the alternate formula for **4** which would have arisen from attack at the other carbonyl in the first step, since it would be expected to give rise to a singlet at higher fields for each geometric isomer.

The ultraviolet spectrum of **4** shows a K band similar to that of styrene.[5] Again this absorption is not in agreement with that expected for the alternate structure which should display a K band similar to stilbene.[6]

Brossi[2] has shown the activity of 1-(*p*-chlorophenethyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline to be comparable to codeine. In the phenylquinone writhing syndrome test[7] codeine has an ED_{50} of 10 mg./kg. *p.o.*; however, isomer A of **5** showed no analgesic activity at doses up to 200 mg./kg. *p.o.* in this test.

Experimental[8]

(*p*-Chlorophenyl)succinic Anhydride (2).—A mixture of 420 g. of (*p*-chlorophenyl)succinic acid,[9] 2800 ml. of acetyl chloride, and 135 ml. of thionyl chloride was refluxed for 5 hr. Removal of the excess acetyl chloride on the steam bath followed by distillation of the residue gave 354 g. (91%) of a colorless oil, b.p. 160–170° (0.4 mm.). Redistillation gave 338 g. of a colorless oil, b.p. 165° (0.4 mm.), which crystallized on standing. Recrystallization from petroleum ether (30–60°) gave an analytical sample: m.p. 64–65°; ν_{max}^{Nujol} 1780, 1860 cm.$^{-1}$; $\lambda_{max}^{CH_3CN}$ 220 mμ (ε 11,000), 252 (160), 258 (200), 265 (235), 275 (160).

Anal. Calcd. for $C_{10}H_7ClO_3$: C, 57.02; H, 3.35; Cl, 16.84. Found: C, 56.79; H, 3.52; Cl, 16.72.

2-(*p*-Chlorophenyl)-N-(3,4-dimethoxyphenethyl)-N-methylsuccinamic Acid (3).—To a solution of 52.5 g. of (*p*-chlorophenyl)-succinic anhydride in 1 l. of ether was added a solution of 107 g. of 3,4-dimethoxy-N-methylphenethylamine in 100 ml. of ether with cooling, such that the temperature remained between 20 and 25°. The mixture was then stirred for 1 hr. The ether was decanted from the precipitated gum, and 500 ml. of water was added followed by 40 ml. of 40% NaOH solution. The resulting solution was acidified by the dropwise addition of 10% HCl. The precipitate was taken up in benzene, washed with water, and dried (Na_2SO_4), and the solvent was removed. The residue was dissolved in 275 ml. of ethanol and on standing there was deposited 55 g. (55%) of a crystalline solid, m.p. 147–149°. Further recrystallization gave an analytical sample: m.p. 151.5–153°; ν_{max}^{Nujol} 1595, 1730 cm.$^{-1}$; $\nu_{max}^{CHCl_3}$ 1640, 1712 cm.$^{-1}$; λ_{max}^{EtOH} 221 mμ (ε 19,400), 275 (3000).

Anal. Calcd. for $C_{21}H_{24}ClNO_5$: C, 62.15; H, 5.92; Cl, 8.73; N, 3.45. Found: C, 62.17; H, 6.08; Cl, 8.93; N, 3.28.

Ethyl α-(*p*-Chlorophenyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-Δ$^{1,\beta}$-isoquinolinepropionate (4).—A solution of 24.3 g. of 2-(*p*-chlorophenyl)-N-(3,4-dimethoxyphenethyl)-N-methylsuccinamic acid and 1 ml. of sulfuric acid in 200 ml. of ethanol was refluxed for 3 hr. After removal of the solvent *in vacuo* on the steam bath, the residue was treated with 100 ml. of saturated sodium bicarbonate solution and benzene. The solvent was removed from the benzene layer, and the residue was refluxed in a solution of 25 ml. of phosphorus oxychloride and 100 ml. of xylene for 2 hr. The reaction mixture was poured into 500 ml. of ether with stirring, the ether was decanted, and the precipitate was treated with 500 ml. of water. The solution was filtered, made basic with NH_4OH, and extracted with ether. The ether layer was washed with water and dried (Na_2SO_4), and the solvent was removed. There remained 6.5 g. (27%) of a viscous gum which crystallized on long standing. Recrystallization from ethanol gave an analytical sample: m.p. 134–139°; ν_{max}^{Nujol} 1600, 1620, 1730 cm.$^{-1}$; λ_{max}^{EtOH} (pH 11) 246–270 mμ plateau (ε 4000); λ_{max}^{EtOH} (0.1 *N* HCl) 219 mμ (ε 17,000), 247 (12,800), 308 (5200), 360 (7700); $\delta_{TMS}^{CDCl_3}$ = 4.75, 4.95 (*J* = 9 c.p.s.), 5.75 p.p.m. (*J* = 9 c.p.s.).

Anal. Calcd. for $C_{23}H_{26}ClNO_4$: C, 66.42; H, 6.30; Cl, 8.53; N, 3.37. Found: C, 66.38; H, 6.33; Cl, 8.51; N, 3.34.

Ethyl α-(*p*-Chlorophenyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-1-isoquinolinepropionate Hydrochloride (5).—To a solution of 6.5 g. of ethyl α-(*p*-chlorophenyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-Δ$^{1,\beta}$-isoquinolinepropionate in 50 ml. of acetic acid, was added 100 mg. of platinum oxide, and the mixture was hydrogenated. After 0.02 equiv. of hydrogen had been absorbed, uptake ceased. The catalyst was filtered and the solvent was removed *in vacuo*. The residue was dissolved in 100 ml. of water, made basic with NH_4OH, and extracted with ether. The ether layer was washed with water and dried (Na_2SO_4), and the solvent was removed. The residue was dissolved in 15 ml. of ethanol and made acidic with HCl. There was deposited 5.1 g. (85%) of a crystalline solid, m.p. 174–181°. Two more recrystallizations from ethanol gave an analytical sample of a mixture of two stereoisomers: m.p. 179–185°; ν_{max}^{Nujol} 1720, 1728, 2420 cm.$^{-1}$; λ_{max}^{EtOH} 224 mμ (ε 18,600), 283 (4000), 290 sh (3200).

Anal. Calcd. for $C_{23}H_{29}Cl_2NO_4$: C, 60.79; H, 6.43; Cl, 15.61; N, 3.08. Found: C, 60.67; H, 6.20; Cl, 15.58; N, 3.17.

Isomer A was obtained by fractional crystallization from ethanol as a crystalline solid: m.p. 190–191.5°; ν_{max}^{Nujol} 1728, 2420 cm.$^{-1}$; λ_{max}^{EtOH} 224 mμ (ε 18,600), 283 (3700), 289 sh (3200).

Anal. Calcd. for $C_{23}H_{29}Cl_2NO_4$: C, 60.79; H, 6.43; Cl, 15.61; N, 3.08. Found: C, 61.00; H, 6.45; Cl, 15.81; N, 3.17

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Synthesis and Biological Activities of Certain Short-Chain Mono- and Bisquaternary Ammonium Compounds[1a,b]

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Plummer and co-workers[2] compared the ganglionic blocking activities of a number of bisquaternary compounds derived from halogenated N-aminoalkylisoindolines. The most potent member of the series and the one possessing the longest duration of action was that in which the two nitrogen atoms were separated by a chain of two methylene units.

The fact that C_2 bisquaternary ammonium compounds block nerve impulses at autonomic ganglia tends to discount the prime importance of interquaternary distance for maximum ganglionic activity in α,ω-bisquaternary ammonium drugs. Biel and DiPierro[3] and Neumeyer, *et al.*,[4] have demonstrated that inser-

(1) (a) Presented to the Division of Medicinal Chemistry of the American Chemical Society, Philadelphia, Pa., April 1964. Abstracted in part from a portion of a thesis submitted by W. L. G. in partial fulfillment of the requirements for the degree of Doctor of Philosophy, University of Wisconsin, 1963. (b) A portion of the investigation was supported by Fellowship Grant GPM-13,132, National Institutes of Health. The pharmacological investigation was supported by Public Health Service Grant HE-03475 from the National Heart Institute. (c) To whom correspondence should be addressed.

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tion of a triple bond into a C_5 or C_6 alkylene chain connecting two quaternary nitrogen heads increases ganglion-blocking potency. In addition, the latter group has shown that when the triple bond in a series of C_5 and C_6 α,ω-bisquaternary ammonium compounds was reduced to a *cis* double bond, ganglion-blocking activity diminished, but reduction to the *trans* double bond increased activity above that observed for the parent saturated molecule. These effects were rationalized[4] on the basis of the concept of an optimum distance between quaternary heads, to permit proper alignment of the drug at its receptor site.

In order to determine whether other C_2 bisquaternary compounds are active at autonomic ganglia, as well as to determine whether their monoquaternary derivatives are also active, a series of mono- and bisquaternary derivatives of C_2 ditertiary amines derived from the quinoline ring was prepared (see Table I). Attempts to diquaternize 2-dimethylaminomethyl-1,2,3,4-tetrahydroquinoline (III) in a sealed tube with methyl bromide in a variety of solvents gave rise to deeply colored oils which eventually crystallized, but which did not show a correct analysis for the expected bisquaternary. The method employed for preparation of 1-methyl-2-dimethylaminomethyl-1,2,3,4-tetrahydroquinoline (VI) represents a reaction sequence not previously reported for this compound.

The procedure for preparation of the monomethiodides was based on the belief that under mild reaction conditions and in ethereal solution the less hindered and more nucleophilic dimethylamino nitrogen would displace iodide ion from methyl iodide to form a quaternary salt which would be highly insoluble in the reaction medium. Thus, quaternization of the ring nitrogen moiety would be prevented. To prove this contention all of the monoquaternary salts were converted to the quaternary hydroxides, and these were subjected to Hofmann degradation conditions. In every instance, a product of the degradation was trimethylamine, which could result only from a quaternary group involving the side-chain nitrogen, not the ring nitrogen.

Experimental[5]

1-(2-Dimethylaminoethyl)-6-methoxy-1,2,3,4-tetrahydroquinoline (I).—This compound was prepared by the method used by Ohki[6] to prepare the desmethoxy analog (see Table I), lit.[7] b.p. 146–152° (1 mm.). The benzenesulfonamide of 6-methoxy-1,2,3,4-tetrahydroquinoline, isolated in attempts to separate the product of the reaction from starting material, crystallized from ethanol in off-white flakes, m.p. 113–114°.

Anal. Calcd. for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65. Found: C, 63.94; H, 5.74.

2-Hydroxymethylquinoline.—Quinoline-2-carboxaldehyde (18.37 g., 0.116 mole, Aldrich Chemical Co., recrystallized from Skelly B) in 75 ml. of 95% ethanol was added dropwise with stirring to a solution of 4.88 g. (0.13 mole) of sodium borohydride (Metal Hydrides, Inc., 98+%) in 150 ml. of 95% ethanol and 15 ml. of 10% aqueous NaOH. The resulting suspension was stirred 2.75 hr., cooled, and made strongly acidic by dropwise addition of 15% HCl. The solvents were removed under reduced pressure, the residue was dissolved in 175 ml. of cold water, and this solution was made strongly alkaline with cold KOH solution. This mixture was extracted repeatedly with ether; the combined extracts were dried (K_2CO_3). Removal of the ether from a steam bath afforded 17.4 g. (93%) of a tan solid. Two recrystallizations from benzene–petroleum ether produced off-white crystals, m.p. 65–67°, lit.[8] m.p. 66–68°.

2-Dimethylaminomethylquinoline (II).—2-Chloromethylquinoline[9] (16.7 g., 0.094 mole) in 50 ml. of absolute ethanol was added dropwise to a stirred solution of 12.9 g. (0.28 mole) of dimethylamine in 100 ml. of absolute ethanol. Stirring was continued overnight; the solvent was removed under reduced pressure, and the residue was mixed with 40 ml. of water and 10 ml. of 10% NaOH solution. This mixture was saturated with K_2CO_3 and was extracted repeatedly with ether. The combined extracts were dried with anhydrous K_2CO_3, the solvent was removed, and the residue was distilled (see Table I). Vapor phase chromatographic analysis of this product revealed that it consisted of a single component.

2-Dimethylaminomethyl-1,2,3,4-tetrahydroquinoline (III).—Sodium (70.0 g.) in small pieces was added during 20 min. to a stirred solution of 21.5 g. (0.12 mole) of II in 1 l. of reagent grade ethanol. The mixture was refluxed 3 hr., cooled, and made strongly acidic by addition of concentrated HCl. The solvent was removed under reduced pressure, and the residue was mixed with 700 ml. of water. This mixture was cooled, made strongly alkaline with cold KOH solution, saturated with K_2CO_3, and extracted repeatedly with ether. The combined extracts were dried (K_2CO_3), the ether was removed, and the residue was distilled. After a forerun of 1,2,3,4-tetrahydroquinaldine[10] and a middle fraction (1.25 g.) consisting of two components, the desired product was obtained as a very pale yellow oil (see Table I). Leonard and co-workers[11] reported synthesis of this compound by another route; b.p. 93–95.2° (0.18–0.30 mm.), $n^{20}D$ 1.5632.

1,2,3,4-Tetrahydroquinaldine was prepared in 80% yield from quinaldine by the method utilized for III; b.p. 76–78.5° (0.75 mm.), $n^{20}D$ 1.5692; lit.[12] b.p. 102–103° (5 mm.), $n^{20}D$ 1.5704.

1-Formyl-2-dimethylaminomethyl-1,2,3,4-tetrahydroquinoline (V).—III (9.07 g., 0.048 mole) and 5.20 g. (0.1 mole) of 88% formic acid were refluxed in benzene–toluene overnight, water being collected in a Dean–Stark trap. An additional 5.2 g. of formic acid was added, and the mixture was refluxed an additional 24 hr. The biphasic mixture was extracted repeatedly with 10% HCl; the combined acid extracts were chilled and made alkaline with cold KOH solution; the mixture was saturated with K_2CO_3 and extracted repeatedly with ether. The combined ether extracts were dried (K_2CO_3) and filtered. The solvent was removed from the filtrate on a steam bath, leaving a residue of 8.9 g. (83%) of a viscous orange oil which could be distilled at 110° (0.01 mm.).

Anal. Calcd. for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.82; H, 8.50; N, 12.98.

1-Methyl-2-dimethylaminomethyl-1,2,3,4-tetrahydroquinoline (VI).—A solution of 4.4 g. (0.02 mole) of crude V in 150 ml. of anhydrous ether was added dropwise and with stirring during 40 min. to a slurry of 1.9 g. (0.05 mole) of $LiAlH_4$ in 150 ml. of anhydrous ether. The mixture was stirred under reflux for 6 hr.; it was then cooled and 8 ml. of water was added dropwise. The resulting suspension was filtered, and the solid on the filter was washed with ether. The combined filtrate and washings were dried (K_2CO_3) and filtered. Removal of the ether from this

(5) All melting points are corrected and were determined on a Thomas-Hoover melting point apparatus. Boiling points are uncorrected. Elemental analyses were performed by Huffman Microanalytical Laboratories, Wheatridge, Colo., and by Schwartzkopf Laboratories, Woodside, N. Y. Infrared spectra were recorded on a Beckman IR5A instrument. Vapor phase chromatographic analyses were carried out on an F and M Model 500 recording gas chromatography apparatus.

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(10) The forerun consisted of 1.61 g., b.p. 76–83° (0.95 mm.). *Anal.* Calcd. for $C_{10}H_{13}N$: C, 81.59; H, 8.90; N, 9.51. Found: C, 81.28; H, 8.96; N, 9.60. The identity of this forerun was confirmed by comparison of its infrared spectrum (chloroform) with that of an authentic sample of 1,2,3,4-tetrahydroquinaldine, the preparation of which is described in this paper.

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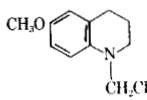
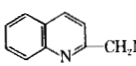
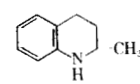
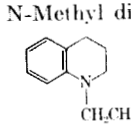
TABLE I

C_2 DIAMINES AND THEIR MONO- AND BISQUATERNARY AMMONIUM SALTS

No.	Structure	B.p. (mm.) or m.p., °C.	Formula	Yield, %	Calcd., % C	H	N	Halogen	Found % C	H	N	Halogen
I		101–116[a] (0.01)	$C_{14}H_{22}N_2O$	29	71.75	9.46	11.96		72.18	9.52	11.65	
Ia	Monomethiodide Tetramethylammonium iodide from Hofmann degradation	188–189.5[b]	$C_{15}H_{25}IN_2O$ $C_4H_{12}IN$	84	47.88 23.85	6.70 5.97	7.44 6.97	33.73 63.30	47.59 23.84	6.96 6.38	7.05 6.77	33.17 63.64
Ib	Dimethiodide	145–148[b,c]	$C_{16}H_{28}I_2N_2O \cdot C_2H_5OH$	32	38.31	6.07	4.96		38.30	6.00	4.47	
II		98–103[d] (0.8)	$C_{12}H_{14}N_2$	84	77.39	7.58	15.04		77.26	7.50	15.10	
IIa	Monomethiodide Tetramethylammonium iodide from Hofmann degradation	184.5–189[e]	$C_{13}H_{17}IN_2$ $C_4H_{12}IN$	57	47.58 23.85	5.22 5.97	8.53 6.97	38.67 63.30	47.78 24.03	5.27 6.87	8.40 6.85	38.53 62.35
IIb	Dimethobromide	191–192[f]	$C_{14}H_{20}Br_2N_2$	49	44.70	5.36	7.44		44.18	5.46	7.78	
III		105.5–108.5 (0.9)	$C_{12}H_{18}N_2$	67	75.75	9.54	14.72		76.00	9.71	14.79	
IIIa	Monomethiodide Tetramethylammonium iodide from Hofmann degradation	197–201[b]	$C_{13}H_{21}IN_2$ $C_4H_{12}IN$	70	47.00 23.85	6.37 5.97	8.43 6.97	38.20 63.30	47.35 23.78	6.44 6.23	8.16 6.56	38.23 61.92
IIIb	N-Methyl dimethobromide	177.5–180[c,f]	$C_{15}H_{26}Br_2N_2$	14			7.10	40.55			7.10	40.29
IV												
IVa	Monomethiodide Tetramethylammonium iodide from Hofmann degradation	209–210.5[b]	$C_{14}H_{23}IN_2$ $C_4H_{12}IN$	77	48.56 23.85	6.70 5.97	8.08 6.97	36.65 63.30	48.76 23.78	6.96 5.98	7.95 7.02	36.51 63.26
IVb	Dimethiodide	134–136[b,c]	$C_{15}H_{26}I_2N_2$	25	36.90	5.37	5.74	51.99	37.53	5.30	5.03	52.50

[a] $n^{30}D$ 1.5500. [b] Recrystallized from absolute ethanol. [c] Foams at melting point. [d] $n^{22}D$ 1.5875. [e] Recrystallized from 2-propanol. [f] Recrystallized from ethanol–Skelly B.

filtrate afforded 3.81 g. of a yellow liquid which was distilled to yield (after a small forerun) 2.85 g. (70%) of a pale yellow liquid, b.p. 101–102° (0.18 mm.), $n^{20}D$ 1.5760. Leonard and his co-workers[11] reported preparation of this compound by another route, b.p. 109–110° (0.5 mm.), $n^{20}D$ 1.5775.

Monomethiodides. General Method.—A solution of diamine (1–2 g.) and a 20-fold excess of methyl iodide in 10–15 ml. of anhydrous ether was allowed to stand at room temperature with occasional shaking for 2 days, then the solid which separated was collected on a filter. This material was dried in a heated vacuum desiccator and was recrystallized (see Table I).

1-(2-Dimethylaminoethyl)-1,2,3,4-tetrahydroquinoline Dimethiodide (IVb).—A solution of 1.3 g. (0.006 mole) of 1-(2-dimethylaminoethyl)-1,2,3,4-tetrahydroquinoline[6] in 30 ml. of methyl iodide was heated at 80° in a sealed tube with shaking for 3 days. An orange solid separated which was collected on a filter, washed successively with hot acetonitrile and a small amount of hot absolute ethanol, and recrystallized (see Table I).

1-(2-Dimethylaminoethyl)-6-methoxy-1,2,3,4-tetrahydroquinoline Dimethiodide (Ib).—I (1.29 g., 0.0055 mole) and 1.7 g. (0.011 mole) of methyl iodide in 20 ml. of anhydrous ether was allowed to stand at room temperature for 3 days. The white solid which separated was heated with 20 ml. of methyl iodide and 10 ml. of absolute ethanol in a sealed tube at 67° with shaking for 1 day, then at 85° for 2 hr. The yellow insoluble product was recrystallized from a mixture of absolute ethanol and methanol. The resulting yellow crystals were washed with hot acetonitrile to afford a white crystalline solid which was washed with a small amount of absolute ethanol and recrystallized (see Table I).

2-Dimethylaminomethylquinoline Dimethobromide (IIb).—II (1.5 g., 0.008 mole) and 5.6 g. (0.059 mole) of methyl bromide in 10 ml. of anhydrous 2-propanol was heated at 80–87° in a sealed tube with shaking for 14 hr. The solid portion of the reaction mixture was collected on a filter and was combined with additional solid which was precipitated from the filtrate by addition of ether. The combined solids were dried at 75° (10 mm.) and were recrystallized (see Table I).

1-Methyl-2-dimethylaminomethyl-1,2,3,4-tetrahydroquinoline dimethobromide (IIIb) was synthesized from VI by the procedure described for IIb (see Table I).

Hofmann Degradations. General Method.—Silver oxide (5.0 g.) was stirred with a solution of 5.0 g. of the monoquaternary salt in 100–200 ml. of water for 3 hr. at room temperature. The filtrate from the resulting mixture was distilled to dryness from an oil bath heated to 190–200°, the receiver being cooled in a Dry Ice–acetone slurry. The distillate (which was strongly alkaline to litmus) was filtered through moistened filter paper; 0.5 g. of KOH was added to the filtrate, and it was extracted repeatedly with ether. The combined ether extracts were dried (Na_2SO_4), filtered, and to the filtrate was added 3.0 ml. of methyl iodide. A white solid separated which, after standing for several hours, was collected on a filter and recrystallized from water. Infrared spectra (Nujol) of the solids from each Hofmann degradation sequence were identical with that of an authentic sample of tetramethylammonium iodide prepared from trimethylamine and methyl iodide (see Table I).

Pharmacology.—Eight of the compounds were screened for their hypotensive activity in anesthetized normotensive rats utilizing the method described by Bickerton and co-workers.[13] An initial 1 or 10 mg./kg. of each compound was administered, intravenously, to anesthetized rats and subsequent dosage was adjusted according to results obtained, in order to determine a 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 hypotensive activity is summarized in Table II.

TABLE II

HYPOTENSIVE ACTIVITY OF CERTAIN SHORT-CHAIN MONO- AND BISQUARTERNARY AMMONIUM COMPOUNDS ON ANESTHETIZED NORMOTENSIVE RATS[a]

Compd.	No. of animals	Dose, mg./kg.	Blood pressure effect, % (range)	Duration, min. (range)
Ia	10	40	0	0
Ib	6	40	−41 (42–46)	26 (9–56)
IIa	4	2.5	0	0
IIa	2	5	+34 (24–45)	
IIa	2	10	−27	4
IIa	4	20	Respiratory stoppage	
IIb	2	10	0	0
IIb	2	20	Respiratory stoppage	
IIIa	4	10	Respiratory stoppage	
IIIb	6	10	Respiratory stoppage	
IVa	4	10	Respiratory stoppage	
IVb	6	10	−43 (40–48)	120 (42–245)
Hexamethonium	8	5	−46	30
Chlorisondamine	8	0.5	−41	120

[a] Anesthetic: urethan, 1.25 g./kg. i.p.

Freshly prepared solutions were also administered, intravenously, to anesthetized mongrel dogs, utilizing doses determined from previous rat studies. The only compound in this series exhibiting potent hypotensive activity was IVb, and all doses ranging from 10–40 mg./kg. i.v. produced similar hypotensive responses in anesthetized rats. Ib produced hypotensive effects of relatively short duration in rats. Quaternization of the nitrogen of the saturated ring, as well as quaternization of the side-chain nitrogen was necessary for hypotensive activity (compare Ib and IVb with Ia and IVa, respectively). Compounds IIa, IIb, IIIa, IIIb, and IVa produced marked but transient depression of respiration.

The administration of Ib (20 mg./kg. i.v.) to an anesthetized dog produced a 50% drop in blood pressure persisting in excess of 2 hr. IVb (20 mg./kg. i.v.) produced a 46% drop in blood pressure persisting in excess of 2 hr. in another dog. Both compounds markedly potentiated the epinephrine and angiotensin II pressor responses and depressed bilateral carotid occlusion. Preliminary data suggest that the hypotensive activity of these two compounds is at least in part due to ganglionic blockade.

The absence of hypotensive activity in monoquaternary compounds Ia and IVa (Tables I and II) as compared with their bisquaternary analogs Ib and IVb suggests that these C_2 bisquaternaries are not mechanistically similar to tetraethylammonium. It was of some interest that IIa and b and IIIa and b, in which one of the carbon atoms of the C_2 unit connecting the nitrogen functions was a part of the heterocyclic ring, exhibited no hypotensive activity, but rather produced respiratory arrest. An earlier study[4] reported a C_6 bisquaternary in which the side chain was placed at position 2 of a quinoline system. This structure also produced respiratory arrest and was not a hypotensive agent.

(13) R. K. Bickerton, M. L. Jacquart, W. J. Kinnard, J. A. Bianculli, and J. P. Buckley, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 183 (1960).