at room temperature for 5 days and was then refluxed with 250 ml. of acetic anhydride for 1 hr. The resulting clear solution was poured into 1000 ml. of water and the precipitate obtained was taken up in ether, washed with saturated sodium chloride solution, and dried over anhydrous sodium sulfate. After removing the ether the residue was distilled at 185–190° (0.1 mm.) and recrystallized twice from ethanol, m.p. 138–139°, yield 79 g. (72%), λ_{max} 227 (ϵ 1.77 × 10^4).

Anal. Calcd. for $C_{23}H_{26}O_4$: C, 75.38; H, 7.15. Found: C, 75.41; H, 7.17.

Bis-(*p*-hydroxyphenyl)-cyclohexylmethane.—A quantity of 18.2 g. (0.05 mole) of bis-(*p*-acetoxyphenyl)-cyclohexylmethane was boiled with 200 ml. of a 20% methanolic solution of potassium hydroxide for 30 min. After cooling, 200 ml. of water was added and the solution neutralized with 2 *N* HCl. The resulting crystalline mass was recrystallized twice from 50% ethanol, m.p. 226–228°.

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 81.0[illegible]; H, 7.67.

Acknowledgment.—The authors wish to express their gratitude to Professor E. Bárány for his interest in this work and valuable discussions. J. F. M. gratefully acknowledges a research grant from the Swedish Cancer Society.

Synthesis and Antibacterial Activity of Symmetrical Bis-quaternaries Derived from β-Ionone and Related Compounds

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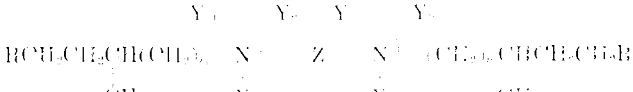
A series of new symmetrical bis-quaternary compounds, derived from alkyl substituted cyclohexenyl-, alkyl substituted cyclohexyl-, alkyl substituted cyclopentyl-, and branched aliphatic amines, have been prepared for evaluation as antimicrobial agents. Most of the compounds showed a strong *in vitro* and local *in vivo* antibacterial activity and, in addition, those derived from tetrahydroionone exhibited a limited systemic antistaphylococcal effect in mice.

Symmetrical bisquaternary compounds, whose cationic groups are derived from amines containing long chain alkyl, alkoxyalkyl, and thioalkyl moieties and are bridged by an alkylene chain, are known to exhibit germicidal activity.[3] Antibacterial activity has also been described for a series of α,ω-bis(2,2'-dipyridylamino)alkanes,[4] as well as for decamethylenebis(4-aminoquinaldinium chloride) and analogs.[5]

This paper describes the preparation and antimicrobial activity of a series of symmetrical bis-quaternary compounds of the general formula I, in which R can be an alkyl substituted cyclohexenyl, an alkyl substituted cyclohexyl, an alkyl substituted cyclopentyl, or a branched aliphatic group, and *m* = 0 or 1, Y_1 = alkyl, Y_2 = Y_1 or substituted alkyl, and Z represents alkylene, alkenylene, alkynylene, *p*-xylylene, or an aliphatic chain containing an ether, hydroxy, ester, or amide function. The new compounds were obtained by several methods, using mainly β-ionone and related compounds as starting materials.



I

Most of the bis-quaternaries exhibited, as expected, a strong *in vitro* antibacterial activity, often accompanied by good local antimicrobial activity. Unexpectedly, some of the compounds also had a limited systemic antistaphylococcal effect in mice, and it was most interesting to find that the structural requirements for this *in vivo* activity were very specific. Only those compounds of structure I, in which R was 2,2,6-trimethylcyclohexyl, *m* was 0 or 1, Y_1 and Y_2 were methyl, and Z ranged from ethylene to decamethylene, showed this systemic activity. One of these compounds, N,N'-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-N,N'-dimethyl-1,6-hexanediamine bis(methochloride)[7] (II), has been tested clinically and found to be useful as a topical antimicrobial agent.

Chemistry.—The new symmetrical bisquaternaries were synthesized by the methods outlined in the flow diagram for the preparation of II. Essentially, two methods were used. In one approach (method E), two equivalents of the appropriate monotertiary amine were treated in refluxing acetonitrile with an α,ω-dihalide. In the alternate route (method F), the appropriate ditertiary amine was treated with a quaternizing agent such as methyl bromide in acetone at room temperature, or methyl chloride in methanol under pressure at 100°. In two instances, the appropriate disecondary amine was directly alkylated and quaternized (method H), using methyl chloride or ethyl bromide in the presence of anhydrous sodium carbonate. Finally, a few of the bis-quaternary bromides or iodides were converted to the corresponding chlorides by treatment with freshly precipitated silver chloride (method G). The bis-quaternaries thus obtained were usually hygroscopic, and were often obtained in various hydrated crystalline forms.

The mono- and diamines (Tables I and II), used as intermediates in the preparation of the bis-quaternaries, were all new compounds, except for a few that were recently described.[8] The tertiary mono- and diamines

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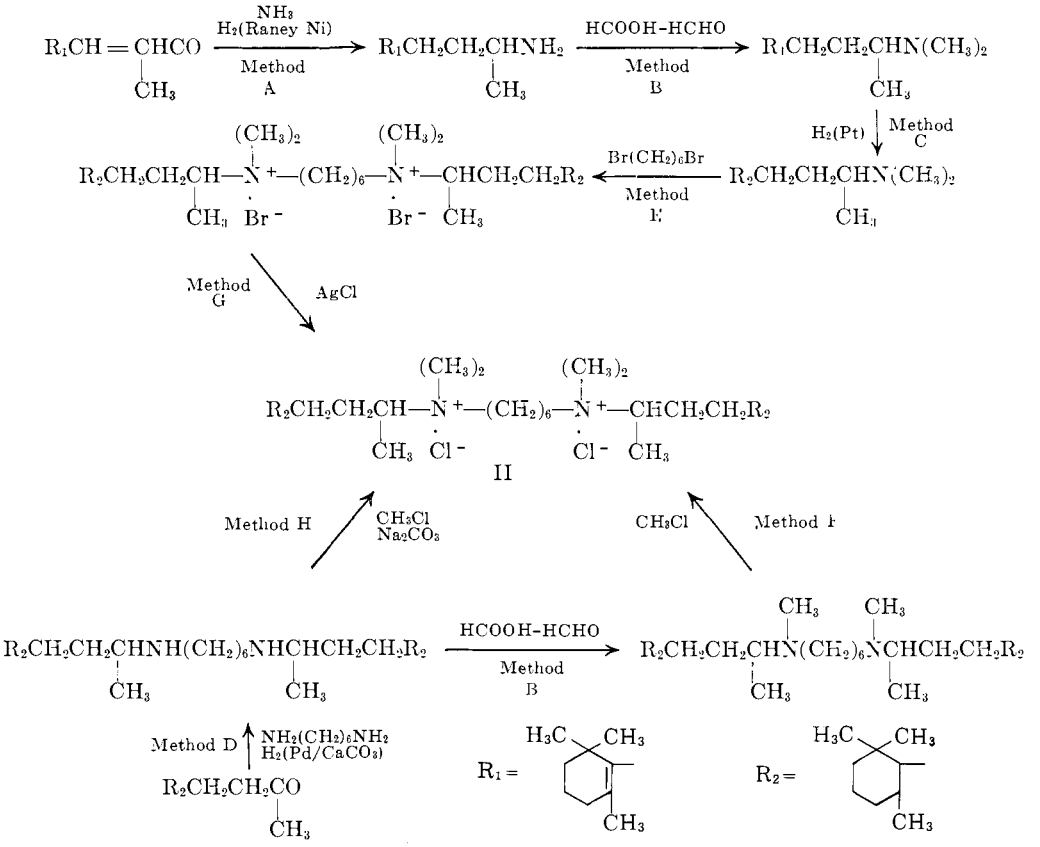
(3) F. L. de Beauville, "Medicinal Chemistry," Vol. III, F. F. Blicke and R. H. Cox, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 124 and 122.

(4) G. H. Cadebusch and C. J. Cavallito, *Antibiot. Chemotherapy*, **7**, 549 (1957).

(5) M. Babbs, G. H. J. Collier, W. C. Austin, M. D. Potter and E. P. Taylor, *J. Pharm. Pharmacol.*, **8**, 110 (1956).

(7) Triclobisonium chloride, Triburon.®

(8) See footnotes h, i (Table I) and footnote e (Table II).



were prepared from the corresponding primary or secondary amines, or secondary diamines, by mono- or dimethylation using formic acid–formaldehyde, according to the procedure of Eschweiler–Clarke[9] (method B). The intermediate primary and secondary monoamines were obtained by reductive condensation of an aldehyde or ketone with ammonia or a primary amine in the presence of Raney nickel catalyst (method A). When α,ω-diamines were reductively condensed with two equivalents of a carbonyl compound, the resulting disecondary amines were most readily obtained when palladium-on-calcium carbonate was used as the catalyst (method D).

All of the carbonyl compounds used as starting materials were known.[10] Many of them contained both *endo*- and *exo*-cyclic double bonds. When these compounds were used in the above reductive condensation procedures (methods A and D), only the *exo*-cyclic double bonds were reduced. The resulting amines still retained the *endo*-cyclic unsaturation. For complete reduction, these unsaturated primary or secondary amines were converted to the corresponding tertiary amine hydrochlorides, which were then hydrogenated in glacial acetic acid at 100° and 73 kg./cm.^{2} in the presence of a platinum catalyst (method C). A more expedient route for the preparation of saturated amines of this type was to hydrogenate a ketone containing both *endo*- and *exo*-cyclic unsaturation at room temperature in the presence of a palladium-on-calcium carbonate catalyst, to form the corresponding saturated ketone (*e.g.*, conversion of β-ionone to *cis*-tetrahydroionone), which was then reductively condensed with ammonia or the appropriate amine.

(9) W. Eschweiler, *Ber.*, **38**, 880 (1905); H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

(10) We are indebted to members of our Technical Development Department for making most of them available to us.

Antibacterial Activity. Materials and Methods.—The *in vitro* bacteriostatic effect was determined by the conventional technique of the serial dilution test[11] in trypticase soy broth. The inoculum consisted of 0.05 ml. of a 10^{-3}-diluted, overnight broth culture, but in case of streptococci and pneumococci the same volume of a 10^{-1}-diluted culture was used. The tubes were read after 24-hr. incubation and verified by subculture on appropriate solid media.

The *in vivo* experiments for demonstration of local antibacterial activity were carried out in albino mice according to the technique of Grunberg, *et al.*[12] It consisted of a subcutaneous injection into the center of the abdominal wall of 0.2 ml. of 10^{-1}–$10^{-1.4}$ dilution of the culture dependent on previous titrations for tissue pathogenicity. This was followed by infiltration of the same area with 1 ml. of graded concentrations of the compound to be tested. At the end of a 24-hr. period the mice were sacrificed, presence or absence of local lesions noted, and cultures taken from the site of infection to determine whether viable organisms were present.

Systemic antistaphylococcal activity[13] was determined in groups of 10 mice infected intraabdominally with 0.5 ml. of a 10^{-3}–10^{-4} diluted suspension of *Staphylococcus aureus* Smith in 5% gastric mucin, corresponding to 100–1000 minimal lethal doses. The infection was followed by a single subcutaneous injection of the desired dilutions of the substances dissolved in saline solution. Groups of untreated mice served as controls. Cultures were taken from dead animals for

(11) E. Grunberg, L. O. Randall, and R. J. Schnitzer, *J. Pharmacol. Exptl. Therap.*, **95**, 336 (1949).

(12) E. Grunberg, R. J. Schnitzer, and C. Unger, *Yale J. Biol. Med.*, **20**, 479 (1948).

(13) R. J. Schnitzer, E. Grunberg, and W. F. DeLorenzo, *Antibiot. Ann.*, 785 (1959–1960).

TABLE I: MONOAMINES: $RCH_2CH_2CHZN(CH_3)\cdot AC$; R_1 = R_2 =

No.	R	Z	Y_1	Y_2	Ar	Prep. method	Yield, %	M.p., °C. or b.p. (mm.)	Recryst. solvent[a]	Empirical formula	Calcd., %: C	Calcd., %: H	Found, %: C	Found, %: H
1	R_1		H	CH_3		A	85	117–119 (5)[b]		$C_{24}H_{37}N$	80.31	13.00	80.00	12.84
2	R_2		CH_3	CH_3	HCl	B	90	189–190[c]	Et	$C_{15}H_{29}N\cdot HCl$	69.32	11.64	69.23	11.81
3	R_1	CH_2	H	CH_3	HCl	A	83[d]	122–124	An	$C_{14}H_{27}N\cdot HCl$	68.40	11.48	68.49	11.34
4	R_2	CH_2	CH_3	CH_3	HCl	B	85	150–151	An–E	$C_{16}H_{31}N\cdot HCl$	70.17	11.78	70.30	11.58
5	R_1		CH_3	CH_3	HCl	C	83	125–127	Et–E	$C_{15}H_{31}N\cdot HCl$	68.79	12.32	69.03	12.01
6	R_2	CH_2	CH_3	CH_3	HCl	C	75	159–160	A–P	$C_{16}H_{33}N\cdot HCl$	69.66	12.42	69.70	12.16
7	R_2		H	CH_2CH_2OH	HCl	A	68	94–95	A–E	$C_{13}H_{31}NO\cdot HCl$	64.81	11.61	64.62	11.77
8	R_2		CH_3	CH_2CH_2OH	HCl	B	65	77–79	An–E	$C_{16}H_{33}NO\cdot HCl$	65.86	11.74	65.87	11.49
9	R_1	$(CH_2)_3$	H	H	$(COOH)_2$[e]	A	59	158–160	Et–W	$C_{16}H_{31}N\cdot C_2H_2O_4\cdot 0.5H_2O$	64.26	10.19	63.99	9.92
10	R_1	$(CH_2)_3$	CH_2	CH_3	$(COOH)_2$	B	70	142–144	Et–E	$C_{18}H_{35}N\cdot C_2H_2O_4$	67.57	10.49	67.85	10.21
11	R_2	$(CH_2)_3$	CH_3	CH_3	$(COOH)_2$	C	80	150–151	Et–A–E	$C_{18}H_{37}N\cdot C_2H_2O_4$	67.19	10.99	67.00	10.69
12	R_1	$(CH_2)_3CH(CH_3)CH_2$	H	H	$(COOH)_2$[e]	A	58	138–140	A–W	$C_{19}H_{37}N\cdot C_2H_2O_4\cdot 0.5H_2O$	66.63	10.65	66.39	10.80
13	R_1	$(CH_2)_3CH(CH_3)CH_2$	CH_3	CH_3		B	85	150 (0.25)		$C_{21}H_{41}N$	82.01	13.44	82.06	13.22
14	R_2	$(CH_2)_3CH(CH_3)CH_2$	CH_3	CH_3	$(COOH)_2$	C	74	145–147	Et	$C_{21}H_{43}N\cdot C_2H_2O_4$	69.11	11.35	69.30	11.59

[a] A, acetone; An, acetonitrile; E, ether; Et, ethanol; P, petroleum ether (30–60°); W, water. [b] T. Kralt, H. D. Moed, and J. van Dijk, *Rec. trav. chim.*, **77**, 177 (1958), give b.p. 112–115° (1.5 mm.). [c] Free base, b.p. 127–128° (11 mm.) (see footnote *b*). [d] Yield of free base. [e] Obtained as the hemihydrate. [f] $n^{25}D$ 1.4759.

identification. The survivors were observed for 21 days.

Results.—All of the bis-quaternaries tested *in vitro* (Table VI) exhibited a moderate to marked effect against representative Gram-positive and Gram-negative bacteria. In disinfection experiments with *Staphylococcus aureus* 209, the phenol coefficient was determined by the Food and Drug Administration method. Furthermore, most of the compounds exhibited a moderate to marked effect against the local streptococcal and staphylococcal infections of mice. A somewhat different picture was noted in studies on the activity of penicillin G and 5-nitro-2-furfuraldehyde semicarbazone. Both agents exerted a marked activity against the streptococcal strain, but in the staphylococcal infection, neither agent was active. None of the compounds tested, including 5-nitro-2-furfuraldehyde semicarbazone, showed any activity against the local *Pseudomonas aeruginosa* infection.

When tested for their activity against the systemic staphylococcal infection of mice, the dihydroionyl bis-quaternaries (Table III) showed no activity whereas the tetrahydroionyl bis-quaternaries (Table IV), in which Y_1 and Y_2 were methyl and Z ranged from ethylene to decamethylene (**1–7, 13, 14**), as well as where Z was xylylene (**17**), showed an appreciable effect against the systemic staphylococcal infection. All other substances of the series (Table IV) were without antistaphylococcal effect.

Only one substance among the miscellaneous bis-quaternaries, namely, N,N′-bis[2-methyl-4-(2,2,6-trimethylcyclohexyl)butyl]-N,N′-dimethyl-1,6-hexanediamine bis(methobromide) (**1**), showed systemic antistaphylococcal activity. This is the homolog of N,N′-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-N,N′-dimethyl-1,6-hexanediamine bis(methochloride) (**7**, Table IV), which not only showed an appreciable local and systemic antibacterial activity in mice, but has also been tested clinically and found to be useful as a topical antimicrobial agent.[14,15]

Experimental[16]

Monoamines (Table I) and Diamines (Table II).—Most of the carbonyl compounds used as starting materials for the amines are known. β-Ionone was used in the preparation of [1-methyl-3-(2,6,6-trimethyl-1-cyclohexen-1-yl)propyl]methylamine (Table I, 1) and N,N′-bis[1-methyl-3-(2,6,6-trimethyl-1-cyclohexen-1-yl)propyl]-1,6-hexanediamine (Table II, 1). 2-Methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-buten-1-al[17] (β-C_{18}-aldehyde) was used in the preparation of 2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)butylamine (Table I, **3**) and N,N′-bis[2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-butyl]-1,4-butanediamine (Table II, **2**). *cis*-Tetrahydroionone[18] was used in the preparation of N-[2-hydroxyethyl)-1-methyl-3-(2,2,6-trimethylcyclohexyl)propylamine (Table I, **7**), N,N′-bis-[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-1,2-ethylenediamine (Table II, **6**) and N,N′-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-1,4-butanediamine (Table II, **8**). 4-Methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4-hexadien-1-al[19] (β-C_{23}-

(14) E. Edelson, E. Grunberg, and T. V. Marton, *Antibiot. Ann.*, 110 (1958–1959).

(15) E. Grunberg, E. Edelson, and R. J. Schmitzer, *Giorn. mal. infett. parassit.*, **12**, 607 (1960).

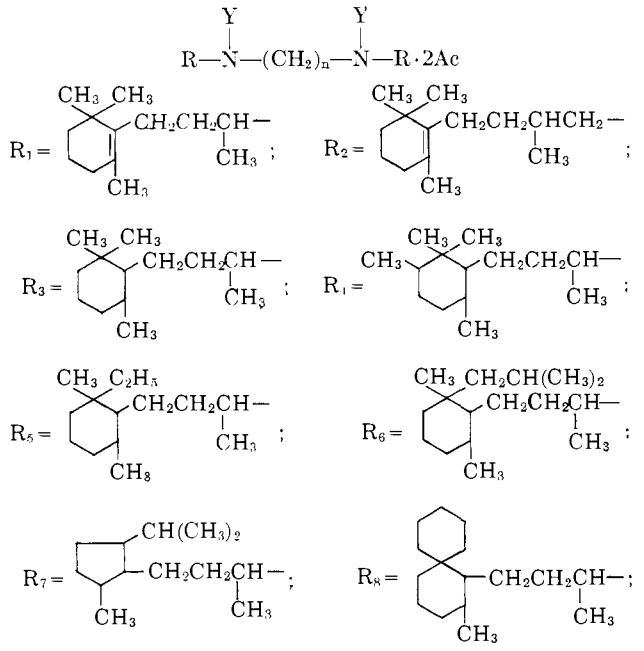
(16) All melting points were taken in a Thomas–Hoover melting point apparatus and are corrected.

(17) O. Isler, W. Huber, A. Ronco, and M. Kofler, *Helv. Chim. Acta*, **30**, 1911 (1947).

(18) A. Skita, *Ber.*, **45**, 3312 (1912); L. Ruzicka, *ibid.*, **2**, 359 (1969).

TABLE II

DIAMINES



$R_9 = (CH_3)_2CH(CH_2)_3CH(CH_2)_3CH(CH_3)CH_2-$; $R_{10} = (CH_3)_2CH(CH_2)_3CH(CH_2)_3CH(CH_2)_3CH(CH_3)CH_2-$

No.	R	Y	n	Ac	Prep. method	Yield, %	M.p., °C. or b.p. (mm.)	Recrystn. solvent[a]	Empirical formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1	R_1	H	6		D	62	210 (0.01)[b]		$C_{32}H_{60}N_2$	80.60	12.68	80.55	12.63
2	R_2	H	4		D	52	190 (0.02)[c]		$C_{32}H_{60}N_2$	81.28	12.79	81.42	12.84
3	R_2	CH_3	4	HCl	B	66	210–212	Et–A–E	$C_{34}H_{64}N_2 \cdot 2HCl$	71.14	11.59	70.87	11.41
4	R_3	H	6	HCl	C[d]	78	197–199	Et–E	$C_{32}H_{64}N_2 \cdot 2HCl$	69.90	12.10	70.10	12.12
5	R_3	CH_3	6	HCl	B	81	183–185	Et–An	$C_{34}H_{68}N_2 \cdot 2HCl$	70.67	12.21	70.37	11.81
6	R_3	H	2	$(COOH)_2$	D	71	210–213	Et-E	$C_{28}H_{56}N_2 \cdot 2C_2H_2O_4$	63.96	10.07	63.85	10.07
7	R_3	CH_3	2	$(COOH)_2$	B	65	206–207	W–Et–E	$C_{30}H_{60}N_2 \cdot 2C_2H_2O_4$	64.93	10.26	65.16	10.40
8	R_3	H	4	HCl	D	69	262–264	Et–E	$C_{30}H_{60}N_2 \cdot 2HCl$	69.08	11.98	68.92	11.86
9	R_3	CH_3	4	HCl[e]	B	73	205–207	An–E	$C_{32}H_{64}N_2 \cdot 2HCl \cdot 0.5H_2O$	68.78	12.09	68.90	11.87
10	R_4	H	6	HCl	D	64	162–164	C–E	$C_{34}H_{68}N_2 \cdot 2HCl$	70.67	12.21	70.47	11.93
11	R_4	CH_3	6	HCl[f]	B	84	116–118	A–E	$C_{36}H_{72}N_2 \cdot 2HCl \cdot H_2O$	69.31	12.28	69.37	11.99
12	R_5	H	6	HCl[e]	D	59	168–170	C–E	$C_{34}H_{68}N_2 \cdot 2HCl \cdot 0.5H_2O$	69.58	12.19	69.29	12.04
13	R_5	CH_3	6	HCl	B	89	182–184	Et–E	$C_{36}H_{72}N_2 \cdot 2HCl$	71.37	12.31	71.12	12.61
14	R_6	H	6	HCl	D	70	112–114	A	$C_{38}H_{76}N_2 \cdot 2HCl$	72.00	12.40	72.24	12.29
15	R_6	CH_3	6	HCl	B	49	173–174	Et–E	$C_{40}H_{80}N_2 \cdot 2HCl$	72.56	12.49	72.32	12.19
16	R_7	H	6	HCl	D	85	111–113	C–A	$C_{32}H_{64}N_2 \cdot 2HCl$	69.90	12.10	69.82	11.99
17	R_7	CH_3	6	HCl[e]	B	60	129–131	C–A	$C_{34}H_{68}N_2 \cdot 2HCl \cdot 0.5H_2O$	69.58	12.19	69.72	12.05
18	R_8	H	6	$(COOH)_2$[f]	D	42	156–158	W–Et	$C_{38}H_{72}N_2 \cdot 2C_2H_2O_4 \cdot H_2O$	66.80	10.41	67.10	10.48
19	R_8	CH_3	6	$(COOH)_2$[g]	B	68	90–92	Et–E	$C_{40}H_{76}N_2 \cdot 2C_2H_2O_4 \cdot 2H_2O$	65.94	10.57	66.01	10.27
20	R_9	H	6	HCl	D	74	150–152	C–A	$C_{32}H_{68}N_2 \cdot 2HCl$	69.40	12.74	69.74	12.48
21	R_9	CH_3	6	HCl	B	81	166–167	C–A–E	$C_{34}H_{72}N_2 \cdot 2HCl$	70.18	12.82	70.04	12.51
22	R_{10}	H	6	HCl	D	57	126–128	Et–An	$C_{42}H_{88}N_2 \cdot 2HCl$	72.65	13.07	72.98	13.10
23	R_{10}	CH_3	6	HCl	B	74	158–160	Et–An	$C_{44}H_{92}N_2 \cdot 2HCl$	73.16	13.12	72.88	12.92

[a] A, acetone; An, acetonitrile; C, chloroform; E, ether; Et, ethanol; W, water. [b] $n^{26}D$ 1.4932; T. Kralt, H. D. Moed, and J. van Dijk, *Rec. trav. chim.*, **77**, 177 (1958), give for the dihydrochloride, m.p. 169-170°. [c] $n^{27}D$ 1.4973. [d] Method D gave an 80% yield. [e] Obtained as the hemihydrate. [f] Obtained as the monohydrate. [g] Obtained as the dihydrate.

aldehyde) was used in the preparation of 4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)hexylamine (Table I, **9**). 2,6-Dimethyl-8-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6-octatrien-1-al[19] (β-C_{19}-aldehyde) served in the preparation of 2,6-dimethyl-8-(2,6,6-trimethyl-1-cyclohexen-1-yl)octylamine (Table I, **12**). *cis*-Tetrahydroirone[20] was used in the preparation of N,N'-bis[1-methyl-3-(2,2,3,6-tetramethylcyclohexyl)propyl]-1,6-hexanediamine (Table II, **10**). 4-(5-Isopropyl-2-methyl-1-cyclopentyl)-2-butanone[21] was employed in the preparation of N,N'-bis[1-methyl-3-(2-methyl-5-isopropylcyclopentyl)propyl]-1,6-hexanediamine (Table II, **16**). 6,10-Dimethyl-2-hendecanone[22] (hexahydropseudoionone) was used in the preparation of N,N'-bis(1,5,9-trimethyldecyl)-1,6-hexanediamine (Table II, **20**). 6,10,14-Trimethyl-2-pentadecanone[23] (hexahydrofarnesylacetone) was used in the preparation of N,N'-bis(1,5,9,13-tetradecyl)-1,6-hexanediamine (Table II, **22**). In a number of instances, the required saturated ketones were obtained from the known unsaturated ketones by hydrogenation at room temperature using a palladium-on-calcium carbonate catalyst. 4-(6-Ethyl-2,6-

(19) O. Isler, H. Lindlar, M. Montavon, R. Rüegg, and P. Zeller, *Helv. Chim. Acta*, **39**, 249 (1956).

(20) C. F. Seidel, H. Schinz, and L. Ruzicka, *ibid.*, **32**, 2115 (1949).

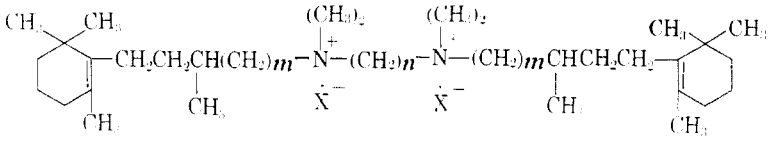
(21) W. Kimel, N. W. Sax, S. Kaiser, G. G. Eichmann, G. O. Chase, and A. Ofner, *J. Org. Chem.*, **23**, 153 (1958).

(22) F. G. Fischer and K. Löwenberg, *Ann.*, **475**, 189 (1929).

(23) F. G. Fischer, *ibid.*, **464**, 70 (1928).

TABLE III

DIHYDRODIONYL BIS-QUATERNARIES



No.	m	n	X	Prep. method	Yield, %	M.p., °C.	Recrystn. solvent[a]	Empirical formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1	0	2	Br	E	14	157–158	A–E	$C_{32}H_{62}Br_2N_2 \cdot H_2O$	58.86	9.88	58.93	9.73
2	0	3	Br	E	45	195–196	A–E	$C_{33}H_{64}Br_2N_2 \cdot 2H_2O$	57.89	10.01	57.96	9.76
3	0	4	Br	E	46	231–233	An–E	$C_{34}H_{66}Br_2N_2 \cdot 0.5H_2O$	60.80	10.07	60.97	10.05
4	0	5	Br	E	51	233–235	An–E	$C_{35}H_{68}Br_2N_2 \cdot 1.5H_2O$	59.71	10.05	59.83	9.85
5	0	6	Br	E	75	245–246	M–An–E	$C_{36}H_{70}Br_2N_2 \cdot H_2O$[b]	60.99	10.27	60.92	10.40
6	0	7	Br	E	47	218–219	Et–I	$C_{37}H_{72}Br_2N_2 \cdot 2H_2O$	59.98	10.34	60.17	10.20
7	0	10	Br	E	64	190–192	Et–A–E	$C_{40}H_{78}Br_2N_2 \cdot 1.5H_2O$	62.07	10.55	61.80	10.30
8	1	4	$O_3SC_6H_4CH_3(p)$	F	40	130–132	An–E	$C_{50}H_{84}N_2O_6S_2 \cdot 1.5H_2O$	66.73	9.74	66.60	9.77
9	1	6	Br	E	73	225–226	I	$C_{38}H_{74}Br_2N_2 \cdot 2H_2O$	60.45	10.41	60.35	10.19

[a] A, acetone; An, acetonitrile; E, ether; Et, ethanol; I, 2-propanol; M, methanol; P, petroleum ether (30–60°). [b] The presence of water of crystallization was demonstrated by infrared studies, carried out by Dr. Motchane and his staff of our physical chemistry laboratories.

dimethyl-1-cyclohexen-1-yl)-3-buten-2-one[24] was reduced to 4-(2,6-dimethyl-2-ethylcyclohexyl)-2-butanone, b.p. 121° (1.7 mm.); $n^{26}D$ 1.4715; yield, 93%.

Anal. Calcd. for $C_{14}H_{26}O$: C, 79.96; H, 12.47. Found: C, 79.65; H, 12.51.

This was used in the preparation of N,N'-bis[1-methyl-3-(2,6-dimethyl-2-ethylcyclohexyl)propyl]-1,6-hexanediamine (Table II, **12**). 4-(6-Isobutyl-2,6-dimethyl-2-cyclohexen-1-yl)-3-buten-2-one was reduced to 4-(2,6-dimethyl-2-isobutylcyclohexyl)-2-butanone, b.p. 96° (0.1 mm.); $n^{26}D$ 1.4670; yield, 83%.

Anal. Calcd. for $C_{16}H_{30}O$: C, 80.62; H, 12.68. Found: C, 80.91; H, 12.50.

This was applied to the preparation of N,N'-bis[1-methyl-3-(2,6-dimethyl-2-isobutylcyclohexyl)propyl]-1,6-hexanediamine (Table II, **14**). 2-Methyl-1-(3-oxo-1-buten-1-yl)-spiro[5.5]undec-2-ene[24] was reduced to 4-(2-methylspiro[5.5]undec-1-yl)-2-butanone, b.p. 93° (0.03 mm.); $n^{25}D$ 1.4980; yield 89%.

Anal. Calcd. for $C_{16}H_{28}O$: C, 81.30; H, 11.94. Found: C, 81.48; H, 11.66.

This was used in the preparation of N,N'-hexamethylene-bis-[1-methyl-3-(2-methylspiro[5.5]undec-1-yl)propylamine] (Table II, **18**).

Most of the monoamines and diamines are new, except as noted in Tables I and II.

2-Methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)butylamine Hydrochloride. Method A.—Compound **3** (Table I) is described as a representative example. To 310 g. (1.5 mole) of 2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-buten-1-al[17] and 200 ml. of liquid ammonia, dissolved in 800 ml. of methanol, was added 45 g. of Raney nickel catalyst. The mixture was hydrogenated at 150° and 107 kg./cm.² pressure. The catalyst was filtered, the excess ammonia and methanol distilled, and the residual oil fractionated *in vacuo*, to give 261 g. (83%) of 2-methyl-4-(2,6,6-trimethyl-1-cyclohexene-1-yl)butylamine, b.p. 94° (1.3 mm.), $n^{28}D$ 1.4850. Treatment with alcoholic hydrogen chloride gave the crystalline hydrochloride, m.p. 122–124°.

[2,6-Dimethyl-8-(2,6,6-trimethyl-1-cyclohexen-1-yl)octyl]-N,N-dimethylamine. Method B.—Compound **13** (Table I) is described as a representative example. To 60 g. (0.215 mole) of 2,6-dimethyl-8-(2,6,6-trimethyl-1-cyclohexen-1-yl)-octylamine (Table I, **12**), dissolved in 55.8 ml. (1.07 moles) of 90% formic acid, was added 41.2 ml. (0.468 mole) of 37% formaldehyde. The solution was stirred on a steam bath for 3 hr., then refluxed for 5 hr. The volatiles were distilled under water vacuum, and the residual oil made strongly alkaline with 15% potassium hydroxide and extracted with ether. The ether extract was washed with water, dried over potassium carbonate, and the ether was distilled. The residual oil was fractionated *in vacuo*, to give 43.5 g. (66%) of material, b.p. 150° (0.25 mm.).

[1-Methyl-3-(2,2,6-trimethylcyclohexyl)propyl]dimethylamine Hydrochloride. Method C.—Compound **5** (Table I) is described as a representative example. To 62 g. (0.24 mole) of [1-methyl-3-(2,6,6-trimethyl-1-cyclohexen-1-yl)propyl] dimethylamine hydrochloride (Table I, **2**), dissolved in 250 ml. of glacial acetic acid, was added 4 g. of platinum oxide. The mixture was hydrogenated at 100° and 71 kg./cm.² pressure. The catalyst was filtered and the colorless filtrate concentrated at steam temperature *in vacuo*. The residual sirup was triturated with ether and crystallized from ethanol–ether, to give 52.1 g. (83%) of product, m.p. 125–127°.

N,N'-Bis[2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-butyl]-1,4-butanediamine. Method D.—Compound **2**, (Table II) may serve as a representative example. Ninety-five grams (0.4 mole) of 2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-buten-1-al[17] and 17.6 g. (0.2 mole) of 1,4-diaminobutane were dissolved in benzene and placed in a flask fitted with a modified Dean-Stark constant water separator attached to a reflux condenser. The reaction mixture was vigorously refluxed until an aqueous layer no longer formed in the distillate. The benzene was distilled, and the residual oil was dissolved in 300 ml. of ethanol and added to 3 g. of 10% palladium-on-carbon. The mixture was hydrogenated at 50° and 3.2 kg./cm.² pressure. The catalyst was filtered, the solution concentrated, and the residual oil fractionated *in vacuo*, to give 49 g. (52%) of the diamine, b.p. 190° (0.02 mm.).

Bis-quaternaries (Tables III, IV and V).—All halogen derivatives used as starting materials for the preparation of the bis-quaternaries were known. When not commercially available, they were prepared according to the published literature procedures. Bis(2-bromoethyl)succinate was obtained from ethylene bromohydrin and succinic acid, according to the procedure of Walker,[25] and was used in the preparation of the succinic acid diester with (2-hydroxyethyl)dimethyl[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]ammonium bromide (Table IV, **21**). Bis(β-chloroethyl)amine hydrochloride, obtained from diethanolamine and thionyl chloride, according to the procedure of Ward,[26] was acetylated according to the method of Childs,[27] to give N,N-bis(2-chloroethyl)acetamide, which was used in the preparation of 4-acetyl-1,7-dimethyl-1,7-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]diethylenetriamine 1,7-bis(methyl chloride) (Table IV, **22**). Ethylene bis(chloroacetamide) was obtained from ethylenediamine and chloroacetyl chloride, according to the procedure of Jacobs and Heidelberger,[28] and used in the preparation of N,N'-ethylene bis{2-[1,N-dimethyl-3-(2,2,6-trimethylcyclohexyl)propylamine] acetamide}bis(methyl chloride) (Table IV, **23**). N,N'-Bis(chloroacetyl)hexamethylenediamine was obtained from chloroacetyl chloride and hexamethylenedi-

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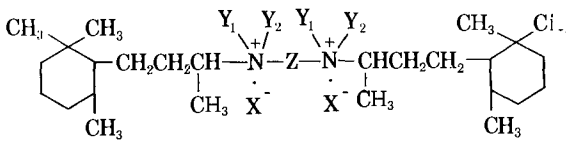
TABLE IV

TETRAHYDROIONYL BIS-QUATERNARIES



No.	Y_1	Y_2	X	Z	Prep. method	Yield, %	M.p., °C.	Recryst. solvent[a]	Empirical formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1	CH_3	CH_3	Br	$(CH_2)_2$	F	65	250–252	W–A	$C_{32}H_{66}Br_2N_2 \cdot H_2O$	58.51	10.44	58.78	10.23
2	CH_3	CH_3	Br	$(CH_2)_3$	E	60	214–216	An–E	$C_{33}H_{68}Br_2N_2$	60.73	10.50	60.43	10.52
3	CH_3	CH_3	Cl	$(CH_2)_4$	F	42	231–232	An–E	$C_{34}H_{70}Cl_2N_2$	70.67	12.21	70.58	12.17
4	CH_3	CH_3	Cl	$CH_2CH{=}CHCH_2$	E	69	217–219	W–A	$C_{34}H_{68}Cl_2N_2 \cdot 0.5H_2O$	69.82	11.89	69.64	12.02
5	CH_3	CH_3	Cl	$CH_2C{\equiv}CCH_2$	E	42	222–224	W–A	$C_{34}H_{66}Cl_2N_2 \cdot 2H_2O$	66.93	11.57	66.92	11.33
6	CH_3	CH_3	Br	$(CH_2)_5$	E	81	253–255	M–E	$C_{35}H_{72}Br_2N_2$	61.76	10.66	61.49	10.41
7	CH_3	CH_3	Cl	$(CH_2)_6$	F[b]	74[b]	255–257	Et–An–E	$C_{36}H_{74}Cl_2N_2$	71.37	12.31	71.29	12.20
8	C_2H_5	CH_3	Br	$(CH_2)_6$	F	39	194–196	A–E	$C_{38}H_{78}Br_2N_2$	63.15	10.87	62.97	10.62
9	C_2H_5	C_2H_5	Br	$(CH_2)_6$	H	18	195–196	C–A–E	$C_{40}H_{82}Br_2N_2 \cdot H_2O$	62.49	11.01	62.44	10.99
10	$HOCH_2CH_2$	CH_3	Br	$(CH_2)_6$	E	8	205–207	Et–A–E	$C_{38}H_{78}Br_2N_2O_2$	60.47	10.42	60.27	10.63
11	$C_6H_5CH_2$	CH_3	Br	$(CH_2)_6$	F	41	162–164	An–E	$C_{48}H_{82}Br_2N_2$	68.07	9.76	68.03	9.59
12	p-$NO_2C_6H_4CH_2$	CH_3	Br	$(CH_2)_6$	F	22	163–165	W–A	$C_{48}H_{80}Br_2N_2O_4 \cdot 0.5H_2O$	60.94	8.63	60.84	8.50
13	CH_3	CH_3	Br	$(CH_2)_8$	E	76	216–217	An–E	$C_{38}H_{78}Br_2N_2$	63.15	10.87	63.39	10.53
14	CH_3	CH_3	Br	$(CH_2)_{10}$	E	61	197–199	Et–A–E	$C_{40}H_{82}Br_2N_2$	63.99	11.01	64.04	11.10
15	CH_3	CH_3	Br	$(CH_2)_{11}$	E	51	89–91	A–B–E	$C_{41}H_{84}Br_2N_2 \cdot 0.5H_2O$	63.62	11.07	63.44	11.08
16	CH_3	CH_3	Br	$(CH_2)_{14}$	E	54	140–142	Bu–E	$C_{44}H_{90}Br_2N_2 \cdot 1.5H_2O$	63.34	10.87	63.63	11.01
17	CH_3	CH_3	Br	$CH_2C_6H_4CH_2$	E	63	227–229	Et–E	$C_{38}H_{70}Br_2N_2$	63.85	9.87	63.95	9.73
18	CH_3	CH_3	Cl	$CH_2CHOHCH_2$	E	40	185–187	An–E	$C_{33}H_{68}Cl_2N_2O \cdot 2H_2O$	64.36	11.79	64.33	11.56
19	CH_3	CH_3	Cl	$CH_2CH_2OCH_2CH_2$	E	19	202–204	A–E	$C_{34}H_{70}Cl_2N_2O \cdot 0.5H_2O$	67.73	11.88	68.03	11.78
20	CH_3	CH_3	Cl	$(CH_2)_2O(CH_2)_2O(CH_2)_2$	G	32[c]	190–192	An–A–E	$C_{36}H_{74}Cl_2N_2O_2$	67.80	11.70	67.56	11.89
21	CH_3	CH_3	Br	$(CH_2)_2COC(CH_2)_2COO(CH_2)_2$	E	23	185–187	Et–A–E	$C_{38}H_{74}Br_2N_2O_4$	58.30	9.53	58.43	9.53
22	CH_3	CH_3	Cl	$(CH_2)_2N(CH_2)_2$ $\vert$ $COCH_3$	E	9	192–194	Et–A–E	$C_{36}H_{73}Cl_2N_3O \cdot 2H_2O$	64.46	11.57	64.71	11.77
23	CH_3	CH_3	Cl	$CH_2CONH(CH_2)_2NHOCCH_2$	E	61	220–222	An–A–E	$C_{36}H_{72}Cl_2N_4O_2$	65.13	10.93	65.12	10.80
24	CH_3	CH_3	Cl	$CH_2CONH(CH_2)_6NHOCCH_2$	E	40	203–206	An–E	$C_{40}H_{80}Cl_2N_4O_2$	66.74	11.20	66.50	11.13

[a] A, acetone; An, acetonitrile; B, benzene; Bu, *t*-butyl alcohol; C, chloroform; E, ether; Et, ethanol; M, methanol; W, water. [b] Method G gave a 74% yield; method H gave an 11% yield. [c] Over-all yield; see Experimental section.

TABLE V: MISCELLANEOUS BIS-QUATERNARIES

$(CH_3)_2$ $(CH_3)_2$

R—N^+—$(CH_2)_n$—N^+—R

$2Br^-$ $2Br^-$

No.	R'	Prep. method	Yield, %	M.p., °C.	Recryst. solvent[a]	Empirical formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1	R_3CH_2—	E	65	235–237	Et–E	$C_{31}H_{38}Br_2N_2$	63.15	10.87	62.89	10.82
2	$R_3(CH_2)_3$—	E	81	213–215	C–A	$C_{42}H_{46}Br_2N_2$	64.71	11.13	64.78	11.13
3	$R_3(CH_2)_4CHCH_2$—	E	56	221–223	C–A	$C_{45}H_{50}Br_2N_2$	66.79	11.15	66.76	11.39
	CH_3									
4	R_3—	F	81	242–244	C–A	$C_{34}H_{38}Br_2N_2 \cdot H_2O$	60.60	10.87	64.83	10.65
5	R_3—	F	74	247–249	Et–E	$C_{38}H_{42}Br_2N_2 \cdot 0.5H_2O$	62.36	10.88	62.21	10.82
6	R_6—	F	81	220–222	Et–E	$C_{42}H_{46}Br_2N_2 \cdot 1.5H_2O$	62.51	11.12	62.76	11.20
7	R_7—	F	87	241–242	C–A	$C_{36}H_{42}Br_2N_2 \cdot 0.5H_2O$	61.43	10.71	61.71	10.72
8	R_8—	F	66	221–223	Et–E	$C_{42}H_{52}Br_2N_2 \cdot 3H_2O$	60.81	10.70	60.43	10.01
9	R_9—	F	90	226–228	C–A	$C_{36}H_{38}Br_2N_2$	64.87	10.25	64.58	11.29
10	R_{10}—	F	67	221–223	C–A	$C_{46}H_{58}Br_2N_2$	65.83	11.77	65.77	11.62

[a] R_2–R_{10} have structures as in Table II. [b] A, acetone; C, chloroform; E, ether; Et, ethanol.

TABLE VI: ANTIBACTERIAL ACTIVITY

	Toxicity[a] LD_{50} mg./kg.	In vitro minimal active concentration, γ/ml. *S. aureus*	*Strep. hemo.*	*Pneumococcus*	*E. coli*	*S. typhi*	Local antibacterial activity PD_{50}[b] γ/ml. subcutaneously *S. aureus*	*Strep. hemo.*	Systemic (oral) staphylococcal activity PD_{50}[c] mg./kg. subcutaneously
Compd. in Table III									
1	175.0	78.0	39.0	78.0	312.0	312.0	>100.0	325.0	>50.0
2	175.0	78.0	<9.8	39.0	39.0	78.0	106.5	35.1	
3	175.0	<9.8	<9.8	<9.8	39.0	39.0	11.8	16.5	>25.0
4	64.0	19.5	<9.8	19.5	<9.8	19.5	10.0	5.3	>25.0
5	175.0	19.5	<9.8	78.0	19.5	39.0			>50.0
6	203.0	<9.8	<9.8	<9.8	<9.8	19.5	28.9	3.5	
7	707.0	0.05	0.20	0.39	3.1	1.6	2.8	2.5	>125.0
8	38.0[d]	1.56	1.56	12.5	25.0	12.5	13.9	8.8	
9	375.0	19.0	78.0	312.5	39.0	78.0	9.7	5.1	>50.0
Compd. in Table IV									
1	125.0	1.56	0.39	0.39	6.25	6.25	12.0	8.9	19.6
2	175.0	1.56	3.12	12.5	25.0	12.5	5.1	3.9	13.1
3	134.0	0.6	0.3	0.3	2.5	2.5	10.0	100.0	16.9
4	75.0	31.25	7.8	7.8	7.8	31.3			19.1
5	82.0	1.56	0.39	0.39	6.25	6.25	5.0	5.0	11.3
6	130.0	0.62	0.78	1.56	0.78	1.56	7.5	2.8	23.0
7	151.0	0.31	0.15	3.12	6.3	3.1	6.2	1.6	16.1
8	33.0	0.6	0.3	2.5	19.5	39.0	12.5	2.1	>10.0
9	>500.0	0.31	19.5	<9.8	09.5	78.0	311.7	171.1	>50.0
10	330.0	1.25	1.25	5.0	2.5	7.5	>180.0		>50.0
11	>250.0	0.63	0.63	0.63	2.5	1.25	66.1	79.5	>125.0
12	>50.0	<9.8	<9.8	<9.8	39.0	156.6	5.2	2.8	>50.0
13	758.0	0.2	0.2	6.25	6.25	3.12	2.5	1.1	19.7
14	549.0	.03	.1	0.98	1.56	1.95	0.5	0.8	31.9
15	298.0	.16	1	0.67	2.5	1.25	1.2	1.1	>100.0
16	175.0	78	.4	0.4	3.12	3.12	5.0	150.0	>25.0
17	153.0	1.56	.39	6.25	6.25	12.5	6.6	1.6	22.1
18	250.0	5.0	1.25	39.0	10.0	5.0	35.6	17.0	>50.0
19	38.0						60.0	18.8	>50.0
20	84.0	<9.8	<9.8	<9.8	<9.8	<9.8	0.1	5.3	>25.0
21	432.0	6.3	6.3	3.0	12.5	12.5	25.0	7.7	>25.0
22	75.0	1.56	0.78	0.78	02.5	12.5	59.2	25.0	>50.0
23	375.0	<9.8	<9.8	<9.8	<9.8	<9.8	8.8	1.8	>125.0
24	150.0	0.3	0.3	0.3	0.3	0.3	2.2	3.1	>50.0
Compd. in Table V									
1	683.0	0.01	0.01	3.9	7.8	3.9	1.2	2.5	31.0
2	75.0	1.25	1.25	0.31	5.0	5.0	8.1	6.3	>50.0
3	85.0	10.0	1.25	0.63	10.0	10.0	50.0	25.0	>50.0
4	90.0	0.63	.08	1.25	5.0	5.0	3.0	8.1	>25.0
5	75.0	.63	.16	0.31	2.5	2.5	2.5	3.8	>25.0
6	30.0	.63	.63	1.25	5.0	5.0	2.6	1.1	>12.5
7	672.0	32	08	2.5	0.25	2.5	6.2	3.1	50.0
8	15.0	<9.8	<9.8	<9.8	<9.8	<9.8	7.1	7.2	>10.0
9	175.0	<9.8	<9.8	<9.8	<9.8	<9.8	1.0	2.3	>50.0
10	132.0	1.25	0.63	2.5	19.5	19.5	25.0	17.1	>50.0

[a] 50% lethal dose by the subcutaneous route. [b] 50% protective dose. [c] Treatment given intraduodenally.

amine, according to the procedure of Phillips,[29] and used in the preparation of N,N'-hexamethylene bis-{2-[1,N-dimethyl-3-(2,2,6-trimethylcyclohexyl)propylamino]acetamide}bis(methyl chloride) (Table IV, **24**). For the preparation of [ethylenebis(oxyethylene)]bis{dimethyl[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]}ammonium chloride (Table IV, **20**), 1,2-bis-(2-iodoethoxy)ethane was used as the starting material. The latter was prepared from the commercially available 1,2-bis(2-chloroethoxy)ethane ("triglycol dichloride") by treatment with sodium iodide in acetone.[30]

N,N'-Bis[1-methyl-3-(2,6,6-trimethyl-1-cyclohexen-1-yl)propyl]-N,N'-dimethyl-1,3-propanediamine Bis(methobromide) Dihydrate. Method E.—Compound **2** (Table III) is described as a representative example. [1-Methyl-3-(2,6,6-trimethyl-1-cyclohexen-1-yl)propyl]dimethylamine (13.4 g., 0.06 mole) (Table I, **2**) and 6.1 g. (0.03 mole) of 1,3-dibromopropane was dissolved in 150 ml. of ethanol and refluxed for 72 hr. The colorless solution was concentrated to a sirup at steam temperature and water vacuum. The sirup was triturated with ether and crystallized from acetone–ether, to give 9.3 g. (45%) of product, m.p. 195–196°.

N,N'-Bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-N,N'-dimethyl-1,6-hexanediamine Bis(methochloride). Method F.—Compound **7** (Table IV) may serve as a representative example. To 5 g. of N,N'-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-N,N'-dimethyl-1,6-hexanediamine (Table II, **5**), dissolved in 100 ml. of methanol, was added, at 4°, 10 g. of methyl chloride dissolved in 100 ml. of methanol. The solution was heated in a closed vessel at 60° for 15 hr. The colorless solution was concentrated and the resulting white solid crystallized from ethanol–acetonitrile–ether, to give 4.5 g. (74%) of material, m.p. 255–257°.

The synthesis of **[ethylenebis(oxyethylene)]bis{dimethyl[1-methyl-3-(2,2,6-dimethylcyclohexyl)propyl]}ammonium chloride** (Table IV, **20**) is an example of Method G.—To 18.5 g. (0.05 mole) of 1,2-bis(2-iodoethoxy)ethane,[30] dissolved in 150 ml. of acetonitrile, was added 24.8 g. (0.11 mole) of [1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]dimethylamine (Table I, **5**). After refluxing for 22 hr., the yellow solution was concentrated to a sirup, at steam temperature and water vacuum. The sirup was triturated with ether and crystallized from acetonitrile–ether, to give 16.5 g. (40%) of the diiodide, m.p. 206–207° dec.

Anal. Calcd. for $C_{36}H_{74}I_2N_2O_2$: C, 52.69; H, 9.09. Found: C, 52.99; H, 8.89.

To 9.85 g. (0.012 mole) of [ethylenebis(oxyethylene)]bis{dimethyl[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]}ammonium iodide suspended in 3 l. of water was added freshly precipitated silver chloride obtained from 25 g. (0.15 mole) of silver nitrate. The mixture was stirred vigorously for 4 hr. then filtered. The filtrate was concentrated and the resulting yellow gum crystallized from acetonitrile–acetone–ether, to give 6 g. (79%) of [ethylenebis(oxyethylene)]bis{dimethyl[1-methyl-3-(2,2,6-dimethylcyclohexyl)propyl]}ammonium chloride, m.p. 190–192°.

N,N'-Bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-N,N'-diethyl-1,6-hexanediamine Bis(ethobromide), Monohydrate. Method H.—Compound **9** (Table IV) is described as an example. To 19 g. (0.04 mole) of N,N'-bis[1-methyl-3-(2,2,6-trimethylcyclohexyl)propyl]-1,6-hexanediamine (Table II, **4**) and 65.5 (0.6 mole) of ethyl bromide, dissolved in 300 ml. of ethanol, was added 8.2 g. (0.08 mole) of anhydrous sodium carbonate. The mixture was heated, with shaking, in a closed vessel at 100° for 15 hr. The solids were filtered and the yellow colored filtrate concentrated to a sirup, at steam temperature and water vacuum. The sirup was extracted with chloroform and the extract taken to dryness. The residue was crystallized from chloroform–acetone–ether, to give 5.5 g. (18%) of product, m.p. 195–196°.

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(30) Procedure provided by Dr. L. M. Jampolsky; b.p. 92–97° (0.05 mm.), $n^{28}D$ 1.5383.

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Antiviral Activity of Glyoxals and Derivatives

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A series of aromatic, polyaromatic, and heterocyclic glyoxals have been prepared. These were treated with *p*-aminobenzoic acid to give a variety of products depending upon the reaction conditions. The chemical and antiviral properties of these compounds are discussed. Many of these compounds possess considerable *in ovo* activity against the herpes simplex virus and the influenza (PR-8) virus.

The antiviral activity of a series of glyoxals and derivatives was first disclosed by Underwood and co-workers.[2] This report, as well as subsequent papers[3–5] on the extension of this work, indicated that certain compounds of this type were effective against Newcastle disease virus (NJKD strain) and influenza virus (PR-8 strain) when administered to embryonated eggs. It was reported later[6] that the compounds did not possess antiviral activity in animals. Shortly thereafter, de Bock and co-workers[7] observed that a series of α,β-dicarbonyl derivatives possessed growth-inhibiting activity toward influenza virus A-USA-47 (A'-strain former designation FM_1). Cavallini and co-workers[8] more recently extended this study to biphenylyl glyoxals and derivatives. Many of these compounds exhibited *in vitro* activity and several were reported to have *in vivo* activity against influenza virus A-PR-8 and hepatitic virus MHV_3. Some of these compounds

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