mined by the Volhard method. The results in each case were negative within the experimental error.

Reimer-Tiemann reaction with mesitol (XVII). Ten g. of mesitol, m.p. 71–72° was heated under reflux for 12 hr. with 200 ml. chloroform, 200 g. of potassium hydroxide, and 170 ml. of water. Upon cooling, the organic layer was extracted with five 50-ml. portions of Claisen's alkali,[22] then dried over magnesium sulfate and the solvent removed under reduced pressure leaving 10.86 g. (67.5%) of neutral oil. Upon standing in the refrigerator overnight in absolute methanol, 0.90 g. (1%) of white crystals m.p. 185–186° had separated. Colorless prisms of *mesityl orthoformate* (XX), m.p. 188.0–188.5° were obtained after three recrystallizations from benzene-methanol.

Anal. Calcd. for $C_{28}H_{34}O_8$: C, 80.35; H, 8.19. Found: C, 80.3; H, 8.19.

Distillation of the remaining oil furnished a mixture of the two cyclohexadienones as a faintly straw colored liquid, b.p. 73.8–74.0° (0.17 mm.), λ_{max} 239 mμ (log ε 3.66) 317 (3.51).

Anal. Calcd. for $C_{10}H_{13}OCl_2$: C, 54.84; H, 5.52. Found: C, 54.7; H, 5.67.

Assuming λ_{max} 239 mμ (ε 12,100) 317 (ε 1000) for the *para* isomer[12] and λ_{max} 317 (4500) 239 (200) for the *ortho* isomer[9] the following calculations can be made:[23]

$$\textit{para}\ \text{isomer}\ \frac{4600 - 1000}{12{,}100 - 1000} \times 100 = 32\%\ \text{and}$$

$$\textit{ortho}\ \text{isomer}\ \frac{3240 - 200}{4500 - 200} \times 100 - 70\%$$

(22) L. F. Fieser, *Experiments in Organic Chemistry*, C. D. Heath and Co., Boston, Mass. 3rd Ed. p. 310.

(23) M. J. S. Dewar and D. S. Urch, *J. Chem. Soc.*, 345 (1957) describe a general method for the analysis of mixtures using ultraviolet spectroscopy.

One g. of this distillate was chromatographed over 70 g. of alumina using 1:10 ether–petroleum ether (b.p. 34°) as the eluant. The first nine 50-ml. fractions furnished 650 mg. of oil. Fractions 3,6, and 8 exhibited sharp maxima at 317 mμ with log ε 3.7, 3.7, and 3.75 respectively. Crystallization of this oil was unsuccessful, while attempted purification by evaporative distillation at 120–150° (8–10 mm.) resulted in some decomposition as indicated by a shift of the absorption maximum in the ultraviolet to 305 mμ. The next four 50-ml. fractions eluted from the column furnished 60 mg. of solid which, after recrystallization from dilute methanol, yielded 20 mg. of colorless crystals of *4-dichloromethyl-2,4,6-trimethyl-3,5-cyclohexadienone* (XIX), m.p. 37.5–38.5° with softening at 36°, λ_{max} 240–242 mμ (log ε 4.0).

Anal. Calcd. for $C_{10}H_{13}OCl_2$: C, 54.84; H, 5.52. Found: C, 54.7; H, 5.45.

In another experiment in which 5.0 g. of mesitol was refluxed for 1 hr. with 25 ml. of chloroform, .25 g. of potassium hydroxide, and 20 ml. of water, 3.85 g. (47.5%) of neutral oil was obtained. Its λ_{max} 317 mμ (log ε 3.58) 240 (3.15) allowed the percentage of isomers to be determined in the manner described above: *para*-isomer 4%, *ortho*-isomer 84%.

Dimer of 2-dichloromethyl-2-methyl-3,5-cyclohexadienone. When 6.0 g. of the abnormal Reimer-Tiemann product[14] of *o*-cresol, m.p. 30.5–32.0°, was allowed to stand in a stoppered flask at room temperature for 2 years, 250 mg. of a white crystalline solid m.p. 188.5–189.5° could be obtained with petroleum ether (b.p. 60–68°). Two crystallizations from methanol-acetone furnished colorless prisms, m.p. 190–190.5°.

Anal. Calcd. for $C_8H_8OCl_2$: C, 50.29; H, 4.22. Found: C, 50.2; H, 4.29.

MADISON, WIS.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

Bicyclic Sulfonium Salts with Sulfur at a Bridgehead[1]

RICHARD H. EASTMAN AND GENE KRITCHEVSKY

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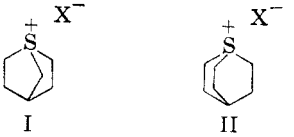
By treatment of the appropriate mercaptans or tetrahydrothiophene derivatives with hydrogen halides, bicyclic sulfonium salts of the bicyclo[3.3.0]octane-1-thianium, bicyclo[4.3.0]nonane-1-thianium, and bicyclo[4.4.0]decane-1-thianium types have been prepared.

A few bicyclic sulfonium compounds in which the sulfonium function is located at a bridgehead have been prepared. In addition to the interest inherent in such structures, the compounds of this type are frequently pharmacologically active. The most active are the bicyclo[2.2.1]heptane-1-thianium (I) and bicyclo[2.2.2]octane-1-thianium (II) halides reported by Prelog,[2] the former having a minimum lethal dose of 30γ in white mice. A few other compounds have been prepared.[3] The compounds which were tested exhibited a lower order of activity, the activity apparently being related to the ability of the bicyclic sulfonium function to act as an alkylating agent.



I II

In connection with the question of valence-shell expansion to 10 electrons in the sulfur atom,[4] we have prepared the bicyclo[3.3.0]octane-1-

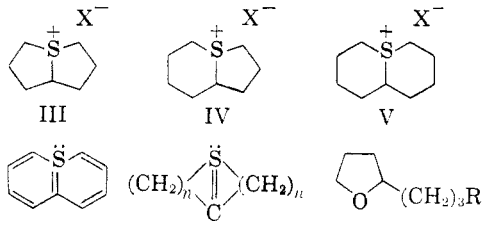
(1) Taken from the Ph.D. dissertation of Gene Kritchevsky in the Department of Chemistry at Stanford University.

(2) V. Prelog and E. Cerkovnikov, *Ann.*, **537**, 214 (1939); V. Prelog and D. Kohlbach, *Ber.*, **72**, 672 (1939).

(3) B. R. Baker, M. Query, S. Safir, and S. Berstein, *J. Org. Chem.*, **12**, 138 (1947); M. W. Goldberg and L. H. Sternbach, U.S. Patent **2,489,232**, U.S. Patent **2,489,235**; W. F. Cockburn and A. F. McKay, *J. Am. Chem. Soc.*, **76**, 5703 (1954); **77**, 397 (1955).

(4) For recent work and a bibliography see W. E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, **77**, 521 (1955).

thianium (III), bicyclo[4.3.0]nonane-1-thianium (IV), and bicyclo[4.4.0]decane-1-thianium (V) salts as possible precursors for the hypothetical systems VI and VII in which the sulfur atom bears a decet of electrons. We were not successful in producing VI or VII, but wish to report here the syntheses and pharmacological activities of III, IV, and V. Compound III has recently become of special interest in regard to transannular effects in macrocyclic thiaketones,[5] and it seems likely that IV and V will similarly become of interest as reference systems.

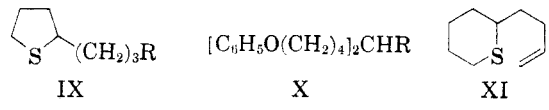


III IV V

VI VII VIII

Bicyclo[3.3.0]octane-1-thianium compounds (III). Treatment of 3-(2-tetrahydrofuryl) propanol (VIII, R=OH) with thionyl chloride in benzene solution, followed by heating the crude chloride (VIII, R=Cl) with thiourea in ethanol gave the corresponding isothiuronium salt [VIII, R=$SC(NH_2)_2^+$ Cl^-] which was then hydrolyzed to 3-(2-tetrahydrofuryl) propyl mercaptan (VIII, R=SH) by warm aqueous ammonia. Bicyclo[3.3.0]octane-1-thianium bromide (III, X=Br) resulted from heating the mercaptan in a mixture of equal volumes of acetic anhydride and 48% hydrobromic acid for 18 hours.

Bicyclo[4.3.0]nonane-1-thianium compounds (IV). The method of Fieser and Kennelly[6] was used to prepare 4-(2-thienyl) butyric acid which was converted to methyl 4-(2-tetrahydrothienyl) butyrate (IX, R=$COOCH_3$) by palladium-on-charcoal catalyzed hydrogenation[7] in methanolic sulfuric acid. The ester was isolated as its mercuric chloride addition product, from which it could be recovered by treatment with hydrogen sulfide. Reduction of methyl 4-(2-tetrahydrothienyl) butyrate with lithium aluminum hydride gave 4-(2-tetrahydrothienyl) butanol (IX, R=CH_2OH). Bicyclo[4.3.0]-nonane-1-thianium chloride (IV, X=Cl) and bromide (IV, X=Br) were prepared by heating 4-(2-tetrahydrothienyl) butanol (IX, R=CH_2OH) with solutions of equal volumes of acetic anhydride with concentrated hydrochloric and hydrobromic acids, respectively. These sulfonium salts were markedly hygroscopic.



IX X XI

Bicyclo[4.4.0]decane-1-thianium compounds (V). The key substance in the synthesis of compounds of type V was 1,9-diphenoxy-5-mercaptononane (X, R=SH) which, on being refluxed with a solution of equal volumes of acetic anhydride and 48% hydrobromic acid, underwent cleavage of the phenoxy groups and cyclization to give bicyclo (4.4.0) decane-1-thianium bromide (V, X=Br). The corresponding picrate (m.p. 178–179°), iodide, chloride, and hydroxide were prepared (Experimental).

Two routes were developed for the preparation of the mercaptan (X, R=SH) from 1,9-diphenoxy-5-bromononane (X, R=Br), in turn prepared by treatment of the corresponding alcohol (X, R=OH) with phosphorus tribromide in carbon disulfide solution. In one, the bromide was converted in essentially quantitative yield to the corresponding thiocyanate (X, R=SCN) which was reduced with lithium aluminum hydride to the desired mercaptan (X, R=SH). Alternatively, the bromide was converted to the isothiuronium salt [X, R=$SC(NH_2)_2^+Br^-$], and the latter hydrolyzed with ammonia to the mercaptan.

The preparation of 1,9-diphenoxy-5-nonane 1 (X,R=OH) is described in the Experimental section.

Discussion. Attempts to dehydrohalogenate and aromatize the bicyclo[4.4.0]decane-1-thianium system to VI using sulfur and palladium gave only tars. When the sulfonium hydroxide V (X=OH) was thermally decomposed, Hoffmann elimination occurred to yield 2-(3-butenyl) tetrahydrothiopyran (XI) as evidenced by intense bands at 990 and 910 $cm.^{-1}$ in the infrared spectrum of the product that are characteristic[8] of the terminal vinyl group.

Although the possibility of *cis-trans* isomerism of the decalin type exists in compounds III, IV, and V, no evidence for the existence of such isomers was obtained.

The most toxic of the compounds tested was bicyclo[4.4.0]decane-1-thianium bromide (V, X=Br) which showed a minimum lethal dose of 43 mg./kg. on intraperitoneal injection in Webster white mice. The drug-induced convulsions and death could be prevented by prior administration of central nervous system depressants (Nembutal) but not by atropine.[9]

(5) N. J. Leonard, T. L. Brown, and T. W. Milligan, *J. Am. Chem. Soc.*, **81**, 504–5 (1959); C. G. Overberger and A. Lusi, *J. Am. Chem. Soc.* **81**, 506–7 (1959).

(6) L. F. Fieser and R. G. Kennelly, *J. Am. Chem. Soc.*, **57**, 1611 (1935).

(7) R. Mozingo, *J. Am. Chem. Soc.*, **67**, 2092 (1945).

(8) N. Sheppard and G. B. B. M. Sutherland, *Proc. Roy. Soc.*, **A196**, 195 (1949).

(9) We wish to express our appreciation of Professor R. H. Dreisbach and J. V. Levy of the Department of Pharmacology and Therapeutics of the Stanford University School of Medicine for testing the compounds.

EXPERIMENTAL[10]

3-(2-Tetrahydrofuryl)propyl isothiuronium picrate [VIII, $R = SC(NH_2)_2^+$ *picrate*]. To a solution of 40 g. of 3-(2-tetrahydrofuryl)propanol in 125 ml. of dry benzene was added 39 g. of thionyl chloride during 15 min. The reaction mixture was boiled for 20 min. and then freed of solvent at room temperature using the aspirator. To the residue was added 120 ml. of ethanol containing 21 g. of thiourea and the resulting solution was heated at 90° for 16 hr. Removal of solvent at the aspirator left a thick glass which could not be induced to crystallize. A small portion was taken up in alcohol and treated with picric acid. Addition of water yielded a bright yellow solid, 3-(2-tetrahydrofuryl)propyl isothiuronium picrate, which was crystallized from ethanol giving yellow crystals of m.p. 177.5–178.7°.

Anal. Calcd. for $C_{14}H_{19}N_5O_9S$: C, 40.28; H, 4.59. Found: C, 40.58; H, 4.75.

Bicyclo[3.3.0]octane-1-thianium picrate (III, X = *picrate*). A mixture of 45 g. of the crude 3-(2-tetrahydrofuryl)propyl isothiuronium chloride (see above) and 100 g. of concentrated ammonia was heated for 3 hr. on the steam bath. The cooled mixture was extracted with benzene and the benzene was removed by distillation leaving 18 g. of crude 3-(2-tetrahydrofuryl)propyl mercaptan (VIII, R = SH). A mixture of 17 g. of the crude mercaptan and 300 ml. of concentrated hydrochloric acid was heated for 16 hr. on the steam bath, cooled, diluted with 200 ml. of water, and filtered to remove a small amount of solid. The filtrate was extracted with 75 ml. of benzene and then evaporated to dryness at 50° and reduced pressure. The residue was taken up in 75 ml. of water, the solution was filtered, and the filtrate combined with a solution of 30 g. of picric acid and 4.6 g. of sodium hydroxide. The yellow precipitate which appeared was separated by filtration and crystallized twice from water to give 31 g. of bicyclo[3.3.0]octane-1-thianium picrate in the form of bright yellow crystals of m.p. 257–258°.

Anal. Calcd. for $C_{13}H_{15}N_3O_7S$: C, 43.69; H, 4.23; N, 11.76. Found: C, 43.83; H, 4.25; N, 11.55.

Bicyclo[3.3.0]octane-1-thianium bromide (III, X = *Br*). The crude 3-(2-tetrahydrofuryl)propyl mercaptan obtained from 3.5 g. of 3-(2-tetrahydrofuryl)propyl isothiuronium picrate by hydrolysis with 50 ml. of concentrated ammonia and hexane extraction of the hydrolysis mixture followed by removal of solvent, was heated at 80° for 18 hr. with a mixture of 15 ml. of 48% hydrobromic acid and 15 ml. of acetic anhydride. The cooled reaction mixture was diluted with an equal volume of water and filtered. The filtrate was extracted with 75 ml. of benzene, and then evaporated to dryness at 70–80° (20 mm.). The residue was taken up in 30 ml. of absolute ethanol, the solution was decolorized with Darco, then evaporated to dryness. The residue was taken up in 20 ml. of absolute ethanol, the solution was decolorized, concentrated to a volume of 4 ml., and then diluted with dry ether to the point of cloudiness. After 10 hr. at 0°, filtration followed by an ether wash of the solid, gave 1.3 g. of white crystals which sublimed above 240°. Recrystallization from absolute ethanol gave material which sublimed sharply at 249.5–250.5°. Treatment with a solution of picric acid in water converted this material to bicyclo[3.3.0]octane-1-thianium picrate, identical in melting point and mixed melting point with that described above.

Methyl 4-(2-tetrahydrothienyl)butyrate (IX, R = $COOCH_3$). A suspension of 6.3 g. of Darco in 130 ml. of methanol containing 0.3 g. of palladium chloride was shaken with hydrogen at 40 p.s.i. during 30 min.[7] Then, 0.20 ml. of concentrated sulfuric acid and 1.2 g. of 4-(2-thienyl) butyric acid[8] were added, and the hydrogenation was effected by shaking the mixture for 6 hr. at 40 p.s.i. hydrogen pressure. After filtering off the catalyst, 3.55 g. of powdered mercuric chloride was added to the filtrate. The mercuric chloride was dissolved by gentle warming, and when a solution was obtained an equal volume of water was added. After 12 hr. at 0°, the white crystals which had formed were separated by filtration, washed with water, dried in air, and crystallized twice from methanol to give a 50% yield of the mercuric chloride adduct of methyl 4-(2-tetrahydrothienyl)-butyrate of m.p. 106.4°–106.9°.

Anal. Calcd. for $C_9H_{16}O_2S.HgCl_2$: C, 23.58; H, 3.51; S, 6.97. Found: C, 23.46; H, 3.48; S, 6.90.

4-(2-Tetrahydrothienyl) butanol (IX, R = CH_2OH). A suspension of 27 g. of the mercuric chloride adduct of methyl 4-(2-tetrahydrothienyl)butyrate in 100 ml. of methanol was saturated with hydrogen sulfide. After filtering off the precipitate of mercuric sulfide, the methanol was removed by distillation at reduced pressure. The oil so obtained was taken up in dry ether, the solution was dried with Drierite, and the solvent was removed to leave 9.9 g. of methyl 4-(2-tetrahydrothienyl)butyrate, a pale yellow oil. This ester was reduced by adding it in solution in 200 ml. of absolute ether, during 30 min. to a solution of 8.0 g. of lithium aluminum hydride in 300 ml. of absolute ether. The reaction mixture was refluxed for 30 min., and the excess hydride was decomposed by the addition of 70 ml. of methanol followed by 6*N* hydrochloric acid in such amount as to dissolve the solids present. The ether layer was separated, the aqueous layer was extracted with five 100-ml. portions of ether, and the combined extracts were dried over potassium carbonate, and freed of solvent by distillation. The residue, crude 4-(2-tetrahydrothienyl)butanol, weighed 8.0 g. (85% yield).

For characterization, the α-naphthylurethane (m.p. 78.6–79.3°) was prepared in the usual manner by heating the reactants at 90° for 4 hr., followed by extraction and crystallization of the product using hexane.

Anal. Calcd. for $C_{19}H_{23}O_2NS$: C, 69.26; H, 7.04; N, 4.25; S, 9.73. Found: C, 69.17; H, 6.90; N, 4.31; S, 9.73.

Bicyclo[4.3.0]nonane-1-thianium chloride (IV, X = *Cl*). A mixture of 100 mg. of crude 4-(2-tetrahydrothienyl)butanol and 5 ml. of concentrated hydrochloric acid was heated at 120° for 3 hr. The clear solution was evaporated to dryness at 50° (25 mm.) and the residue was 4 times taken up in 3-ml. portions of absolute ethanol with intervening evaporations to dryness at 50° (25 mm.). The final residue was dissolved in 5 ml. of hot water and the solution was combined with a solution of 0.16 g. of picric acid in 5 ml. of hot water. After 12 hr. at 0°, the yellow crystals which had separated were collected and crystallized from 5 ml. of water to yield 0.15 g. of bicyclo[4.3.0]nonane-1-thianium picrate of m.p. 234.5–235°.

Anal. Calcd. for $C_{14}H_{17}O_7N_3S$: C, 45.28; H, 4.61; N, 11.31; S, 8.63. Found: C, 45.48; H, 4.56; N, 11.39; S, 8.52.

The picrate (0.10 g.), dissolved in 15 ml. of warm water, was passed through a 1 × 20 cm. column of Dowex 2 anion exchange resin which had previously been washed with 4*N* hydrochloric acid and water. The solution of the picrate was followed by 20 ml. of water, and the eluate was evaporated to dryness to yield bicyclo[4.3.0]nonane-1-thianium chloride in the form of highly hygroscopic white crystals. Treatment of an aqueous solution of the chloride with picric acid regenerated the picrate.

Bicyclo[4.3.0]nonane-1-thianium bromide (IV R = *Br*). The bromide was prepared in 87% yield from 4-(2-tetrahydrothienyl)butanol (4.0 g.) by treatment with 80 ml. of a 1:1 mixture by volume of 48% hydrobromic acid and acetic anhydride for 17 hr. at 85°. The reaction mixture was diluted with an equal volume of water and extracted with 75 ml. of benzene. The aqueous layer was filtered and taken to dryness at 80° (25 mm.). The residue was taken up in absolute ethanol and ether was added to incipient crystallization. After refrigeration, the crystalline mass was collected and crystallized from absolute ethanol to yield 4.9 g. of the bromide, m.p. 216.5–217° (sublimes).

Anal. Calcd. for $C_8H_{15}BrS$: C, 43.05; H, 6.77; Br, 35.81. Found: C, 43.14; H, 6.79; Br, 35.91.

(10) Melting points are not corrected. Analyses by Microchemical Specialties, Berkeley, Calif.

1,9-Diphenoxy-5-nonanol (X, *R* = *OH*). The preparation of this compound was effected by two procedures.

Procedure A. A solution of 56 g. of 1,9-diphenoxy-5-nonanone (prepared by the method of Walther,[11] and having m.p. 77.8–78.1°) in 600 ml. of methanol was maintained at 55–60° during the addition of a solution of 5 g. of sodium borohydride in 50 ml. of methanol. The solution was allowed to stand at room temperature for 2 hr., then acidified to *p*H 5 by the addition of concentrated hydrochloric acid. The solvent was removed at reduced pressure and the residue was extracted with the minimum amount of carbon tetrachloride. The extract was cooled to 3° and the crystals which separated were filtered off to yield 50.4 g. of 1,9-diphenoxy-5-nonanol of m.p. 58.3–59.0°. This material did not depress the melting point of that prepared by procedure B in a mixture.

Procedure B. A mixture of 59.1 g. of magnesium turnings and 400 ml. of dry ether was combined with a solution of 450 g. of ε-phenoxybutyl chloride (prepared in 63% yield by the action of sodium phenolate on 1,4-dichlorobutane in aqueous solution and having b.p. 92–93° (0.5 mm.) m.p. *ca.* 20°) in 1 l. of anhydrous ether, at such a rate as to maintain gentle reflux. To the solution of the Grignard reagent, cooled in an ice bath, was added a solution of 87.5 g. of ethyl formate in 250 ml. of dry ether during 4 hr. The reaction mixture was decomposed with 160 ml. of water followed by a solution of 136 g. of concentrated sulfuric acid in 640 ml. of water. The ether layer was separated, the aqueous layer was extracted with ether, and the combined ether solutions were dried over potassium carbonate, and distilled to dryness. The oily residue was crystallized from carbon tetrachloride to yield 315 g. of 1,9-diphenoxy-5-nonanol of m.p. 59–60°. Several crystallizations from carbon tetrachloride gave material of m.p. 60.0–60.5°.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.84; H, 8.67.

1,9-Diphenoxy-5-bromononane. A mixture of 125 g. of 1,9-diphenoxy-5-nonanol and 125 g. of phosphorus tribromide was dissolved in 100 ml. of carbon disulfide and the solution was allowed to stand for 1 week. The carbon disulfide was removed in a current of air, the residue was decomposed by the addition of ice and the product was taken up in ether. Evaporation of the dried ether solution followed by crystallization of the residue from 300 ml. of methanol (0°) gave 128 g. of 1,9-diphenoxy-5-bromononane, m.p. 44–46°. Recrystallization from methanol raised the m.p. to 45.4–46.8°.

Anal. Calcd. for $C_{21}H_{27}BrO_2$: C, 64.43; H, 6.95. Found: C, 64.35; H, 7.02.

1,9-Diphenoxy-5-mercaptononane-S-mercuribromide (X, *R* = *SHgBr*). This derivative of the mercaptan X (R = SH), was prepared in two ways.

Procedure A. A solution of 10 g. of 1,9-diphenoxy-5-bromononane and 5.0 g. of potassium thiocyanate in 120 ml. of ethanol was boiled for 15 min., then cooled to yield 9.5 g. of 1,9-diphenoxy-5-thiocyanononane (X, R = SCN) in the form of white crystals of m.p. 62.8–64°.

Anal. Calcd. for: $C_{22}H_{27}NO_2S$: C, 71.50: H, 7.37; N, 3.79. Found: C, 71.55; H, 7.36; N, 4.00.

A mixture of 0.2 g. of thiocyanate and 3.5 g. of granulated zinc in 7 ml. of acetic acid was heated for 90 min. on the steam bath. The supernatant liquid was decanted, diluted with several volumes of water, and extracted with hexane. The hexane was boiled off and the residue was treated with a solution of mercuric bromide in ethanol to give a white precipitate of 1,9-diphenoxy-5-mercaptononane-*S*-mercuribromide of m.p. 117–118°. The yield was 50% of the theory and recrystallization from ethanol raised the m.p. to 118.5–120.1°.

Anal. Calcd. for $C_{21}H_{27}BrHgO_2S$: C, 40.42; H, 4.36. Found: C, 40.72; H, 4.61.

Reduction of the thiocyanate (14.4 g.) with lithium aluminum hydride (8 g.) in ether, followed by addition of mercuric bromide to an alcoholic solution of the product gave a 58% yield of the mercaptan-mercuribromide, identical with that described herewith.

Procedure B. A solution of 8.0 g. of 1,9-diphenoxy-5-bromononane and 1.6 g. of thiourea in 75 ml. of ethanol was refluxed for 48 hr. Five g. of picric acid was added to the reaction mixture and the product was precipitated as an oil which, after being cooled to 0°, crystallized. Crystallization of the solid from ethanol gave 7.5 g. of yellow crystals of m.p. 117.5–119.5°. Recrystallization gave pure 1,9-diphenoxynonane-5-isothiuronium picrate [X, R = $SC(NH_2)_2^+$ picrate$^-$] of m.p. 119.5–121°.

Anal. Calcd. for $C_{28}H_{33}N_5O_9S$: C, 54.62; H, 5.40; N, 11.38. Found: C, 54.81; H, 5.64; N, 11.12.

An 8.6-g. sample of the isothiuronium picrate was combined with 50 ml. of concentrated ammonia and 10 ml. of hexane, and the mixture was heated on the steam bath for 1-hr. The cooled reaction mixture was extracted with hexane, the extract was dried over sodium sulfate, and freed of solvent using the aspirator. The product, crude 1,9-diphenoxy-5-mercaptononane, was a pale yellow oil which crystallized when cooled to −10°. The oil was combined with a solution of 5.0 g. of mercuric bromide in 230 ml. of ethanol. The solution was brought to a boil, then allowed to cool. Filtration yielded 7.7 g. of 1,9-diphenoxy-5-mercaptononane-*S*-mercuribromide which melted at 117.5–119.2°. Digestion of the mercuribromide with hexane raised the melting point to 118.5–120.1°. This material showed no melting point depression when combined with the mercuribromide prepared by procedure A.

Bicyclo[4.4.0]decane-1-thianium picrate (V, *X* = *picrate*). A mixture of 4 g. of 1,9-diphenoxy-5-mercaptononane (prepared by treatment of the equivalent amount of the mercuribromide with H_2S in ethanol, followed by filtration and solvent removal), 20 ml. of 48% hydrobromic acid, and 20 ml. of acetic anhydride was refluxed for 18 hr. The cooled reaction mixture was diluted with water to a volume of 80 ml. and then extracted with 100 ml. of benzene. The aqueous layer was evaporated to dryness at 70° (20 mm.), and the residue was combined with a hot solution of 2.5 g. of picric acid in 200 ml. of water to give a yellow precipitate which after 2 crystallizations from water melted at 178.6–179.7° and constituted 2.9 g. of bicyclo[4.4.0]decane-1-thianium picrate.

Anal. Calcd. for $C_{15}H_{19}N_3O_7S$: C, 46.74; H, 4.97; N, 10.90. Found: C, 47.04; H, 5.06; N, 10.84.

In a similar experiment, the residue left after the removal of the aqueous layer (see above) was repeatedly crystallized from absolute alcohol to give a 66% yield of *bicyclo[4.4.0]-decane-1-thianium bromide* (V, *X* = *Br*), a white nonhygroscopic solid which sublimed at 266–267°.

Anal. Calcd. for $C_9H_{17}BrS$: C, 45.57; H, 7.25. Found: C, 45.82; H, 7.35.

Treatment of the bromide with picric acid in aqueous solution gave a picrate of m.p. 179–179.6°, identical with that described above.

When 1,9-diphenoxy-5-mercaptononane-*S*-mercuribromide was subjected to the hydrobromic acid–acetic anhydride treatment described above, a small amount of a green solid was obtained, which, after crystallization from ethanol, had m.p. 59.2–62.2°. Analysis indicated that this green solid was a double salt of mercuric bromide with bicyclo-[4.4.0]decane-1-thianium bromide.

Anal. Calcd. for $(C_9H_{17}S)_2HgBr_4$: C, 25.89; H, 4.10. Found: C, 25.89; H, 4.21.

Saturation of a suspension of the green solid in water with hydrogen sulfide, followed by filtration and addition of picric acid to the filtrate gave bicyclo[4.4.0]decane-1-thianium picrate of m.p. 177.5–179.0° which did not depress the melting point of the picrate described above.

Bicyclo[4.4.0]decane-1-thianium hydroxide (V, *R* = *OH*). The hydroxide was obtained as colorless, viscous, strongly basic sirup on evaporation of the filtrate from the combina-

(11) G. Walther, *Ber.*, **84**, 306 (1951).

tion of 50 ml. of water, 9.0 g. of silver oxide, and 4.5 g. of bicyclo[4.4.0]decane-1-thianium bromide.

A 3.5-g. sample of the hydroxide was heated for 6 hr. at 150°. The product was taken up in hexane, the solution was dried and freed of solvent. Distillation of the residual oil gave a mobile, colorless liquid, b.p. 100° (15 mm.), believed to be *2-(3-butenyl)tetrahydrothiopyran.*

Anal. Calcd. for $C_9H_{16}S$: C, 69.16; H, 10.32. Found: C, 68.94; H, 10.44.

Bicyclo[4.4.0]decane-1-thianium iodide (V, $X = I$). The iodide was prepared by titrating a sample of the sulfonium hydroxide with 47% hydriodic acid, followed by removal of water at 80° (20 mm.), and crystallization of the residue from absolute alcohol. The iodide was a white crystalline, relatively nonhygroscopic solid which sublimed at 264–265° with decomposition. Treatment with a solution of the iodide with picric acid gave the picrate, identical with that described herewith in a mixed melting point determination.

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Structures Related to Morphine. XI.[1] Analogs and a Diastereoisomer of 2′-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan

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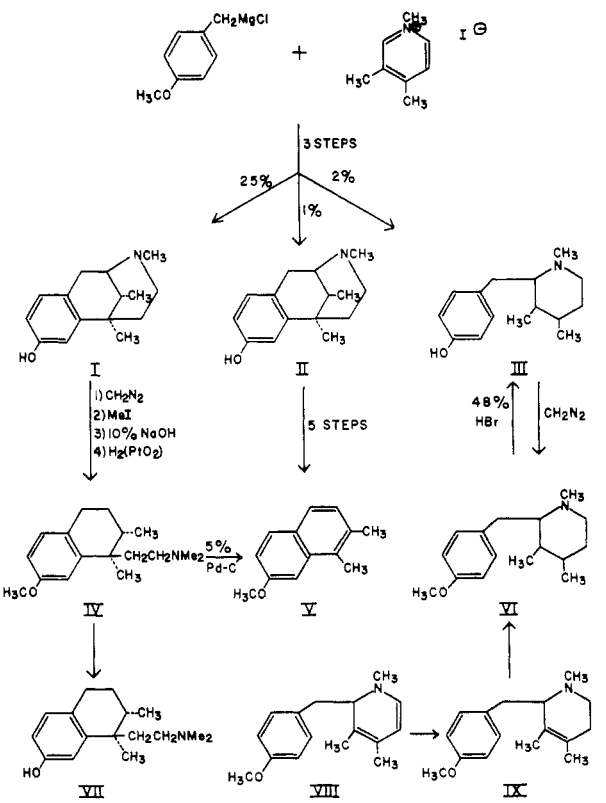
2′-Hydroxy-2,5,9-trimethyl-6,7-benzomorphan (I) has been degraded to 7-methoxy-1,2-dimethylnaphthalene (V) *via* 7-methoxy-1,2-dimethyl-1-(2-di-methylaminoethyl)-1,2,3,4-tetrahydronaphthalene (IV). Similar degradation of an isomeric by-product (II) obtained in 1% yield in the synthesis of I also gave V proving diastereoisomerism for I and II at carbon 9. Another by-product isolated in 2% yield appears to be the piperidine derivative (III). Hydrobromic acid treatment of IV yielded the phenolic base (VII) which is practically devoid of analgesic activity, paralleling results obtained in another series (*cf.* reference 3).

It has been amply demonstrated[2–4] that the introduction of a phenolic hydroxyl *meta* to the quaternary carbon in a number of synthetic compounds containing a phenyl- or benzo-azabicyclo structure characteristic of morphine, markedly improves analgesic behavior. On the other hand in the one published instance of similar substitution in an open nitrogen counterpart[3] there was an increase in acute toxicity and a fourfold decrease of analgesic potency unless the phenolic hydroxyl was protected by methyl. To determine whether this would be true in another series, 2′-hydroxy-2,5,9-trimethyl-6,7-benzomorphan (I) has been converted to 7 - hydroxy - 1,2 - dimethyl - 1 - (2 - dimethylaminoethyl)-1,2,3,4-tetrahydronaphthalene (VII) for comparison with the corresponding methoxy (IV) and deoxy[4] compounds. The transformation of I to VII was effected by exhaustive methylation of the methyl ether of I, hydrogenation of the resulting methine to the methyl ether (IV), and *O*-demethylation of IV with aqueous hydrobromic acid. Either the methine or the corresponding hydrogenated base (IV) could be aromatized to 7-methoxy-1,2-dimethylnaphthalene (V) which was used as a reference compound as described here.



In synthesizing larger amounts of I[4a] not only was an improved procedure developed but, in

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