary salts.

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Experimental[10]

Method A. 1,4-Diamino-2-butynes were prepared by a modification of a

(10) All melting points are uncorrected and were obtained in a Hershberg-type, silicone filled melting point apparatus equipped with Anschütz immersion thermometers. The samples were placed in the circulating silicone bath 10° below the melting points and heated at the rate of 1–2° per min. Elemental analyses were performed by Drs. Weiler and Strauss, Oxford, England, and Huffman Microanalytical Laboratories, Wheatridge, Colorado.

I

$Am_1(CH_2)_m—C\equiv C—(CH_2)_n—Am_2$

Formula	Calcd. C	H	N	Halogen	Found C	H	N	Halogen
$C_{12}H_{24}N_2$	73.57	12.25	14.28		73.28	12.15	14.20	
$C_{12}H_{26}Cl_2N_2$	53.62	9.67	10.41	Cl 26.40	53.47	9.70	10.00	25.88
$C_{14}H_{30}I_2N_2$	35.00	6.25	5.83	I 52.92	34.73	6.59	5.74	53.09
$C_{15}H_{20}N_2$	79.00	8.78	12.22		79.04	9.03	12.02	
$C_{15}H_{22}Cl_2N_2$			9.29	Cl 23.5			8.95	23.56
$C_{18}H_{28}Cl_2N_2$	63.00	8.15	8.15	Cl 20.7	62.55	8.13	8.53	21.05
$C_{20}H_{32}Br_2N_2$	52.20	6.96	6.09	Br 34.75	51.90	7.26	6.27	34.30
$C_{16}H_{22}N_2$	79.32	9.12	11.56		79.39	9.12	11.55	
$C_{18}H_{28}Br_2N_2$	46.20[f]	6.84[f]	5.93[f]	Br 34.20[f]	46.49	6.99	5.95	34.20
$C_{17}H_{24}N_2$	79.65	9.38	10.97		79.81	9.24	11.20	
$C_{19}H_{30}Br_2N_2$			6.27	Br 35.80			6.31	36.21
$C_{16}H_{22}N_2O$	74.41	8.53	10.85		74.39	8.71	10.75	
$C_{16}H_{24}Cl_2N_2O$	58.00	7.25	8.46	Cl 21.46	58.00	7.34	8.61	21.58
$C_{17}H_{24}N_2O$	75.00	8.83	10.30		75.82	8.88	10.84	
$C_{18}H_{26}N_2O$	75.50	9.08	9.98		75.24	8.70	10.54	
$C_{16}H_{22}N_2O$	74.41	8.53	10.85		74.19	8.73	10.91	
$C_{16}H_{24}Cl_2N_2O$	58.00	7.25	8.46	Cl 21.46	57.68	7.51	8.06	21.15
$C_{18}H_{28}Br_2N_2O$			6.00[h]	Br 34.40[h]			5.94	34.39
$C_{17}H_{24}N_2O$	75.00	8.83	10.30		74.75	9.24	10.30	
$C_{19}H_{30}Br_2N_2$	49.10	6.50	6.06	Br 34.70	49.14	6.73	5.54	34.75
$C_{18}H_{26}N_2O$	75.50	9.08	9.98		75.68	8.90	10.49	
$C_{16}H_{18}N_2$	80.70	7.55	11.75		80.10	7.82	11.95	
			6.53	Br 37.33			6.00	37.55

quinolino. [d] Recrystallized from 1-butanol-Skelly C. [e] For the dihydrate. [f] Recrystallized from isopropyl alcohol–ether.

Mannich procedure[11] used by Gautier, Marszak and Miocque.[12] A mixture of 2.8 g. (0.062 mole) of dimethylamine, 2.16 g. (0.068 mole) of paraformaldehyde, 0.062 mole of appropriate acetylenic amine,[13] and 48 ml. of purified dioxane was placed in a Carius tube containing several crystals of cupric acetate. The sealed tube was maintained at 70° in a heating jacket for 24 hr. The product was isolated by fractional distillation (see Table I). The higher boiling fraction showed no CH stretching bands at 3.03–3.12 μ.

Method B. 1,4-Bis-diethylamino-2-butyne.—To 56.4 g. (0.8 mole) of diethylamine in 100 ml. of anhydrous ether was added slowly and with stirring 24.4 g. (0.2 mole) of 1,4-dichloro-2-butyne (Farchan Research Laboratories), while cooling the reaction mixture in an ice bath. The reaction mixture was stirred for 4 hr., the crystals of diethylamine hydrochloride were removed by filtration, washed with ether and the ether washings were combined with the filtrate. The product was isolated by fraction distillation after removal of the ether (see Table I).

(11) C. Mannich and F. T. Chang, *Ber.*, **66**, 418 (1933).
(12) J. A. Gautier, I. Marszak, and M. Miocque, *Bull. Soc. Chim. France*, **4**, 415 (1958).
(13) J. L. Neumeyer and J. G. Cannon, *J. Pharm. Sci.*, in press.

Method C. N-(5-Dialkylamino-2-pentynyl)-1,2,3,4-tetrahydroquinolines.—A mixture of 4.95 g. (0.127 mole) of sodamide, 0.085 mole of the appropriate N-propargyl-1,2,3,4-tetrahydroquinoline,[13] and 70 ml. of anhydrous toluene was stirred under reflux until ammonia ceased to be evolved (4 hr.). An aqueous solution of 0.127 mole of 2-chloro-(N,N-dialkyl)-ethylamine hydrochloride was made alkaline with potassium hydroxide pellets; the amine was extracted with three 15-ml. portions of toluene. The toluene extracts were combined and were dried over anhydrous potassium carbonate and the aminoalkyl halide solution was added to the refluxing suspension of the sodium salt of the N-propargyl-amine in toluene. Stirring and refluxing were continued for 17 hr.; the reaction mixture was allowed to cool, and 100 ml. of water was added. The aqueous layer was discarded and the toluene was removed at reduced pressure. The residual black oil was subjected to fractional distillation (see Table I); $\lambda_{max(\mu)}^{film}$ m 10.3 (C≡C—C—N).

Method D. N-(6-Dimethylamino-2-hexynyl)-1,2,3,4-tetrahydroquinolines were prepared in a manner analogous to method C, using 3-chloro-N,N-dimethylpropylamine hydrochloride.

***cis*-Olefinic Diamines.**[14,15]—A mixture of 0.01 mole of the acetylenic diamine, 50 ml. of anhydrous ethanol, one drop of synthetic quinoline, and 0.1 g. of 5% palladium-on-barium sulfate catalyst[16] was subjected to hydrogenation at room temperature and 2.62 kg./cm.^{2}; the uptake of 0.01 mole of hydrogen required 13 hr. The catalyst was removed by filtration and the product was isolated by fractional distillation; $\lambda_{max(\mu)}^{film}$ 10.3 w (C=C *cis*) (see Table II).

***trans*-Olefinic Diamines.**[15,17,18]—To a solution of 4.5 g. of sodium in 50 ml. of liquid ammonia was added 0.0126 mole of acetylenic diamine, and the reaction mixture was stirred for 2 hr. Ammonium nitrate was added until the blue color disappeared. After the addition of 20 ml. of concentrated ammonium hydroxide, the reaction mixture was extracted repeatedly with ether. The ethereal extracts were dried with potassium carbonate, filtered, the ether was removed from the filtrate, and the residue was distilled; $\lambda_{max(\mu)}^{film}$ 6.1 m (C=C stretching); 10.35s (C=C *trans*) (see Table II).

α,ω-Diaminoalkanes.—A mixture of 0.0062 mole of acetylenic diamine in 50 ml. of ethanol and 0.25 g. (0.25 teaspoonful) of Raney nickel W-2 catalyst was reduced at 2.12 kg./cm.^{2} and at room temperature until hydrogen uptake ceased (15 min.). The catalyst was removed by filtration and the product was isolated by distillation (see Table III).

Dimethobromide salts were prepared in a Carius tube in isopropyl alcohol solution with a 2-4 *M* excess of methyl bromide. The acetylenic diamines required more vigorous conditions (48 hr. at 80°) to achieve diquaternization than did the olefins or the alkanes. The dimethobromide salts were isolated by evaporating the solvent, washing the residue with chloroform, ether or isopropyl alcohol, and recrystallizing the crude salts from isopropyl alcohol or isopropyl alcohol-ether

(14) D. J. Cram and N. L. Allinger, *J. Am. Chem. Soc.*, **78**, 2518 (1956).
(15) K. N. Campbell and B. K. Campbell, *Chem. Revs.*, **31**, 77 (1931).
(16) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).
(17) A. L. Henne and K. N. Greenlee, *J. Am. Chem. Soc.*, **65**, 2020 (1943)
(18) K. N. Campbell and T. L. Eby, *ibid.*, **63**, 216, 2683 (1941).

TABLE II

OLEFINIC DIAMINES AND DERIVATIVES, $Am_1(CH_2)_mCH{=}CH(CH_2)_nAm_2$

No.	Am_1	m	n	Am_2	Isomer	B.p. or m.p. °C.	Mm.	$n^{25}D$	Yield, %	Formula	C	H	N	C	H	N
13	THQ[a]	1	2	$(CH_3)_2N$—	*cis*	87–90	0.02	1.5528	80	$C_{16}H_{24}N_2$	78.70	9.83	11.47	78.25	9.89	11.51
	Dimethobromide					155–156[b,c]				$C_{18}H_{30}Br_2N_2$	49.80	6.92	6.45	49.22	7.22	6.09
14	THQ[a]	1	2	$(CH_3)_2N$—	*trans*	112	0.03	1.5572	59	$C_{16}H_{24}N_2$	78.70	9.83	11.47	78.84	9.94	11.45
15	THQ[a]	1	3	$(CH_3)_2N$—	*cis*	139–140	0.02	1.5462	92	$C_{17}H_{26}N_2$	79.10	10.06	10.84	79.38	10.03	10.62
	Dimethobromide					128–129[c,d]				$C_{19}H_{32}Br_2N_2$	Br 35.70		6.24	Br,	36.25	5.94
16	THQ[a]	1	3	$(CH_3)_2N$—	*trans*	134–137	0.03	1.6027	25	$C_{17}H_{26}N_2$	79.10	10.06	10.84	79.17	9.74	11.00

[a] 1,2,3,4-Tetrahydroquinolino. [b] Recrystallized from ethanol–ethyl acetate. [c] Melts with decomposition. [d] Recrystallized from isopropyl alcohol.

TABLE III

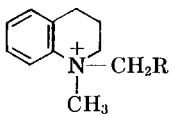
ALKANE DIAMINES AND DERIVATIVES, $Am_1(CH_2)_nAm_2$

No.	Am_1	n	Am	B.p. or m.p. °C.	Mm.	$n^{25}D$	Yield, %	Formula	Calcd. C	Calcd. H	Calcd. N	Calcd. Br	Found C	Found H	Found N	Found Br
17	THQ[a]	6	$(CH_3)_2N$—	122–130	0.02	1.5343	87	$C_{17}H_{28}N_2$	78.50	10.75	10.75		78.56	10.91	10.46	
	Dimethobromide			159–161[b,c,d]				$C_{19}H_{34}Br_2N_2$	48.70[d]	7.71[d]	5.98[d]	34.20[d]	48.72	7.83	5.72	34.50
18	THQ[a]	5	$(CH_3)_2N$—	106	0.02	1.5412	85	$C_{16}H_{26}N_2$	78.20	10.55	11.35		78.21	10.63	11.30	
	Dimethobromide			185–187[b,c]				$C_{18}H_{32}Br_2N_2$	48.20[d]	7.32	6.03		47.43	7.52	5.76	
19	THQ[a]	4	$(CH_3)_2N$—	102–105	0.04	1.5434	85	$C_{15}H_{24}N_2$	77.60	10.35	12.05		77.81	10.26	12.12	

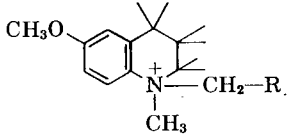
[a] 1,2,3,4-Tetrahydroquinolino. [b] Recrystallized from isopropyl alcohol. [c] Melts with decomposition. [d] For monohydrate.

TABLE IV

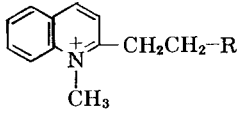
HYPOTENSIVE ACTIVITY OF ACETYLENIC DI-QUATERNARY AMINES AND THEIR REDUCTION PRODUCTS



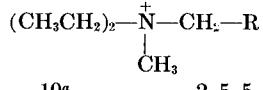
No.	R	No. of animals tested	Evaluation dose mg./kg. i.v.	Av. blood pressure Lowering %	Duration min.
3	$C\equiv C-(CH_2)_2N^+(CH_3)(C_2H_5)_2$	20[a]	4	50 ± 10.7	133 ± 74
4	$-C\equiv C-(CH_2)_2N^+(CH_3)_3$	16[a]	2.5	43 ± 8.7	210 ± 63.6
		9[a]	1.25	45 ± 11	260
		1[b]	1.0	63	320+
13	$-C=C-(CH_2)_2-N^+(CH_3)_3$ H H *cis*	5	5.0	36	109
		1	10.0	45	172
18	$(-CH_2)_4-{}^+N(CH_3)_3$	18[a]	15.0	39 ± 9.3	177 ± 73.7
5	$-C\equiv C-(CH_2)_3-{}^+N(CH_3)_3$	17[a]	5.0	56	151
15	$-C=C-(CH_2)_3-{}^+N(CH_3)_3$ H H *cis*	17[a]	5.0	42 ± 10.2	96 ± 70
		1[b]	5.0	71	264
17	$-(CH_2)_5-N^+(CH_3)_3$	8[a]	1–20.0	0	0
	Hexamethonium	1[b]	10.0	66	132+
		8[a]	5.0	46 ± 17.9	30.0 ± 15.2
	Chlorisoudamine	14[a]	0.5	45 ± 13.8	141.2 ± 51.6



9	—C≡C—CH_2—N^+—$(CH_3)_3$	16[a]	10	62 ± 12.3[c]	194 ± 76.1
10	—C≡C—$(CH_2)_2$—N^+—$(CH_3)_3$	15[a]	7.5	55 ± 11	238 ± 307
11	—C≡C—$(CH_2)_3$—N^+—$(CH_3)_3$	3[a]	2.5	38	126



12	—C≡C—CH_2—$N^+(CH_3)_3$	1[a]	5.0	21 (rise)	32
		1[a]	10.0	21 (rise)	25



1	—C≡C—CH_2—N^+—$(C_2H_5)_2$	10[a]	2.5–5.0	24 (rise)	..
	CH_3	2[a]	40.0	36	42
		1[b]	20.0	40	96

[a] Normotensive rat. [b] Anesthetized normotensive dog. [c] Compound is toxic.

Pharmacological Results

The bis-quaternary amines synthesized in our laboratory were screened for their hypotensive activity in anesthetized normotensive rats and dogs utilizing the method described by Bickerton, *et al.*[4] An initial 1 mg./kg. dose of each compound was administered, intravenously, to anesthetized rats and subsequent dosage was adjusted according to results obtained in order to determine the dose that would produce a drop in blood pressure of approximately 50%. All compounds were dissolved in distilled water immediately before use and each rat received a single dose of hypotensive compound. The approximate ED_{50} of a compound was administered to a group of anesthetized rats and the mean time for the blood pressure to return to pre-drug levels was determined. Freshly prepared solutions were also administered, intravenous, to anesthetized mongrel dogs utilizing dosages determined from previous rat studies. The hypotensive activity is summarized in Table IV.

The introduction of a triple bond into the linking chain potentiated the activity of the tetrahydroquinoline compounds (compare 4 and 18, 5 and 17).

The 2-quinolyl derivative (12) was a mild pressor compound in doses of 5 and 10 mg./kg. in the anesthetized normotensive rats. Although Table IV includes data on only two animals, the compound was administered to 6 rats in doses ranging from 2.5–10.0 mg./kg. producing a marked depression of respiration and appeared to be quite toxic.

The data on the hypotensive activity of this series of compounds are, in general, consistent with Gill's concept of the significance of interquaternary distance in ganglionic blockade. Although these compounds were not specifically investigated for ganglionic blocking activity, the effects of several of the experimental agents on the pressor activity of epinephrine, angiotensin II, and bilateral carotid occlusion pressor activity in anesthetized dogs were studied. In all instances, they blocked bilateral carotid occlusion pressor activity and potentiated the responses to epinephrine and angiotensin. These responses are consistent with the effects obtained with ganglionic blockers.