1,5-Dicyano-8,10-dimethyl-9-oxa-3-azaspiro[5.5]undecane-2,4-dione.—Condensation of 66 g. of 2,6-dimethyltetrahydro-γ-pyrone with 2 molar equiv. (117 g.) of ethyl cyanoacetate in an excess of saturated anhydrous ammonia in absolute alcohol for 5 days at 5° yielded 87 g. of the ammonium salt of the dicyanoimide. This was dissolved in a minimum of boiling water and acidified with concd. hydrochloric acid. Cooling overnight in the refrigerator and filtering yielded 63 g. of the dicyanoimide (m.p. 230–231°). Recrystallization from water resulted in a product, m.p. 231–232°.

3,5-Dimethyl-4-oxacyclohexane-1,1-diacetic Acid.—Hydrolysis of the dicyanoimide with 40–60% sulfuric acid resulted in poor yields of the desired acid due to destruction of the pyrone ring by the sulfuric acid. The desired acid was obtained by stepwise hydrolysis as follows: the imide was boiled for several hours with a 2% aqueous solution of sodium hydroxide until ammonia ceased to be evolved. This procedure ruptured the imide ring. The resultant solution was concentrated under reduced pressure and the hydrolysis completed either by (A) boiling with 15% NaOH or (B) concd. hydrochloric acid. The acid was extracted by continuous ether extraction overnight. This yielded the tetracarboxylic acid mixed with the desired dicarboxylic acid. The mixture of acids was heated slowly until effervescence of carbon dioxide ceased (decarboxylation of the tetracarboxylic acid), cooled, and recrystallized from water after treating with decolorizing charcoal. The crude acid melted at 137–141° by either alternative hydrolysis procedure. On recrystallization from acetone–petroleum ether, it melted at 155–156°.

3,5-Dimethyl-4-oxacyclohexane-1,1-diacetic Acid Anhydride.—The anhydride was formed by treating the acid with excess acetic anhydride and vacuum distilling the residue. The resultant anhydride boiled at 132–137° (0.04 mm.) and melted at 110–111°.

1,5-Dicyano-8-thia-3-azaspiro[5:4]decane-2,4-dione.—At 0°, a mixture of 30 g. of 3-ketotetrahydrothiophene and 68 g. of ethyl cyanoacetate was added to 200 ml. of alcohol which had previously been saturated with ammonia at 0°. The reaction vessel with stopper wired down was allowed to stand for 1 week and filtered. After washing the product with a little alcohol–ether mixture, the ammonium salt was dissolved in a minimum amount of water and acidified with hydrochloric acid. The product was filtered, dried, and recrystallized from ethanol water. It weighed 20 g. and melted at 221–222°. When attempts were made to hydrolyze this product to the diacetic acid with sulfuric acid, extensive decomposition occurred.

1,5-Dicyano-9-thia-3-azaspiro[5:5]undecane-2,4-dione.—Fifty g. of penthianone and 98 g. of ethyl cyanoacetate were mixed, cooled, and added to a solution of 400 ml. of alcohol saturated with ammonia at 0°. The stopper was wired down. After standing in a cold room for 1 week, the mixture was filtered and washed with an alcohol–ether mixture. When almost dry, the precipitate was dissolved in a minimum amount of hot water and acidified with hydrochloric acid. The solution was cooled and the product filtered off. It weighed 32 g. and on recrystallization from alcohol–water melted at 208–210°.

4-Thiacyclohexane-1,1-diacetic Acid.—The above dicyanoimide (30 g.) was refluxed with 200 ml. of concd. hydrochloric acid for 24 hr. There was a large amount of material which did not go into solution. The mixture was filtered hot and 16 g. of material was collected. This was only partly hydrolyzed material and is described below. The filtrate was cooled and 10.5 g. of off-white crystals were collected which melted at 172–173°. Recrystallization from water raised the melting point to 174–175°.

The 16 g. of insoluble partly hydrolyzed material obtained above did not melt at 360° and was insoluble in ether, alcohol, water, and most of the usual organic solvents. It did dissolve in sodium hydroxide. In conjunction with infrared spectra, it is believed that this material is the internal imide of 9-thia-3-azaspiro[5:5]undecane-2,4-dione formed at positions 1 and 5 from 9-thia-3-azaspiro[5:5]undecane-1-carboxy-5-carbanido-2,4-dione.

Anal. Calcd. for $C_{11}H_{12}N_2O_4S$: C, 49.23; H, 4.51; N, 10.44; S, 11.95. Found: C, 49.37; H, 4.60; N, 10.61; S, 11.61.

Cyclopropane Methonium Compounds[1]

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In a study of the effect of limiting the flexibility of the chains of methonium compounds on the pharmacological actions of certain stereoisomers, analogs of hexamethonium and succinylcholine carrying a *cis* or *trans* oriented cyclopropane ring in the center of the chain were synthesized. The geometric isomers of bis(trimethylammoniumethyl)cyclopropane-1,2-dicarboxylate and of the homologous cyclopropane-1,2-diacetate ester diiodides caused predominantly neuromuscular block and resembled succinylcholine. The geometric isomers of 1,2-di-(β-trimethylammoniumethyl)cyclopropane diiodide exerted primarily ganglionic blockade of the hexamethonium type. The *trans* isomer was the more potent in each case.

The methonium compounds have provided relatively simple examples for the study of quantitative and qualitative differences in biological response depending on chain length and intramolecular distances between onium centers.[2] On the whole, linear chains of 5 to 7 carbon atoms [or their equivalent such as —O—, —N(CH$_3$)—] favor ganglionic blocking activity, while 9–11 chain atoms produce primarily agents which depolarize the cholinergic end plate. Longer alkyl chains lead to surface active agents although a bulky aromatic substituent in the middle of the chain may under some circumstances increase curaremimetic activity up to 13 chain atoms; at this chain length increases of the blood pressure may be observed.[3] However, ganglionic blocking is optimal also when a methonium ion is separated from another ammonium group by only two carbon atoms, provided that this other ammonium nitrogen is shielded by the bulk of surrounding structures.[4] The inactivity of *p*-(CH$_3$)$_3$N$^+$C$_6$H$_4$CH$_2$N$^+$(CH$_3$)$_3$ and similar rigid structures in

(1) This research was supported by Grant B-1445 from the Institute of Neurological Diseases and Blindness, National Institutes of Health, U. S. Public Health Service.

(2) (a) R. B. Barlow and R. H. Ing, *Nature*, **161**, 718 (1948); *Brit. J. Pharmacol.*, **3**, 298 (1948); (b) I. E. Balaban, M. B. Levy, and B. E. Wilde, *J. Pharm. Pharmacol.*, **1**, 603 (1949); (c) W. D. M. Paton and E. J. Zaimis, *Nature*, **161**, 718 (1948); for reviews, see, for example, A. Burger, *Farmaco. (Pavia) Ed. Sci.*, **10**, 47 (1955); K. Nador, *Progr. Drug Res.*, **2**, 297 (1960).

(3) W. T. Smith, Jr. and J. W. Ryan, *J. Org. Chem.*, **26**, 3856 (1961); cf. A. P. Phillips, *J. Am. Chem. Soc.*, **77**, 2400 (1955).

(4) J. H. Trapold, A. J. Plummer, and J. A. Schneider, *J. Pharmacol. Expll. Therap.*, **113**, 50 (1955); **115**, 172 (1955).

ganglionic blockade[5] led Gill[6] to postulate that there is a range of interreceptor distances, and for maximum blocking action of a compound there must be a corresponding range of inter-quaternary distances as would be provided by a flexible molecule. These conclusions are similar to those of Sörum,[7] who demonstrated *cis*-oid and *trans*-oid conformations of acetylcholine, and suggested that the biphasic activity of this hormone may be explained by conformational changes.

Flexibility can be preserved, with a certain limitation on random conformations of extended methonium chains, by insertion of a sterically rigid linkage at least two carbons removed from the quaternary groups. Biel[8] noted that hypotensive activity was increased in 3-hexyne-1,6-bis-trimethylammonium dibromide over that of hexamethonium while *cis*-3-hexene-1,6-bis-trimethylammonium dibromide had no activity. We have now prepared the corresponding *trans* isomer (I). The internitrogen distance for I is 8.90 Å., for the *cis* isomer, 7.20 Å. Compound I exhibits ganglionic blocking activity.

Our objective is to report the preparation and properties of several methonium compounds which contain a cyclopropane ring at the center of the chain. Depending on the configuration at the cyclopropane ring, their onium groups are spaced differently (Table I). It appeared interesting to study whether these differences would affect cholinergic properties and thus aid in appraising steric features of the cholinergic receptor site.

Synthesis.—For the synthesis of *trans*-3-hexene-1,6-bistrimethylammonium dibromide, diethyl *trans*-3-hexene-1,6-dioate[9] was reduced to *trans*-3-hexene-1,6-diol in a manner more convenient than reported before.[10] This diol was converted to the corresponding 1,6-dibromo compound and hence to the bisquaternary salt.

cis-1,2-Di-(β-trimethylammoniumethyl)cyclopropane was described recently by Vogel, *et al.*,[11] but before that time we attempted to synthesize this compound by another route. *cis*-1,2-Cyclopropanediacetonitrile[12] was hydrogenated catalyti ally to *cis*-1,2-di-(β-aminoethyl)cyclopropane, this diamine was methylated by the Eschweiler–Clarke modification of the Leuckart reaction, and the bis-tertiary amine was quaternized with methyl iodide. The dimethiodide thus obtained was identical by direct comparison with a sample of *cis*-1,2-di-(β-trimethylammoniumethyl)cyclopropane diiodide kindly provided by Prof. Vogel. A previous attempt to synthesize the same quaternary compound by a different route did not furnish this material. *cis*-1,2-Cyclopropanediacetic acid was prepared by the method of Hofmann, *et al.*,[13] and reduced to *cis*-1,2-di-(β-hydroxyethyl)cyclopropane. When this diol was brominated with phosphorus tribromide, an oily product, presumably *cis*-1,2-di-(β-bromoethyl)-cyclopropane, was formed. On standing with excess methanolic trimethylamine at 25° for two weeks, this dibromide yielded 73% of a crystalline compound which analyzed for *cis*-1-(β-bromoethyl)-2-(β-trimethylammoniumethyl)cyclopropane bromide. Its infrared spectrum (670–4000 cm.$^{-1}$) was in agreement with this interpretation. A model of this compound indicates that the reactivity of its bromoethyl group could be restricted by the proximity of the quaternary ammonium group. In an effort to overcome this hindrance, the monoquaternary halide was heated at 100° with excess trimethylamine under pressure for 7 days. From the reaction mixture, about 20% of tetramethylammonium bromide was isolated as well as a waxy material which was characterized as a dipicrate, $C_{11}H_{24}N_2 \cdot 2C_6H_3N_3O_7$. It was not identical with the dipicrates of either *cis*- or *trans*-1,2-di-(β-dimethylaminoethyl)cyclopropane.

For the synthesis of *trans*-1,2-bis(β-trimethylammoniumethyl)cyclopropane, *trans*-1,2-cyclopropanediacetonitrile was synthesized from *trans*-1,2-cyclopropanedicarboxylic acid in four steps analogous to those described by Vogel, *et al.*, for the *cis* isomer.[11,14] Hydrogenation over Raney nickel as in the *cis* series gave *trans*-1,2-di-(β-aminoethyl)cyclopropane. The structure of this diamine was proved by the identity of its di-*p*-aminobenzoate salt with that obtained by sodium and ethanol reduction of the dinitrile, conditions known to leave the cyclopropane ring intact in the reduction of similar nitriles.[15,16] The subsequent steps for the conversion of the *trans*-di-(β-aminoethyl) compound to *trans*-1,2-bis(β-trimethylammonium)cyclopropane were the same as those in the *cis* series.

Choline esters of *cis*- and *trans*-1,2-cyclopropanedicarboxylic and -diacetic acids were obtained *via* the bis-acid chlorides, the bis(β-dimethylaminoethyl) esters, and quaternization of these derivatives with methyl iodide.

Pharmacology.—Biological testing and interpretation of the test data were contributed by Mr. Robert G. Hauser and Dr. Floyd R. Domer, Department of Pharmacology, University of Cincinnati, College of Medicine, to whom we are very grateful for permission to quote their results.

LD_{50} values were determined on intraperitoneal injection of the compounds into mice weighing 20–35 g. In anesthetized dogs, arterial pressure (mercury manometer) and twitches of the leg muscles on maximal nerve stimulation were recorded. Chicks (3 days old) received the compounds through the jugular vein. Responses of the nictitating membrane to pre- and postganglionic maximal stimulation were recorded in anesthetized cats.

The LD_{50} values were: I, 75 mg./kg.; III, 3 mg./kg.; V, 6 mg./kg.; XI, 100 mg./kg.; XIII, 30 mg./kg.; XV, >100 mg./kg.; XVII, 85 mg./kg. Aqueous solutions of the compounds were stable for over 1 hr. except that of XV which decomposed over 15 min. as judged by its effects on the mice. Death by respiratory paralysis occurred within 10 min.; muscular fasciculations were noted with III and XIII.

Up to doses of 1 mg./kg. for III and V, and 5 mg./kg. for XIII and XVII, these compounds were similar in their effects. They did not affect the response of the nictitating membrane of the cat to preganglionic stimulation. They had little effect on the arterial pressure of the dog, in doses up to 100 μg./kg. for III, XIII, and

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(6) E. W. Gill, *Proc. Roy. Soc.* (London), **B150**, 381 (1959).
(7) H. Sörum, *Acta Chem. Scand.*, **13**, 345 (1959).
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(9) This compound had been previously prepared by a different route; H.-F. Piepenbrink, *Ann. Chem.*, **572**, 83 (1951).
(10) R. A. Raphael and C. M. Roxbury, *J. Chem. Soc.*, 3875 (1952).
(11) E. Vogel, K.-H. Ott, and K. Gajek, *Ann. Chem.*, **644**, 172 (1961).
(12) We thank Prof. Vogel for advance notice of the synthesis of this compound.
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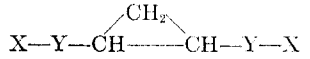
(14) Prof. Vogel advised us privately of the validity of these steps in the *trans* series and reported in his letter the melting point, 117–118°, for his *trans*-1,2-cyclopropanediacetic acid.
(15) J. von Braun, M. Kühn, and S. Siddiqui, *Ber.*, **59**, 1081 (1926).
(16) J. D. Roberts and R. H. Mazur, *J. Am. Chem. Soc.*, **73**, 2509 (1951).

TABLE I



CYCLOPROPANE METHONIUM COMPOUNDS

	X	Y	Yield, %	M.p., °C (corr.) B.p., °C (mm.)	Composition	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	A[o]
II	$N(CH_3)_2$	*trans*-$CO_2(CH_2)_2$[a]	89									
	·Dipicrate	[b]		163–164[f]	$C_{28}H_{30}N_8O_{15}$			15.33			15.44	
III	$N^+(CH_3)_3 \cdot 2I^-$	*trans*-$CO_2(CH_2)_2$[c]		254.5–256 dec.	$C_{16}H_{30}I_2N_2O_4$	32.38	5.44		32.53	5.55		13.67
IV	$N(CH_3)_2$	*cis*-$CO_2(CH_2)_2$[e]										
	·Dipicrate	[b,d]		132–133[n]	$C_{28}H_{30}N_8O_{18}$	41.10	4.11	15.33	40.37	4.54	15.44	
V	$N^+(CH_3)_3 \cdot 2I^-$	*cis*-$CO_2(CH_2)_2$[f]		193–195 dec.	$C_{16}H_{30}I_2N_2O_4$	32.38	5.44		32.66	5.48		10.07
VI	*p*-$OSO_2C_6H_4CH_3$	*trans*-CH_2	80	62–64	$C_{18}H_{22}O_6S_2$	55.59	5.40		55.84	5.62		
VII	CN	*trans*-CH_2	73	136–139 (1)[g]	$C_7H_9N_2$	69.97	6.71		69.59	7.35		
VIII	CO_2H	*trans*-CH_2	93[h]	118–119	$C_5H_{10}O_4$	53.16	6.38		53.04	6.48		
IX	NH_2	*trans*-$(CH_2)_2$	72	93–95(1)								
	·Di-*p*-aminobenzoate[i]			185–186	$C_{21}H_{26}N_4O_4$	62.67	7.52	13.92	62.44	7.58	13.94	
X	$N(CH_3)_2$	*trans*-$(CH_2)_2$	52	72–73 (1)[j]								
	·Di-HCl			242–244[f]	$C_{12}H_{26}Cl_2N_2$	51.56	10.20		51.39	9.93		
	·Dipicrate			152.5–154.5[b,e]	$C_{28}H_{30}N_8O_{14}$			17.50			17.37	
XI	$N^+(CH_3)_3 \cdot 2I^-$	*trans*-$(CH_2)_2$		262–264[d]	$C_{18}H_{34}I_2N_2$	33.35	6.46	5.99	33.71	6.62	6.00	9.15
XII	$N(CH_3)_2$	*trans*-$CH_2CO_2(CH_2)_2$	80[k]									
	·Dipicrate			173–174[f]	$C_{32}H_{34}N_8O_{18}$	42.74	4.51	14.78	42.74	4.98	14.60	
XIII	$N^+(CH_3)_3 \cdot 2I^-$	*trans*-$CH_2CO_2(CH_2)_2$		208–209 dec.[d]	$C_{17}H_{34}I_2N_2O_4$	34.94	5.86		34.80	5.64		16.20
	NH_2	*cis*-$(CH_2)_2$	65[l]	93–95 (2.5)								
	·Di-*p*-aminobenzoate			204–205.5 dec.[b]	$C_{21}H_{26}N_4O_4$	62.67	7.51		62.35	7.01		
XIV	$N(CH_3)_2$	*cis*-$(CH_2)_2$	55[m]	97–99 (4)								
	·Di-HCl			276–277[b]	$C_{12}H_{26}Cl_2N_2$	51.56	10.20		51.91	10.18		
	·Dipicrate			151–152[n]	$C_{28}H_{30}N_8O_{14}$	43.00	4.71		42.03[q]	4.87		
XV	$N^+(CH_3)_3 \cdot 2I^-$	*cis*-$(CH_2)_2$[e]		281–282[n]								7.53
XVI	$N(CH_3)_2$	*cis*-$CH_2CO_2(CH_2)_2$	58[o]									
	·Dipicrate			150–152[r]	$C_{27}H_{34}N_8O_{18}$			14.78			14.57	
XVII	$N^+(CH_3)_3 \cdot 2I^-$	*cis*-$CH_2CO_2(CH_2)_2$		192–194[b]	$C_{17}H_{34}I_2N_2O_4$	34.94	5.86		34.91	5.56		15.07
	Hexamethonium											9.33
	Decamethonium											14.60
	Succinylcholine											13.73

[a] From *trans*-1,2-cyclopropanedicarboxylic acid [K. B. Wiberg, R. K. Barnes, and J. Albin, *J. Am. Chem. Soc.*, **79**, 4994 (1957)] (0.02 mole) and thionyl chloride (0.08 mole), 3 hr. at reflux, then treatment with 0.06 mole of dimethylaminoethanol in 10 ml. of dry ether with cooling over 3 hr., and work-up. [b] Recrystallized from EtOH. [c] From the tertiary amine with methyl iodide in acetone. [d] Recrystallized from MeOH. [e] From *cis*-1,2-cyclopropanedicarbonyl chloride [F. Fichter and H. Spiegelberg, *Helv. Chim. Acta.*, **12**, 1152 (1929)] as in [a]. [f] Recrystallized from MeOH–HEtOAc. [g] $n^{23}D$ 1.4670. [h] From VII by hydrolysis with boiling 20% aqueous NaOH solution for 3 hr. Colorless needles.[14] [i] Prepared in ether solution, white needles from ethanol. [j] $n^{20}D$ 1.4460. [k] From *trans*-1,2-cyclopropanediacetic acid as in footnote *a*. [l] From *cis*-1,2-cyclopropanediacetonitrile[11] as described for the *trans* isomer (IX). [m] From XIV with formic acid and formaldehyde (see X). [n] Undepressed on admixture with a sample provided by Prof. E. Vogel. [o] From *cis*-1,2-cyclopropanediacetic acid[13] as described in footnote *a*. [p] Measured with Stuart and Briegleb Molecular Models, A. S. La Pine Co., Chicago 29, Illinois. [q] Only a 2 mg. sample was available for analysis. [r] Mixture melting point with XIV dipicrate was 129–140°.

XVII, and 750 μg./kg. for V. All 4 compounds blocked the twitches of the leg muscles on stimulation of the sciatic nerve in the dog; potency varied in the following order: III > XIII > XVII = succinylcholine > V. Succinylcholine produced complete block at 100 μg./kg., the effects disappearing within about 5 min. In the chick, all 5 compounds caused opisthotonus when given in these doses.

Compounds XI and XV resembled each other in their effects, and as far as it was tested, I had similar actions. The first two compounds did not diminish the responses of the leg muscles to stimulation of the sciatic nerve in the dog or induce opisthotonus in the chick, in doses up to 1 mg./kg. for XI and 5 mg./kg. for XV. At 1 mg./kg. all 3 compounds elicited a fall of arterial blood pressure in the dog similar in degree as elicited by 1 mg./kg. of hexamethonium. A similar degree of block of the nictitating membrane of the cat to preganglionic (but not to postganglionic) nerve stimulation was produced by 5 mg./kg. of XV and 1 mg./kg. of XI. The effect of XV in both cat and dog lasted only a few minutes, whereas those of XI were like those of hexamethonium in lasting more than 1 hr.

The predominant action of III, V, XIII, and XVII is neuromuscular block. These compounds resemble succinylcholine but are of varying potency. The predominant action of XI and XV is ganglionic blockade, and these two compounds resemble hexamethonium; XV is unstable *in vivo* and *in vitro*. The *trans* isomer was the more potent in each case, the difference being most striking between III and V. The similarity of the spacing of the onium heads in III and succinylcholine is noteworthy in this connection.

Experimental

Melting points are corrected, boiling points uncorrected. Microanalyses by Miss W. Sheffield, and Alfred Bernhard, Mühlheim, Germany. For physical and analytical data of cyclopropane compounds, see Table I.

Diethyl *trans*-3-Hexene-1,6-dioate.—Into a solution of 10.6 g. (0.1 mole) of *trans*-1,4-dicyano-2-butene[17] in 123.6 ml. of 97.1% ethanol, dry hydrogen chloride was passed for 3 hr. The solution was cooled, filtered from ammonium chloride, the filtrate was mixed with an equal volume of a saturated sodium chloride solution, and extracted with four 100 ml. portions of ether. The ether extracts were washed with saturated potassium carbonate solution and water, dried, and distilled. The main fraction, b.p. 122–124° (8 mm.); $n^{26}D$ 1.4401, weighed 12.6 g. (63%); lit.,[9] b.p. 133–135° (14 mm.).

***trans*-3-Hexene-1,6-diol.**—To a stirred slurry of lithium aluminum hydride (14.3 g.) in anhydrous ether (400 ml.) was added dropwise with cooling a solution of diethyl *trans*-3-hexene-1,6-dioate (25 g.) in anhydrous ether (500 ml.) over a period of 1.5 hr. The mixture was then gently refluxed for 2 hr., cooled, and water (16 ml.) slowly added followed by the calculated amount of 20% sulfuric acid. The ether layer was separated and the aqueous layer extracted with ether (5 × 100 ml.). The ether layer and extracts were combined, dried over anhydrous sodium sulfate, and the ether was evaporated. The oily residue

(17) P. Kurtz, *Ann. Chem.*, **631**, 21 (1960). *trans*-1,4-Dibromo-2-butene [E. M. Shantz, *J. Am. Chem. Soc.*, **68**, 2553 (1946)] in one-half volume of dioxane was used in place of the 1,4-dichloro compounds.

on distillation gave a main fraction (9.2 g., 63.5%), b.p. 112–115° (2 mm.), $n^{26}D$ 1.4726. The bisphenylurethane melted at 160–161°. Lit.[10] b.p. for *trans*-3-hexene-1,6-diol, 88–90° (0.3 mm.), $n^{18}D$ 1.4747 (prepared by a different route). Lit. m.p. for the bisphenylurethane, 161–162°.

***trans*-3-Hexene-1,6-bistrimethylammonium Dibromide (I).**—A solution of 5.8 g. (0.05 mole) of *trans*-3-hexene-1,6-diol in 2.6 g. (0.063 mole) of dry pyridine was cooled to −30°, and 9 g. (0.033 mole) of phosphorus tribromide was added dropwise with stirring at −20 to −10°. After another hour at −10° the mixture was distilled and 7.0 g. (58%) of *trans*-1,6-dibromo-3-hexene, b.p. 84–85° (5 mm.); $n^{28}D$ 1.5228, was collected.[18] This oil was dissolved in 25 ml. of ether, cooled to −40°, 25 ml. of a 25% methanolic solution of trimethylamine was added, and the solution was allowed to stand in a pressure bottle at 25° for 5 days. The precipitated colorless solid was filtered off and recrystallized from ethanol. The colorless needles, m.p. 279–281° dec., represented *trans*-3-hexene-1,6-bis-trimethylammonium dibromide sesquihydrate (6.7 g., 71%).

Anal. Calcd. for $C_{12}H_{28}Br_2N_2 \cdot 1.5\ H_2O$: C, 37.23; H, 8.07. Found: C, 37.34, 37.07; H, 8.19, 8.14.

The **dipicrate** was prepared in aqueous solution and recrystallized from acetone; yellow needles, m.p. 263–264°.

Anal. Calcd. for $C_{24}H_{32}N_8O_{14}$: C, 43.90; H, 4.91. Found: C, 43.49; H, 5.11.

The dibromide (0.35 g.) was saturated by hydrogenation in methanolic solution over a palladium oxide catalyst at room temperature and pressure. One mole of hydrogen was absorbed, and the product was purified by crystallization from ethanol. Colorless needles (0.32 g., 91%), m.p. 272–273° dec. Hexamethonium dibromide melts at 272° dec.[2b]

***trans*-1,2-Cyclopropanedimethyl Ditosylate (VI).**—To a solution of 60 g. of *p*-toluenesulfonyl chloride in 120 ml. of dry pyridine at −5° was added a solution of 14 g. of *trans*-1,2-di-(hydroxymethyl)cyclopropane in 28 ml. of dry pyridine over a period of 30 min. After standing for another hour at −10 to −5°, the mixture was poured into ice water, most of the pyridine was neutralized with 25% sulfuric acid, and the precipitated white solid was filtered and recrystallized from methanol.[19]

***trans*-1,2-Cyclopropanediacetonitrile (VII).**—A solution of VI (40 g.) and 50 g. of sodium iodide in 280 ml. of acetone was stirred and refluxed for 1 hr., sodium *p*-toluenesulfonate was filtered off, the filtrate concentrated, and the residue dissolved in water and extracted with ether. The ether extracts were washed with sodium thiosulfate solution, dried, and evaporated. The residual oily *trans*-1,2-di(iodomethyl)cyclopropane (28 g.) was dissolved in 140 ml. of ethanol and treated, with stirring, with a solution of 22 g. of potassium cyanide in 35 ml. of water. The mixture was refluxed for 4 hr., concentrated *in vacuo* to 50 ml., and extracted with ten 50-ml. portions of ether.

***trans*-1,2-Di-(β-aminoethyl)cyclopropane (IX).**—(a) A saturated ammoniacal methanolic solution (350 ml.) of VII (4 g.) was hydrogenated with Raney nickel at 3 kg./cm.² for 12 hr.; the catalyst was filtered and the oily residue distilled. (b) To a solution of 1.2 g. of VII in absolute ethanol (100 ml.) was added sodium (2.5 g.) in small pieces, a steady evolution of hydrogen being maintained. Then concentrated hydrochloric acid was added to pH 1; the mixture was concentrated *in vacuo* and ether extracted. The ether solution was concentrated, neutralized with ethereal *p*-aminobenzoic acid, and the precipitated oil was triturated with ethanol. It crystallized after 1 week and was recrystallized from ethanol. A mixture melting point with a sample prepared by method (a) was undepressed, and the infrared spectra of the two salts were identical.

***trans*-1,2-Di-(β-dimethylaminoethyl)cyclopropane (X).**—To 10.5 ml. of 95% formic acid was added 2.6 g. of the diamine IX, then 10 ml. of formaldehyde solution, and the mixture was heated on a steam bath for 9 hr. After cooling and addition of 20 ml. of 4 *N* hydrochloric acid, it was concentrated to about 12 ml. under reduced pressure, made basic with 20% sodium hydroxide solution, ether extracted, and worked up.

***cis*-1-(β-Bromoethyl)-2-(β-trimethylammoniumethyl)cyclopropane Bromide.**—*cis*-1,2-Di-(hydroxyethyl)cyclopropane[11] (3.2 g.) was treated with phosphorus tribromide as described for *trans*-1,6-dibromo-3-hexene above. The resulting *cis*-1,2-di-(bromoethyl) cyclopropane (2.1 g., 33%) had b.p. 102–104° (4 mm.), $n^{28}D$ 1.5245. A solution of 2 g. of this dibromo compound in 10 ml. of ether was added to 15 ml. of a 25% ethanolic solution of trimethylamine at −50° and allowed to stand in a pressure bottle for 14 days. Evaporation furnished an oil which crystallized to a colorless solid on treatment with ethyl acetate and acetone. Recrystallization from ethanol gave 1.8 g. (73%) of needles, m.p. 287–289° dec.

Anal. Calcd. for $C_{10}H_{21}Br_2N$: C, 38.12; H, 6.72. Found: C, 38.51; H, 7.02.

When this salt (0.5 g.) was heated with 30 ml. of a 12.5% anhydrous methanolic solution of trimethylamine in a sealed tube at 100–110° for 7 days and the reaction mixture was evaporated, a waxy residue was obtained from which 0.1 g. (20%) of tetramethylammonium bromide was elaborated by trituration with 30 ml. of dry acetone. It sublimed above 200°.

Anal. Calcd. for $C_4H_{12}BrN$: C, 31.18; H, 7.85. Found: C, 31.05; H, 7.46.

The residual oil was converted to a **dipicrate** which crystallized from ethanol, m.p. 175.5–177°.

Anal. Calcd. for $C_{23}H_{30}N_8O_{14}$: C, 43.00; H, 4.71; N, 17.44. Found: C, 42.90; H, 4.61; N, 18.06.

(18) This dibromo compound has been mentioned without any description by LeR. W. Clemence and M. T. Leffler, U. S. Patent 2,545,876 (March 20, 1951).

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6-Deoxytetracyclines. V.[1a] 7,9-Disubstituted Products

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The preparation and antibacterial activity of a number of 7 and 9 disubstituted 6-deoxytetracyclines are described.

The successful introduction of various functional groups into the 7 or 9 positions of the aromatic ring of the 6-deoxytetracyclines[2] and the effects of these substituents on *in vitro* antibacterial activity have been previously reported.[3,4] The retention of broad spectrum antibiotic properties by many of these new derivatives as well as a marked increase in antibacterial potency in some cases was noted. In order to under-

(1) (a) For the previous paper in this series see J. Hlavka, H. Krazinski, and J. Boothe, *J. Org. Chem.*, **27**, 3674 (1962); a preliminary report of this material has been published in *J. Am. Chem. Soc.*, **82**, 1253 (1960). (b) Please address reprint requests to J. H. Boothe.

(2) Recently it has been shown that the stereochemistry of the 6 position in the 6-deoxytetracyclines is the unnatural or *epi* configuration (β), M. Schach von Wittenau, J. Beereboom, R. Blackwood, and C. Stephens, *J. Am. Chem. Soc.*, **84**, 2645 (1962).

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(4) J. J. Hlavka, A. Schneller, H. Krazinski, and J. H. Boothe, *ibid.*, **84**, 1426 (1962).