6-Chloro-3-(α-hydroxybenzyl)-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide. 5-Chloro-2,4-disulfamylaniline (4.5 g.), phenylglyoxal diethyl acetal (9.0 g.), and 8% ethanolic hydrogen chloride (70 ml.) were heated on the steam bath for 2 hr. Chloroform (100 ml.) was then added and the solution chilled. The solid which separated was collected by filtration; 2.8 g., m.p. 276–277° dec. Recrystallization from methanol-water gave 6-chloro-3-(α-hydroxybenzyl)-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (2.42 g.), m.p. 282–283° dec. λ_{max} 224 mμ (ε 30,700); 278 mμ (ε 12,700).

Anal. Calcd. for $C_{14}H_{12}ClN_3O_5S_2$: N, 10.44; Cl, 8.83. Found: N, 10.44; Cl, 8.67.

5,6-Dichloro-3-hydroxymethyl-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide. 2,3-Dichloro-4,6-disulfamylaniline (10 g.) was dissolved in 95% ethanol (800 ml.) and refluxed overnight with 30% aqueous glyoxal (23 g.). The solvent was evaporated on a steam bath leaving a gummy residue which was dissolved in a water-alcohol mixture affording after concentration and cooling, a product (5.7 g.), m.p. 267–269° dec. Recrystallization from acetone furnished 5,6-dichloro-3-hydroxymethyl-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (2.95 g.) m.p. 278–280° dec. λ_{max} 231 mμ (ε 30,000); 278 mμ (ε 10,500).

Anal. Calcd. for $C_8H_7Cl_2N_3O_5S_2$: N, 11.66; Cl, 19.68. Found: N, 11.43; Cl, 19.56.

6-Chloro-3,4-dihydro-3-β-hydroxyethyl-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide. Sodium borohydride (5.90 g.) was added to a solution of 6-chloro-3-β-hydroxyethyl-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (5.90 g.) dissolved in tetrahydrofuran (250 ml.) and the mixture refluxed for 21 hr. The solvent was evaporated on the steam bath, the residue chilled in an ice bath and then acidified to *p*H 5 with 5% hydrochloric acid. The gum which first separated solidified when the mixture was allowed to warm to room temperature. The solid product was collected by filtration (4.69 g.), m.p. *ca.* 150° dec. Crystallization from methanol-chloroform afforded 6-chloro-3,4-dihydro-3-β-hydroxyethyl-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide (1.72 g.), m.p. 234° dec. λ_{max} 226 mμ (ε 36,700); 271 mμ (ε 20,200); 316 mμ (ε 3000).

An analogous procedure was used for the preparation of 5,6-dichloro-3,4-dihydro-3-hydroxymethyl-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide.

6-Chloro-3-α-chlorobenzyl-3,4-dihydro-7-sulfamyl-1,2,4-benzothiadiazine 1,1-dioxide. (a) A mixture of 5-chloro-2,4-disulfamylaniline (2 g.), α-chlorophenylacetaldehyde dimethyl acetal[19] (2.8 g.), absolute ethanol (100 ml.), 23% ethanolic hydrogen chloride (40 ml.), and 3 drops of water was refluxed for 1 hr. The excess ethanol was distilled and the residue triturated with hexane to give 3.7 g. of a tacky solid. After two recrystallizations from ethyl acetate-hexane the solid melted at 182–184° dec. and after drying under high vacuum melted at 198–205° dec. The infrared spectrum showed a strong carbonyl absorption due to solvation with ethyl acetate.

Anal. Calcd. for $C_{14}H_{13}Cl_2N_3O_4S_2 \cdot {}^1/_2\ CH_3COOC_2H_5$: C, 41.20; H, 3.68; Cl, 15.21; N, 9.01; Found: C, 41.54; H, 3.76; Cl, 15.30; N, 9.30.

(b) A mixture of 5-chloro-2,4-disulfamylaniline (2 g.), α-bromophenylacetaldehyde dimethyl acetal (3.4 g.), absolute ethanol (100 ml.), 23% ethanolic hydrogen chloride (40 ml.), and 3 drops of water was treated in the same manner as above. There was obtained 1.4 g. of a solid melting at 184–185.5° dec. which did not depress the melting point of the sample prepared in (a). The infrared spectra of the materials obtained in (a) and (b) were identical.

Anal. Calcd. for $C_{14}H_{13}Cl_2N_3O_4S_2 \cdot {}^1/_2\ CH_3COOC_2H_5$: Cl, 15.21; N, 9.01; S, 13.75. Found: Cl, 15.28; N, 8.92; S, 13.91.

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[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Thyroxine Analogs. I. Methylated Thyroformic Acids

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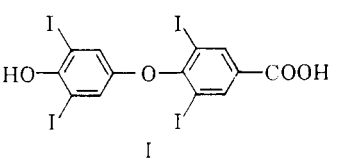
The preparations of several thyroformic acids variously substituted with methyl groups in the 3,5,3′,5′- positions are reported. The unusual debromination of 4-(4′-methoxy-3′,5′-dimethylphenoxy)-3,5-dimethylphenylbromide (XIII) and decarboxylation of the carboxylic acid (XIV) derived from bromide (XIII) were observed in 57% hydriodic acid in glacial acetic acid.

A greater separation of the hypocholesterolemic and metabolic effects was observed in the thyroxine analog, tetraiodothyroformic acid I, than in thyroxine, itself.[1] The effect of replacing the iodines of compound I with other groups was therefore investigated. The syntheses of compounds in which methyl group(s) or hydrogen(s) replace iodine(s) are reported in this paper.[2]



I

The general method used for preparing three methylated thyroformic acids is shown in Fig. 1.

(1) M. M. Best, C. H. Duncan, and E. Van Heyningen, *Endocrinology*, **60**, 161 (1957).

(2) The pharmacological results obtained with these compounds will be reported elsewhere.

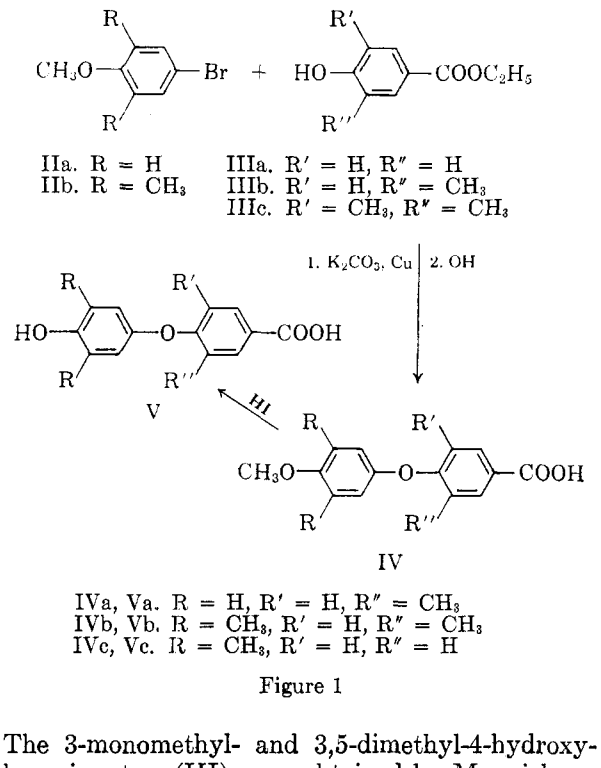


Figure 1

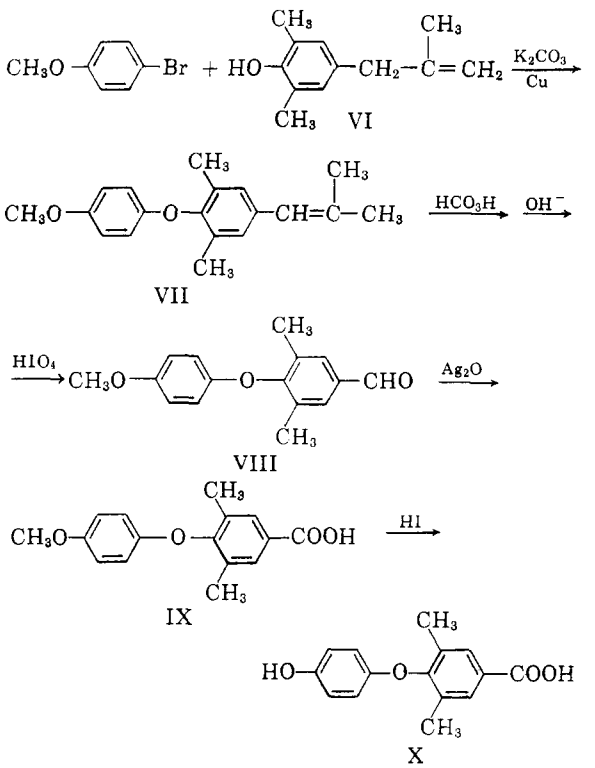


Figure 2

The 3-monomethyl- and 3,5-dimethyl-4-hydroxybenzoic esters (III) were obtained by Mannich reactions with ethyl 4-hydroxybenzoate and ethyl 3-methyl-4-hydroxybenzoate, respectively, followed by hydrogenolysis of the dimethylamino group. The appropriately substituted bromoanisole (II) was next treated with the hydroxy ester, by the method of Walker,[3] to give the diphenyl ethers (IV). Evidently, one methyl group, even though *ortho* to the hydroxyl, has little steric effect, since the yields with or without this substituent are about the same. Thus, acids IVa and IVb were formed in 39 and 35% yields, respectively. However, if two methyl groups are situated *ortho* to the hydroxyl, as in ethyl 3,5-dimethyl-4-hydroxybenzoate (IIIc), this Ullmann reaction with either bromide IIa or IIb fails. This corresponds with the finding of Bielig and Lützel[4] that the potassium salt of 4-nitro-2,6-dimethylphenol did not condense with 4-bromo-2,6-dimethylanisole.

The subsequent cleavage of the methoxyl group of these methoxy acids proceeds normally in 57% hydriodic acid and glacial acetic acid. The 3-methylthyroformic acid Va was iodinated in ammonium hydroxide to yield 3′,5′-diiodo-3-methylthyroformic acid.

Because the Ullmann reaction of Fig. 1 failed for the preparation of thyroformic acids with 3,5-dimethyl substitution, another more tedious route was employed (Fig. 2). Fortunately, when an alkyl group is substituted for the electronegative carbalkoxyl group, ether formation proceeds, although in low yield. In the present example, the β-methylallyl group was used as the substituent group because the unsaturation permitted preferential oxidation and because the unsubstituted allyl compound gave lower yields. The double bond in the diphenyl ether derivative VII was presumed to have shifted into conjugation with the benzene ring, as expected in strong alkali and supported by the infrared and ultraviolet spectra. The isopropenyl group was epoxidized with performic acid, converted into the glycol, and the glycol was cleaved by periodic acid to give aldehyde (VIII). None of these compounds was characterized. The aldehyde was converted by reaction with silver oxide into the acid, which readily cleaved with hydriodic acid to the desired 3,5-dimethylthyroformic acid (X).

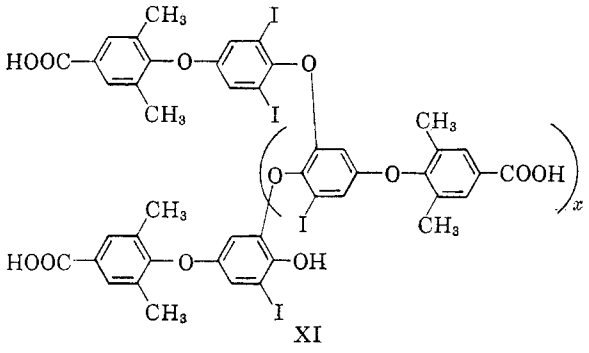
One attempt was made to convert the acid (X) into its 3′,5′-diiodo analog. The product isolated from the iodination quite obviously had the properties of a polymer (see Experimental). Although this polymer was not unequivocally characterized, its elemental analysis suggests that it was formed by a polymerization similar to that described by Staffin and Price[5] for 2,6-dimethyl-4-bromophenol. A possible structure for the polymer is XI.

When X was treated with a molar equivalent of iodine under like conditions, the monoiodo derivative was isolated successfully.

(3) J. Walker, *J. Chem. Soc.*, 347 (1942).

(4) H.-J. Bielig and G. Lützel, *Ann.*, **608**, 140 (1957). The reason for electronegative groups such as nitro or carboxylate prohibiting the coupling is not explained by Bielig and Lützel and neither is it apparent to the writer.

(5) G. D. Staffin and C. C. Price, *J. Am. Chem. Soc.*, **82**, 3632 (1960).

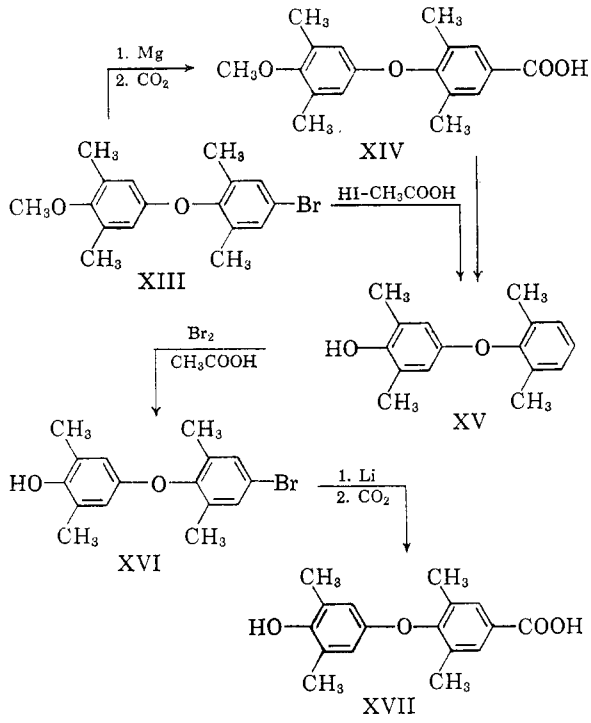


XI

Bielig and Lützel[4] described the synthesis of 4-(4′-methoxy-3′,5′-dimethylphenoxy)-3,5-dimethylbenzamide. They reported that prolonged treatment of this compound with base failed to yield the corresponding acid. In the present work, in the hope that the corresponding hydroxynitrile could be saponified, it was prepared by the ether cleavage of the methoxynitrile (XII) and subjected to prolonged treatment with alkali. No carboxylic material could be detected in the product, which, on purification, proved to be mainly starting material.

Consequently, the preparation of the desired compound (XVII) was attempted through its methyl ether. The ether cleavage of nitrile (XII) had been successful and no difficulty was anticipated. The carbonation of the Grignard reagent prepared from 4-(4′-methoxy-3,5′-dimethylphenoxy)-3,5-dimethylphenyl bromide (XIII) gave the expected methyl ether of tetramethylthyroformic acid (XIV). Treatment of this compound with 57% hydriodic acid in glacial acetic acid to effect ether cleavage, not only split the ether but also caused complete decarboxylation to the hydroxy tetramethyldiphenyl ether (XV). Neither *o*-cresotinic acid nor 4-methoxy-3,5-dimethylbenzoic acid was decarboxylated under like conditions. Obviously, in XIV the additive effect of all substituents, the two methyls and the methoxydimethylphenoxy group, are necessary to give a benzoic acid ring possessing a π-electron field of sufficient strength to yield a protonated intermediate. How critical this requirement is, is emphasized by the stability to refluxing hydriodic acid of compound IVb, which has only one less methyl group in the benzoic acid ring. The decarboxylation of acid XIV is then visualized as one means of stabilizing an unstable protonated intermediate, the other being simply deprotonation to XIV. It was considered that this unanticipated result could be circumvented by carbonating the lithium reagent of the hydroxy bromide (XVI), a reaction which has precedent.[6] An attempt was made, therefore, to prepare the hydroxybromo compound (XVI) from the methoxybromo compound (XIII) by ether cleavage with hydriodic acid.

(6) H. Gillman, C. E. Arntzen, and F. J. Webb, *J. Org. Chem.*, **10**, 374 (1945).



XIII XIV XV XVI XVII

The product of this cleavage was not the expected compound but the debrominated hydroxytetramethyldiphenyl ether (XV). To determine if this reduction was specific for XIII, 4-bromo-2,6-dimethylanisole was cleaved similarly. The product isolated was 2,6-dimethylphenol. Evidently, bromine situated *para* to an ether linkage is particularly labile toward hydrogen iodide reduction.[7]

The desired tetramethylthyroformic acid was finally prepared by lithiation and carbonation of the hydroxybromo compound (XVI) obtained by bromination of the hydroxydiphenyl ether (XV).

EXPERIMENTAL[8]

Preparation of ethyl 4-hydroxy-3-dimethylaminomethylbenzoate. A mixture of 166 g. (1.0 mole) of ethyl 4-hydroxybenzoate and 192 g. (1.06 moles) of 25% aqueous dimethylamine was stirred while 76 g. (0.94 mole) of 37% formalin was added dropwise, with temperature kept below 25°. Stirring was continued at room temperature overnight and the reaction mixture then was heated at 90° for 2 hr. Sodium chloride (53.2 g.) was added and the hot solution was stirred for 20 min. The mixture was diluted with water and chilled, whereupon the product crystallized. It was collected, sucked dry on a funnel, and recrystallized three times from petroleum ether (b.p. 30–60°). The product separated as white prisms, m.p. 64–66°, 102.9 g. (0.516 mole, 51.6%).

Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.68; N, 6.27. Found: C, 64.08; H, 7.23; N, 6.37.

Preparation of ethyl 4-hydroxy-3-methylbenzoate (IIIb). A solution of 79.6 g. (0.4 mole) of ethyl 4-hydroxy-3-di-

(7) H. Meerwein *et al.*, *J. prakt. Chem.*, [2], **154**, 266 (1940), describe experiments on the lability of halogens substituted *para* to alkoxyl groups. These halogens were removed with boron trifluoride and halogenated other ethers or phenols.

(8) The melting points and boiling points recorded are uncorrected.

methylaminomethylbenzoate in 300 ml. of ethanol was divided into two portions and hydrogenated in a 300-ml. bottle at 50 p.s.i. with 2 g. of palladium (5%) on charcoal per charge. The combined solutions were filtered and evaporated. The residue was dissolved in ether; after extraction with dilute hydrochloric acid, the ether was evaporated and the product recrystallized from benzene-petroleum ether (b.p. 60–71°), m.p. 98–100°,[9] 61.2 g. (0.34 mole, 85% yield).

Preparation of ethyl 4-hydroxy-3-methyl-5-dimethylaminomethylbenzoate. In the same way as the Mannich reaction with ethyl 4-hydroxybenzoate was performed above, 23.1 g. (0.128 mole) of ethyl 4-hydroxy-3-methylbenzoate was treated with 24.5 g. (0.136 mole) of 25% aqueous dimethylamine and 10.75 g. (0.136 mole) of 37% formalin. The product was noncrystalline, hence was distilled, b.p. 143° (1.2 mm.), n_D^{25} 1.5258. The yield was 21.1 g. (0.089 mole, 69.5%).

Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.75; H, 7.86; N, 5.79.

Preparation of ethyl 4-hydroxy-3,5-dimethylbenzoate (IIIc). A 21.1-g. (0.089 mole) sample of ethyl 4-hydroxy-3-methyl-5-dimethylaminobenzoate was reduced in 130 ml. of ethanol with 2 g. of 5% palladium on charcoal at 40 p.s.i. of hydrogen. The solid obtained by evaporating the filtrate was twice recrystallized from absolute ethanol and had a m.p. of 113–114° (lit.[10] m.p. 113°). The yield was 4.9 g. (28.4%).

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.73; H, 6.76.

This ester was treated with *p*-bromoanisole, as described below for the monomethyl ester (IVa), and also under a variety of other conditions that Bielig and Lützel[4] had found successful for their compounds, but all attempts failed to yield diphenyl ether derivatives.

Preparation of 2,6-dimethyl-4-(2-methylallyl)phenol (VI). A solution of 103.5 g. (0.924 mole) of 2,6-dimethylphenol in 200 ml. of dry benzene was added to 22.2 g. (0.924 mole) of sodium hydride in 100 ml. of dry benzene. After refluxing to cause complete reaction, heating was stopped and 135 g. (1.5 moles) of 2-methallyl chloride was added to the stirred reaction mixture. After complete addition the reaction mixture was refluxed for 8 hr., allowed to cool, added to water, acidified and extracted with benzene. The benzene was evaporated in vacuum and the residue treated with 200 ml. of Claisen's alkali. The nonphenolic material was extracted with petroleum ether, and the phenolic material recovered by acidification with hydrochloric acid and ether extraction. The washed and dried ether extract was evaporated and the residue distilled, b.p. 84° (0.33 mm.), n_D^{25} 1.5322, to yield the product in 41.5 g. (0.235 mole), 25.5% yield.

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.75; H, 8.95.

The material was made in identical yield as above by preparing 2-methallyl-2,6-dimethylphenyl ether, and rearranging it as reported by Tarbell and Kincaid[11] for the corresponding allyl ether.

Preparation of 1-(4-methoxyphenoxy)-2,6-dimethyl-4-(2-methylpropenyl)benzene (VII). 2,6-Dimethyl-4-(2-methallyl)phenol (41.5 g., 0.235 mole) was dissolved in a solution of 13.2 g. (0.235 mole) of potassium hydroxide in 125 ml. of methanol. The solution was evaporated to dryness on the steam bath and 43 g. (0.23 mole) of 4-bromoanisole and 0.5 g. of copper-bronze powder were added and the mixture heated for 45 hr., under nitrogen, at 220° (bath temperature). The cooled reaction mixture was treated with petroleum ether (b.p. 30–60°) and 200 ml. of Claisen's alkali. The petroleum ether extract was dried with magnesium sulfate (anhydrous), evaporated and the residue distilled at 0.55 mm. A fraction boiling at 145–168° was redistilled and the fraction boiling at 150–152° (0.43 mm.), n_D^{25} 1.5589, was collected; yield, 9.0 g. (0.0319 mole, 14%). The yield was reproducible.

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.60; H, 7.77.

The ultraviolet spectrum of this compound (compare below) indicated that the double bond had isomerized into conjugation with the ring.

Preparation of 1-(4-methoxyphenoxy)-2,6-dimethyl-4-propenylbenzene. 4-Allyl-2,6-dimethylphenol, prepared according to Tarbell and Kincaid,[11] was submitted to the same reaction as for its next higher homolog. From 52 g. (0.32 mole) of the phenol there was obtained 3.6 g. (0.0134 mole) of product, a yield of 4.1%, n_D^{25} 1.5774, b.p. 150–158° (0.7 mm.). An ultraviolet spectrum proved that rearrangement of the allyl group to propenyl had occurred. The maximum absorption occurred at 254 mμ (ε 14,400) and the rest of the curve showed styrene-like fine structure at 289 and 300 mμ.

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.33; H, 8.03.

Preparation of 4-(4'-methoxyphenoxy)-3,5-dimethylbenzoic acid (IX). The 2-methylpropenyl group of VII was converted into the carboxyl group by epoxidation, hydrolysis, glycol cleavage, and oxidation to the acid, without purification and characterization of the intermediates.

(a) *Epoxidation.* A solution of 17.0 g. (0.06 mole) of 4-(4'-methoxyphenoxy)-3,5-dimethyl-1-(2-methylpropenyl)benzene in 100 ml. of 98–100% formic acid was stirred at 25° while 7.3 g. (0.065 mole) of 30% hydrogen peroxide was added dropwise. The mixture was stirred and heated at 40° for 24 hr., evaporated to dryness, chloroform was added, and the resulting solution washed with water. Evaporation to dryness gave a dark, thick oil—presumably the formate ester of the glycol.

(b) *Saponification.* The oil was dissolved in 42 ml. of ethanol containing 7 g. of potassium hydroxide (0.125 mole) and refluxed for 2 hr. The alcohol was removed in vacuum on the steam bath and the residue was treated with water and extracted with ether. The extract on concentration in vacuum yielded the crude product.

(c) *Cleavage.* The saponification product was dissolved in 900 ml. of ethanol and heated to 40°, stirred and treated with a solution of 13.8 g. (0.06 mole) of potassium periodate in 690 ml. of *N* sulfuric acid which was initially at 20°. After 30 min. the initially cloudy solution had deposited an oil. Saturated ammonium chloride solution was added to salt out the alcohol and the mixture was extracted with ether. The ether extract was washed with ammonium chloride solution and then evaporated to dryness in vacuum on the steam bath to give the oily aldehyde.

(d) *Oxidation to acid.* The crude aldehyde was dissolved in 575 ml. of 95% ethanol and 23.1 g. (0.124 mole) of silver nitrate in 46 ml. of water was added. To this stirred solution there was added during 2 hr., at 10-min. intervals, a solution of 7.4 g. (0.185 mole) of sodium hydroxide in 410 ml. of water, in equal portions. After stirring overnight, the solution was treated with gaseous carbon dioxide. A voluminous black precipitate was separated by filtration, and the filtrate combined with those obtained by successive extractions of the black precipitate and the tars in the flask with hot *N* sodium hydroxide solution. The basic filtrates were acidified with dilute nitric acid and the solid precipitate was removed by ether extraction. The ether extract was evaporated to dryness and the solid residue recrystallized from alcohol with charcoal treatment. Two recrystallizations gave 3.62 g. (0.0131 mole), 21.8%, of the desired acid, m.p. 188°; 0.22 g. more of acid was recovered from the filtrates.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.83; H, 6.20.

Preparation of 4-(4'-hydroxyphenoxy)-3,5-dimethylbenzoic acid (X). A mixture of 3.84 g. (0.0139 mole) of 4-(4'-methoxyphenoxy)-3,5-dimethylbenzoic acid in 20 ml. of glacial acetic acid and 20 ml. of 57% hydriodic acid was refluxed for 1.5 hr. Upon cooling, long, white needles formed. The reaction

(9) K. Auwers, *Ber.*, 39, 3174 (1906), gives a melting point of 98–99°.

(10) O. Jacobsen, *Ber.*, 12, 608 (1879).

(11) D. S. Tarbell and J. F. Kincaid, *J. Am. Chem. Soc.*, 62, 728 (1940).

mixture was diluted with 60 ml. of water, chilled, and filtered. The product could be recrystallized from 50% acetic acid–water (m.p. 187.5–189.5°) in a yield of 2.9 g. (0.0112 mole), 81%.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.65; H, 5.36.

Polymer formation during the iodination of 4-(4'-hydroxyphenoxy)-3,5-dimethylbenzoic acid. To a stirred solution of 3.8 g. (0.0147 mole) of 4-(4'-hydroxyphenoxy)-3,5-dimethylbenzoic acid in 250 ml. of concd. ammonium hydroxide, chilled to 10°, there was added during 30 min. a solution of 7.2 g. (0.0294 mole) of iodine in 40 ml. of water containing 9.0 g. (0.0542 mole) of potassium iodide. After one half of the iodine solution was added, the solution darkened considerably and at the end of the addition it was nearly black, which color was not due to nitrogen triiodide alone, although removal of the ice bath and stirring for 30 min. longer caused a considerable lightening of the color of the reaction mixture. Most of the excess ammonia was removed by evaporation in vacuum without external heating. The solution was acidified with dilute hydrochloric acid to give a gelatinous precipitate. This precipitate was insoluble in ether or chloroform. The precipitate was collected and dissolved in ethanol. This solution was filtered and the ethanol evaporated. The residue was also insoluble in acetone. Attempted purification from acetic acid–water gave a colored product which was not decolorized by activated charcoal. It did not melt at 295° and appeared to be polymeric. The product showed no shift in the ultraviolet with base, but the infrared showed the presence of the carboxyl by the absorption at 5.88 μ and strong diphenyl ether absorption occurred at 8.5 μ. The analysis, although poor, indicates that there is approximately one iodine per thyroformic acid moiety and supports the polymeric structure (XI).

Anal. Calcd. for $C_{15}H_{11}IO_4$: C, 47.14; H, 2.90; I, 33.21. Found: C, 47.94; H, 4.01; I, 27.42.

Preparation of 4-(4'-hydroxy-3'-iodophenoxy)-3,5-dimethylbenzoic acid. A 0.5-g. sample of 4-(4'-hydroxyphenoxy)-3,5-dimethylbenzoic acid (0.00194 mole) was dissolved in 150 ml. of concd. ammonium hydroxide. The air in the flask was flushed out with nitrogen, and then a solution of 0.492 g. (0.00194 mole) of iodine in a solution of 1.32 g. (0.004 mole) of potassium iodide in 20 ml. of water was added over 1.25 hr. while stirring rapidly. The colorless solution turned pale green at the end of the addition. The excess ammonia was evaporated in vacuum with gentle heating on the steam bath until most of it was gone. Then the solution was acidified with dilute hydrochloric acid to obtain a sticky, white product. This was recrystallized from alcohol-water to give white needles, melting after several recrystallizations at 187.5–188.5°. A yield of 0.34 g. (45.5%) was obtained.

Anal. Calcd. for $C_{15}H_{13}IO_4$: C, 46.89; H, 3.41; I, 33.04. Found: C, 46.75; H, 3.53; I, 33.29.

Preparation of 4-(4'-methoxyphenoxy)-3-methylbenzoic acid (IVa). In a 100-ml. flask 17.5 g. (0.097 mole) of ethyl 4-hydroxy-3-methylbenzoate was mixed with 18 g. (0.096 mole) of 4-bromoanisole, 13.6 g. (0.098 mole) of potassium carbonate and 0.9 g. of copper-bronze and heated for 12 hr. at 220°. After cooling, the solid mass was crushed and transferred to a 1-l. flask, 200 ml. of water was added, and the mixture steam-distilled to remove excess bromoanisole. When no more distilled, 25 ml. of 50% sodium hydroxide was added and steam-distillation continued for 30 min. The hot distillland was diluted to 1 l. with ice and water, filtered, and the filtrate was acidified with 20% acetic acid. The precipitate was collected, washed with water, and recrystallized from glacial acetic acid, melting point after three recrystallizations, 153°, with prior softening at 147°. The yield was 3.8 g. (0.024 mole), 25%.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.80; H, 5.61.

Preparation of 4-(4'-hydroxyphenoxy)-3-methylbenzoic acid (Va). (a) *Cleavage with pyridine hydrochloride.* Pure, dry pyridine (13.5 g., 0.17 mole) was dissolved in 100 ml. of dry ether and converted into the hydrochloride with dry hydrogen chloride. The pyridine hydrochloride, isolated by evaporation in vacuum, was mixed with 9.2 g. (0.0356 mole) of 4-(4'-methoxyphenoxy)-3-methylbenzoic acid and heated for 4.5 hr. at 200° in an oil bath. The cooled reaction mixture was treated with 10 volumes of water and the insoluble acid extracted with ether after adding a few milliliters of hydrochloric acid. The residue from evaporation of the ether extracts was recrystallized from 3.5 l. of boiling water, yielding white crystals; m.p. 150–151°, with prior softening. The acid, after drying over calcium chloride in vacuum, weighed 8.5 g. (0.0348 mole, 98%).

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95. Found: C, 68.58; H, 5.13.

(b) *Cleavage with hydriodic acid.* A 3-g. sample of the methoxy acid in 20 ml. of 57% hydriodic acid and 20 ml. of glacial acetic acid after 2.5 hr. of refluxing gave an 88.5% yield of the desired product; m.p. 148–150°.

Preparation of 4-(4'-methoxy-3',5'-dimethylphenoxy)-3-methylbenzoic acid (IVb). A reaction similar to that for preparing IVa, using ethyl 3-methyl-4-hydroxybenzoate (32.5 g.) and 4-bromo-2,6-dimethylanisole (38.6 g.) led to 18.1 g. of IVb (35% yield), m.p. 165.5°, after recrystallizing from acetic acid-water.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.05; H, 6.08.

Preparation of 4-(4'-methoxy-3',5'-dimethylphenoxy)benzoic acid (IVc). In an identical fashion, as above, 30 g. of ethyl 4-hydroxybenzoate and 38.6 g. of 4-bromo-2,6-dimethylanisole gave trimethyl compound (IVc) in a 39% yield (19 g.); rhombic prisms from glacial acetic acid, m.p. 146–148°.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.44; H, 5.96.

Preparation of 4-(4'-hydroxy-3',5'-dimethylphenoxy)-3-methylbenzoic acid (Vb). This cleavage was performed with 57% hydriodic acid in glacial acetic acid in the usual manner, with 3.32 g. of the methoxy ester IVb. The product was crystallized from ethanol-water, giving needles, m.p. 198.5–199°, 2.6 g. (82.5%).

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.84; H, 6.01.

Preparation of 4-(4'-hydroxy-3',5'-dimethylphenoxy) benzoic acid (Vc). In a procedure identical to the preceding, 11 g. of the methoxy acid (IVc) was converted into 9.1 g. (87%) of the hydroxy acid, m.p. 175.5–176.5° (ethanol-water).

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.61; H, 5.51.

Preparation of 4-(4'-hydroxy-3',5'-diiodophenoxy)-3-methylbenzoic acid. The iodination was performed similarly to that attempted on the hydroxydimethyl analog (X), above. Thus, 9.4 g. of 4-(4'-hydroxyphenoxy)-3-methylbenzoic acid in ammonium hydroxide was treated with iodine-potassium iodide solution (2 moles) at 0°. At the end of the addition the mixture darkened but could be decolorized with sodium bisulfite. Isolation, by vacuum evaporation of excess ammonia and acidification with hydrochloric acid, gave a tan-brown solid. After drying, the solid was fractionally reprecipitated from acetone by addition of petroleum ether (b.p. 60–71°) until turbid; chilling and filtration of this initial tan-brown powder (m.p. 240–260° with decomposition), and then addition of more petroleum ether and further chilling gave a light tan powder, m.p. 222–224°. This tan powder was recrystallized from acetone three times to give a pale yellow, microcrystalline material, m.p. 228–231°, with decomposition and evolution of violet fumes. The analysis indicated there was about 8% of monoiodo compound contaminating the desired diiodo compound. The infrared spectrum was consistent with the acid, and titration in 66% aqueous dimethylformamide gave pK_a 6.7 and 8.7 and an apparent mol. wt. of approximately 500 (calcd. 496).

Anal. Calcd. for $C_{14}H_{10}I_2O_4$: C, 33.90; H, 2.03; I, 51.17. Found: C, 34.80; H, 2.66; I, 49.80.

Preparation of 4-(4'-methoxy-3',5'-dimethylphenoxy)-3,5-dimethylbenzoic acid (XIV). Intermediates for this preparation were made according to the directions given by Bielig and Lützel.[4] 4-Methoxy-3,5,2',6'-tetramethyldiphenyl ether was prepared in 18–19.5% yield by formation of the potassium salt of 2,6-dimethylphenol in methanol, removing methanol first at 100°, then the last traces at 200°, cooling, adding 4-bromo-2,6-dimethylanisole and heating to reflux for 5 hr. under nitrogen at 235° with copper bronze catalyst, b.p. 130° (0.75 mm.), n_D^{25} 1.5538. It was brominated in acetic acid in 89% yield, m.p. 73.5° (ethanol).

The bromo compound was converted into the acid through the Grignard reagent. To 3.9 g. (0.16 g.-atom) of magnesium layered with 100 ml. of dry ether and stirred under anhydrous conditions was added 0.4 g. of methyl iodide, followed by the dropwise addition of 26.9 g. (0.083 mole) of 4-(4'-methoxy-3',5'-dimethylphenoxy)-3,5-dimethylbromobenzene in 100 ml. of dry ether over 1 hr. The reaction mixture was stirred and refluxed for two more hours and then poured onto 150 g. of crushed solid carbon dioxide. After standing at room temperature overnight, when all the carbon dioxide had evaporated, the suspension was decomposed with dilute hydrochloric acid. The acid was extracted into ether and the ether solution extracted with dilute sodium hydroxide. The basic solution was acidified with dilute hydrochloric acid and the precipitate collected and recrystallized from ethanol-water, m.p. 160.5–161.5°, to yield 22.2 g. (0.074 mole), 92%, of the acid, white needles.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.95; H, 6.83.

Acid-catalyzed decarboxylation of 4-(4'-methoxy-3',5'-dimethylphenoxy)-3,5-dimethylbenzoic acid. (a) The methoxy acid (10 g.) was refluxed for 2.5 hr. in 80 ml. of 1:1 hydriodic acid–acetic acid. Inversion of the reaction mixture into 500 ml. of water containing a trace of sodium bisulfite gave a white, crystalline product. Recrystallized from ethanol-water, it melted at 104.5–106.5°, yield, 5.2 g. (0.0215 mole, 64.5%).

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.30; H, 7.83.

The product had the same physical characteristics as the 4-(2',6'-dimethylphenoxy)-2,6-dimethylphenol prepared below; that is, identical melting point, infrared, and ultraviolet spectra.

(b) The above experiment was repeated except 48% hydrobromic acid was substituted for the hydriodic acid. No material soluble in a bicarbonate solution was obtained and the purified decarboxylation-product was obtained in 54% yield.

Attempted decarboxylations of analogs of XIV. (a) *o*-Cresotinic acid was refluxed for 2 days in a hydriodic-acetic acid mixture as above, collecting the evolved gases. Only a small amount of gas was liberated, however. The purely phenolic material was separated from the carboxylated material by extraction of the isolated product of the reaction in ether with sodium bicarbonate. Evaporation of the ether gave only a trace of phenol which had the odor of cresol but was not identified. The acid recovered was 68.5% of the starting amount.

(b) 4-Methoxy-3,5-dimethylbenzoic acid was prepared by carbonation with crushed solid carbon dioxide of the Grignard reagent prepared from 21.5 g. (0.1 mole) of 4-bromo-3,5-dimethylanisole. This reagent was made by addition over 6–8 hr. of a mixture of the above bromide and 18.8 g. (0.1 mole) of ethylene bromide in 100 ml. of ether to 5.4 g. (0.22 g.-atom) of magnesium under 150 ml. of ether. Acidification of the magnesium salt of the acid with dilute hydrochloric acid and extraction with chloroform followed by base extraction of the chloroform solution and acidification of the alkaline solution gave the benzoic acid. It was recrystallized from ethanol-water, m.p. 192–194°, 8.2 g. (45.5%).

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.42; H, 7.06.

The customary hydriodic-acetic acid cleavage of this acid gave 82% 4-hydroxy-3,5-dimethylbenzoic acid, m.p. 224–225.5°. No elimination of carbon dioxide was observable.

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.12; H, 6.29.

Preparation of 4-(4'-hydroxy-3',5'-dimethylphenoxy)-3,5-dimethylbenzonitrile (XII). 4-(4'-Methoxy-3',5'-dimethylphenoxy)-3,5-dimethylbenzonitrile was prepared according to the directions of Bielig and Lützel.[4] Thus from 19 g. of the corresponding bromide a 75.5% yield (12 g.) of product melting at 97° (Bielig, 103°) was obtained as the solidifie distillate from a distillation, b.p. 167–170° (0.45 mm.).

The methoxynitrile was cleaved by refluxing 4.0 g. (0.0142 mole) in 20 ml. of 1:1 glacial acetic–hydriodic acid (57%). The cooled reaction mixture deposited a white solid which twice recrystallized from ethanol-water melted at 175–176.5°, 3.5 g. (0.0131 mole), 92%.

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.14; H, 6.34; N, 5.23.

The infrared spectrum showed no carbonyl absorption but had a relatively intense aromatic nitrile band at 4.5 μ. Attempted saponification of this nitrile in aqueous potassium hydroxide-Methyl Cellosolve gave no acidic material on acidification.

Debromination during hydriodic acid cleavage of 4-(4'-methoxy-3',5'-dimethylphenoxy)-3,5-dimethylphenyl bromide (XIII). 4-(4'-Methoxy-3',5'-dimethylphenoxy)-3,5-dimethylphenyl bromide (16 g.) was heated to reflux in 1:1 glacial acetic–57% hydriodic acid (170 ml.) for 2 hr. The reaction, although run under nitrogen, had become colored red-brown from iodine. The reaction mixture was poured into 1 l. of water and the oil that separated chilled to cause solidification and then filtered. It was recrystallized three times from ethanol-water, m.p. 101.5–103.5°. Its infrared and ultraviolet spectra were practically identical to that of 4-(4'-hydroxy-3',5'-dimethylphenoxy)-3,5-dimethylbenzene prepared below except that the intensity of the ultraviolet maximum was not quite so high, λ_{max} 288 mμ (ϵ 2940). The yield was 6.6 g. (0.028 mole), 58.3%.

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 78.79; H, 7.64; Br, 0.00.

Preparation of 4-(4'-hydroxy-3',5'-dimethylphenoxy)-2,6-dimethylbenzene (XV). In a 500-ml. flask 25.5 g. (0.1 mole) of 4-(4'-methoxy-3',5'-dimethylphenoxy)-3,5-dimethylbenzene was heated to reflux for 3 hr. in 300 ml. of 1:1 glacial acetic acid–57% hydriodic acid under nitrogen. The cooled reaction mixture was diluted with water and the oily product extracted with ether, the ether layer was washed with sodium bicarbonate solution, and the ether finally evaporated. The residue, twice recrystallized from petroleum ether (b.p. 60–64°), melted at 104–106°, yield, 12.7 g. (0.0524 mole, 52.4%). The ultraviolet maximum occurred at 287.5 mμ (ϵ 3040).

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.48; H, 7.61.

Preparation of 4-(4'-hydroxy-3',5'-dimethylphenoxy)-3,5-dimethylphenyl bromide (XVI). A solution of 12.7 g. (0.0524 mole) of 4-(4'-hydroxy-3',5'-dimethylphenoxy)-3,5-dimethylbenzene in 125 ml. of glacial acetic acid was cooled to 20° and then a solution of 8.4 g. (0.0524 mole) of bromine in 20 ml. of glacial acetic acid was added portionwise. After addition was complete the reaction mixture was stirred at 15° for 30 min. and then allowed to rise to room temperature during the course of 1 hr. It was then poured into 2 l. of water containing 2 g. of sodium bisulfite. After some time the oily product solidified and was filtered and recrystallized from petroleum ether (b.p. 60–64°), m.p. 101–103°, yielding 12.5 g. (0.039 mole, 74%).

Anal. Calcd. for $C_{16}H_{17}BrO_2$: C, 59.82; H, 5.33. Found: C, 60.01; H, 5.61.

Preparation of 4-(4'-hydroxy-3',5'-dimethylphenoxy)-3,5-dimethylbenzoic acid. Butyllithium was prepared by adding 1.74 g. 0.25 g.-atom) of lithium strips to a previously dried 200-ml. flask through which dry nitrogen was passing. Then 40 ml. of dry ether was added followed by the dropwise addition of 13.7 g. (0.1 mole) of *n*-butyl bromide in 20 ml. of

dry ether, maintaining the temperature throughout at −10° by a Dry Ice–acetone bath. At the completion of addition the temperature was allowed to rise to 4° and stirred for 30 min. The solution was decanted into a dropping funnel through a glass-wool plug and protected from moisture. It was added dropwise to a stirred solution of 12.5 g. (0.039 mole) of 4-(4′-hydroxy-3′,5′-dimethylphenoxy)-3,5-dimethylphenyl bromide in 30 ml. of dry ether at room temperature. After stirring for 0.5 hr. it was allowed to stand for 2 hr. and then poured onto a large amount of powdered Dry Ice covered with ether in a 1-l. flask. After standing overnight, dilute hydrochloric acid was added and the product extracted with ether. The ether solution was in turn extracted with saturated sodium bicarbonate solution until no more carbon dioxide was liberated. The bicarbonate extract was acidified to give an oil that crystallized and was purified from ethanol-water, m.p. 187.5–190.5° after three recrystallizations. There was obtained 5.0 g. (0.0175 mole, 45%).

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.09; H, 6.37.

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Potential Curare-Like Compounds Derived from Bisdialkylaminoalkyl Esters of Some 3-Phenylglutaric Acids

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A series of bisquaternary ammonium salts derived from dialkylaminoalkyl esters of substituted 3-phenylglutaric acids has been prepared and tested for curare-like activity and for possible hypotensive activity. The esters were prepared by reaction of basic alcohols with the substituted glutaric anhydride, followed by esterification of the resulting half-esters.

Studies on relatively simple molecules[1-3] have indicated that many compounds exhibit some degree of curare-like activity if they possess two quaternary ammonium groups properly spaced with respect to each other. In some cases the activity of the compound can be correlated with the number of atoms between the two quaternary groups. While the importance of the correctly spaced quaternary groups has been discounted,[4] various experimental results[5] do indicate that the nature of the intervening groups, as well as the distance between quaternary ammonium groups, is of importance in determining the degree of curare-like activity.

In order to learn more about the effects of structural changes in that part of the molecular between the quaternary ammonium groups we have prepared a series of esters in which two quaternary ammonium groups are either eleven or thirteen atoms apart and in which certain variations are made in the nature of the molecule between the two quaternary ammonium groups (Table I). It will be noted that in all of these structures a rather bulky group (phenyl or substituted phenyl) is present in the central part of the molecule. This is in contrast to some of the other synthetic curare-like compounds[1-3] which are essentially linear molecules with no bulky groups in the central part of the molecule. Tubocurarine chloride, by contrast, is a very bulky molecule.

The compounds listed in Table I are of interest both for their value in correlating structure with curare-like activity and also for their possible value as hypotensive agents.

The substituted phenylglutaric acids could not be converted to basic esters by direct esterification in benzene because of the low solubility of the acid in benzene. The satisfactory synthesis of the esters made use of the increased solubility of the anhydrides, compared with the acids, and the faster reaction rate in toluene, compared with benzene. The basic esters prepared in this way were oils, and were converted without purification to the corresponding bisquaternary ammonium salts.

The curare-like activity of compounds in this series (Table II) decreases with substitution on the phenyl ring. This decrease in activity is noted whether the substituent is methoxyl, nitro, or both. The detrimental effect of these substituents appears to be cumulative.

A comparison of compounds 6 and 7 indicates that lengthening the chain between the quaternary ammonium groups from eleven atoms to thirteen atoms increases the activity of the compound. However, no such correlation is found with compounds 8 and 9. These differ only with respect to the distance between quaternary groups, but both have the same activity.

In this series, minor changes in structure can give rise to striking changes in effect on blood pressure. The two compounds which cause an in-

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