Although several of the compounds were able to effect reductions of more than 90% in the worm burdens in mice with *Nippostrongylus brasiliensis*, this activity was only observed at doses near the toxic levels and it appears unlikely that they will be useful in anthelmintic therapy.

Experimental Section[21]

General Procedure for the Preparation of Methine Cyanine Iodides.—The legend in Tables II–IV described the methods whereby the methine cyanines were prepared. A representative example of each of these methods is herein outlined.

Method A.—5,6,7,8-Tetrahydro-4-methylthio-2-phenyl-1,3-benzoxazin-1-ium iodide[9] (23.0 g, 0.06 mole), 2-methylbenzothiazole methiodide (7.5 g, 0.06 mole), 350 ml of ethanol, and 10 ml of triethylamine were combined and heated near reflux for 1 hr. After cooling the reaction mixture, the solid was collected on a filter to yield 14.7 g (49%) of crude material. Recrystallization of this material from methanol yielded 2-[(5,6,7,8-tetrahydro-2-phenyl-4H-1,3-benzoxazin-4-ylidene)methyl]-3-methylbenzothiazolium iodide (**3**). See Table I for analytical data of this substance and other compounds prepared by this method.

(21) Melting points were obtained on a Thomas–Hoover capillary melting point apparatus and are corrected. Ultraviolet spectra were recorded on a Cary 14 recording spectrophotometer.

Compound **3** (1.0 g, 0.002 mole) and 10 ml of aniline were refluxed for 1 hr. Upon cooling, a solid formed which was collected and crystallized from ethanol to yield 400 mg (35%) of 2-[(5,6,7,8-tetrahydro-1,2-diphenyl-4(1H)-quinazolidene)methyl]-3-methylbenzothiazolium iodide (**6**).

Method B. 5,6,7,8-Tetrahydro-1,2-diphenyl-4-methylthioquinazolin-1-ium Iodide (5).—To 5,6,7,8-Tetrahydro-1,2-diphenyl-4-quinazolinethione (4.0 g, 0.012 mole) in 200 ml of acetone there was added dropwise 1.7 g (0.012 mole) of methyl iodide. After refluxing the reaction mixture overnight the solvent was removed *in vacuo* to give a yellow solid. Crystallization of this material from acetone gave 3.2 g of **5**, mp 262–263°.

Anal. Calcd for $C_{21}H_{21}IN_2S$: C, 54.78; H, 4.60; N, 6.09. Found: C, 54.63; H, 4.92; N, 5.88.

5,6,7,8-Tetrahydro-1-*p*-fluorophenyl-2-phenyl-4-methylthioquinazolin-1-ium iodide was prepared as above.

Anal. Calcd for $C_{21}H_{20}FIN_2S$: C, 52.72; H, 4.22; N, 5.86. Found: C, 52.67; H, 4.44; N, 5.67.

5,6,7,8-Tetrahydro-1-decyl-2-phenyl-4-methylthioquinazolin-1-ium iodide was prepared as above.

Anal. Calcd for $C_{25}H_{37}IN_2S$: C, 57.24; H, 7.11; N, 5.34. Found: C, 56.94; H, 7.51; N, 5.07.

5,6,7,8-Tetrahydro-1,2-diphenyl-4-methylthioquinazolin-1-ium iodide (**5**) (2.5 g, 0.0054 mole), 2-methylbenzothiazole methiodide (1.6 g, 0.0054 mole), 50 ml of ethanol, and 2 ml of triethylamine were combined and the solution was heated under reflux for 16 hr. After cooling the solution in an ice bath, the crystals were collected and recrystallized from ethanol to yield 1.6 g (52%) of **6**.

Notes

Tremorine-Antagonistic Cyclic Ketals. The Reactions of Epoxy Ethers with Ethylene Chlorohydrin[1]

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As part of a study of unsymmetrical amino ketals possessing pharmacological activity,[3] we have examined the reactions of epoxy ethers (I)[4,5] with ethylene chlorohydrin. In one instance spontaneous rearrangement of Ia to 1-methoxy-1-phenyl-2-propanone was observed.[6] Treatment of Ia with ethylene chlorohydrin afforded a small amount of α-methoxypropiophenone and a mixture of dioxanes (III and IV) (see Scheme I). The strong methoxyl peak (3.2 ppm) of IV was apparent in the nmr spectrum of a crude product mixture (Figure 1a). Purification resulted in the loss of the methoxyl signal and an nmr spectrum consistent with structure III (Figure 1b). The dioxane ring proton quartet at 4.0 ppm (J = 7 cps) was distinguished from the chloroethoxyl multiplet at 3.7 ppm in a 100-Mc spectrum. The second reaction product (IV) was never isolated in pure form and its structure is inferred solely on the basis of the similarity of its nmr spectral features to those of the major product (III) with the additional methoxyl peak and the absence of any obvious differences in the infrared spectra of pure and impure samples of III. In addition, analytical data on impure samples could be rationalized on the presence of amounts of IV consistent with the indications of thin layer chromatograms and nmr spectra. Similarly, no direct evidence is available for the intermediate formation of the monomeric chloro ketal (IIa). The intervention of IIa is probable, however, as analogous compounds were isolated in connection with other epoxy ethers.[3] Furthermore, the dimerization of IIa with elimination of alkoxyl in the presence of excess ethylene chlorohydrin provides a logical route to III and IV. Analogous dimerization of α-hydroxy ketals and acetals has been reported.[3,7] Chemical evidence substantiated the above conclusions. The ketal dioxane (III) was resistant to basic hydrolytic conditions, but unstable in acid media. Treatment of III with hydrochloric acid in aqueous dioxane resulted in a yellow oil believed to be a mixture of the isomeric hydroxy ketones Va and Vb. The infrared spectrum of the yellow oil was similar to that obtained from a sample of Va prepared by the method of Temni-

(1) Abstracted in part from theses submitted by H. L. Johnson and A. R. Patel in partial fulfillment of Ph.D. degree requirements.

(2) Fellow of the American Foundation for Pharmaceutical Education, 1959–1961. Recipient of the Josiah Kirby Lilly Memorial Fellowship, 1961. Inquiries should be sent to the Department of Pharmaceutical Chemistry, Life Sciences Research, Stanford Research Institute, Menlo Park, Calif.

(3) H. L. Johnson and J. F. Oneto, *J. Pharm. Sci.*, **54**, 59 (1965).

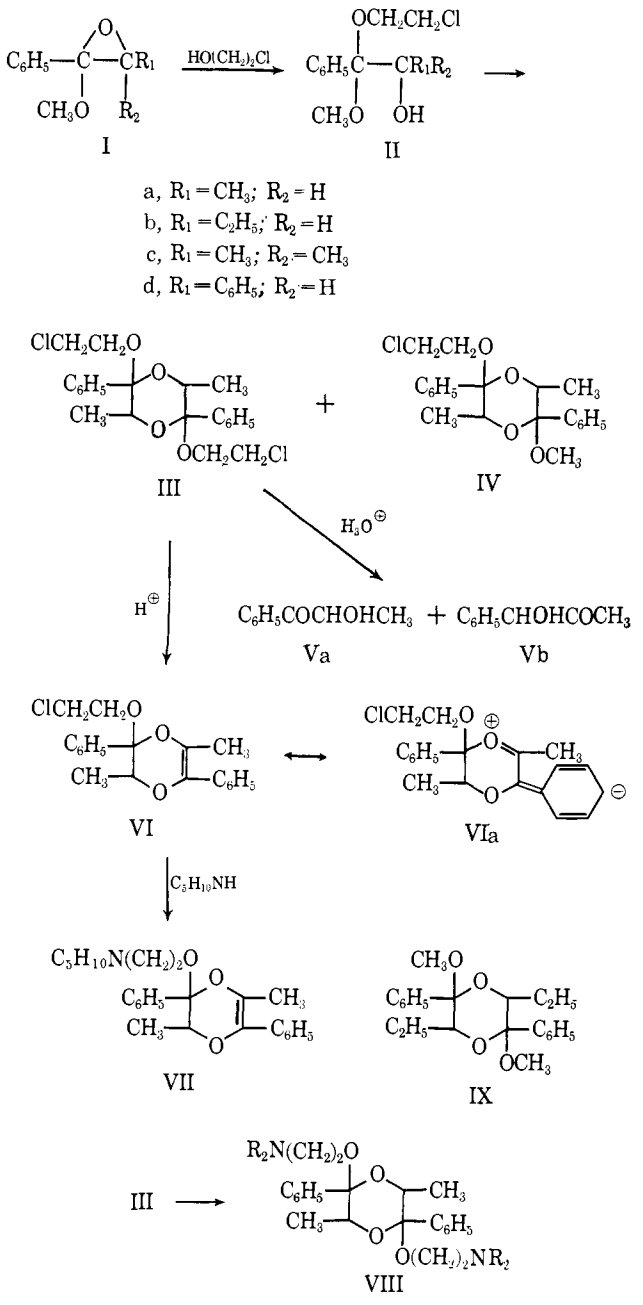
(4) T. I. Temnikova and E. N. Kropacheva, *J. Gen. Chem. USSR*, **19**, 1917 (1949).

(5) C. L. Stevens, W. Malik, and R. Pratt, *J. Am. Chem. Soc.*, **72**, 4758 (1950).

(6) C. L. Stevens and S. J. Dykstra, *ibid.*, **76**, 1102 (1954).

(7) (a) T. I. Temnikova and E. N. Kropacheva, *J. Gen. Chem. USSR*, **22**, 1197 (1952); (b) W. E. Parham and H. E. Reiff, *J. Am. Chem. Soc.*, **77**, 6391 (1955).

SCHEME I



kova.[8,9] Nitric acid oxidation of III gave a nearly quantitative yield of benzoic acid.

Pyrolysis of III in an open tube at 200° or its treatment with hydrochloric acid in chloroform for a short period of time produced the same derivative (VI). The ultraviolet spectrum of VI indicated a conjugated chromophore of modified styrene type. The infrared and ultraviolet data are consistent with the cyclic enol nature of the system and the limited possibility for extended conjugation through resonance structures such as VIa. The nmr spectrum of VI (Figure 2) as compared to that of III (Figure 1b) showed an unresolved multiplet at *ca.* 3.6 ppm corresponding to the 2,5-proton quartet and the chloroethoxyl multiplet of

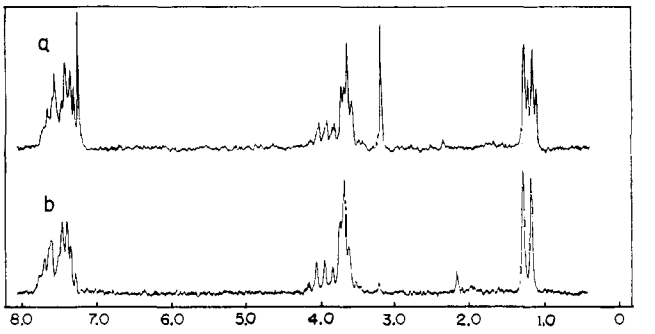


Figure 1.—Proton nmr spectra of samples of increasing purity of 2,5-dimethyl-3,6-diphenyl-3,6-di(β-chloroethoxy)-1,4-dioxane (III) in $CDCl_3$ at 60 Mc. Chemical shifts are in parts per million (δ).

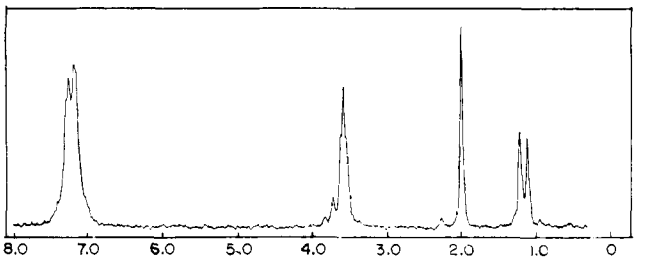


Figure 2.—Proton nmr spectrum of 2,5-dimethyl-3,6-diphenyl-6-(β-chloroethoxy)-1,4-dioxene (VI) in $CDCl_3$ at 60 Mc. Chemical shifts are in ppm (δ).

III, but of one-half intensity. The 2-methyl group of VI, now bonded to an olefinic carbon, produced a single peak at 2.05 ppm and the remaining methyl group gave the doublet at 1.20 ppm (J = 7 cps) with one-half the intensity of that in the spectrum of III. The areas obtained by electronic integration of the spectrum were in the ratio of 10:5:3:3 for phenyl, 5-proton and chloroethoxyl, 5-methyl, and 2-methyl, respectively. Treatment of the dioxene derivative (VI) with piperidine resulted in a viscous, noncrystallizable oil. The oxalate salt of the oil showed a correct analysis for VII oxalate. The formation of VI serves as additional support for the structure of III. Similar eliminations in substituted dioxanes have been described in the literature.[7b,10] That the reaction involved in the conversion of III to VI might have some bearing on the anomolous methoxyl analysis obtained for III is suggested by the observation that VI failed to give a positive Zeisel methoxyl test. The monomeric α-hydroxy ketal IId, obtained from Id and ethylene chlorohydrin and containing both β-chloroethoxyl and methoxyl groups, analyzed correctly for methoxyl.[3] This indicates noninterference of the β-chloroethoxyl moiety in the determination. Treatment of III with pyrrolidine yielded VIIIa [$N(R)_2$ = pyrrolidino] and with piperidine yielded VIIIb [$N(R)_2$ = piperidino]. Infrared and nmr data indicated the absence of hydroxyl, carbonyl, and alkene moieties and supported structures VIIIa and VIIIb. In particular, the 2- and 5-proton quartet was clearly visible in both nmr spectra. Epoxy ethers Ib[11] and Ic[11,12] reacted with ethylene chlorohydrin to yield known dimeric

(8) T. I. Temnikova, *J. Gen. Chem. USSR*, **10**, 468 (1940).

(9) It is reported that Va isomerizes to Vb and that derivatives of the alternate isomer or both are obtained from either Va or Vb: A. E. Favorskii and T. I. Temnikova, *Compt. Rend.*, **198**, 1998 (1934).

(10) M. Bergmann and A. Miekeley, *Ber.*, **62**, 2297 (1929); M. Bergmann and G. Weil, *ibid.*, **63**, 1911 (1930).

(11) T. I. Temnikova and N. Almashi, *Dokl. Akad. Nauk USSR*, **81**, 211 (1951).

(12) C. L. Stevens and T. H. Coffield, *J. Am. Chem. Soc.*, **80**, 1919 (1958).

products (IX[11] and the anhydro dimer of α-hydroxyisobutyrophenone[13]).

Preliminary pharmacologic examination of the tertiary amine derivatives (VIII) disclosed less potent antitremorine activity than exhibited by the previously prepared monomeric amino ketals.[3] By the same test method in mice VIIIa completely prevented the tremor and some parasympathomimetic effects of tremorine (20 mg/kg) in doses of 100–200 mg/kg. Such doses were tolerated acutely by the animals but were productive of apparent CNS depression and/or motor deficit. Salivation and lacrimation were not consistently antagonized. Doses of 25–75 mg/kg were not completely effective but resulted in delayed onset of tremor. Because of fatal toxicity at the highest dosages and relatively low potency the compounds were not studied further.

Experimental Section[14]

Preparation of Epoxy Ethers.—The epoxy ethers 1-methoxy-1-phenyl-1,2-epoxypropane (Ia) and 1-methoxy-1-phenyl-1,2-epoxybutane (Ib) were prepared according to the method of Stevens and co-workers.[5] The yield of Ia from α-chloropropiophenone was 57%, bp 58–60° (3 mm), 79–82° (8 mm) [lit.[4] bp 63–65° (4 mm)]. The yield of Ia from α-bromopropiophenone was 65%, bp 58–62° (3 mm); benzoate derivative (α-hydroxypropiophenone benzoate), mp 109–110° (lit.[5] mp 108–109°); phenylhydrazone derivative (phenylhydrazidophenylhydrazone of methylbenzoylcarbinol), mp 126–127° (lit.[4] mp 126°). The yield of Ib from α-bromobutyrophenone was 62%, bp 64–68° (3 mm) [lit.[11] bp 94–95° (10 mm)]. The epoxy ether 1-methoxy-1-phenyl-2-methyl-1,2-epoxypropane (Ic) was prepared by the method of Stevens and Coffield.[12] The yield of Ic from α-bromoisobutyrophenone was 72%, bp 61–63° (3 mm) [lit.[12] bp 68–70° (3 mm)].

1-Methoxy-1-phenyl-2-propanone.—α-Bromopropiophenone (175.0 g, 0.82 mole) was added dropwise at room temperature to a stirred suspension of sodium methoxide (45.0 g, 0.83 mole) in anhydrous ether (500 ml). The mixture was refluxed for 2 hr, filtered, and refrigerated overnight. The ether was removed *in vacuo* and the yellow oil residue distilled. The initial fraction [bp 58–65° (3 mm)] was redistilled. The major fraction was identified as 1-methoxy-1-phenyl-2-propanone, bp 70–75° (3 mm) [lit.[15] bp 109° (14 mm)]. Ultraviolet and infrared spectra showed the presence of a nonconjugated carbonyl function. The product gave positive iodoform and Zeisel alkoxyl tests and formed an unstable phenylhydrazone derivative, mp 90.5–91.5°.

Anal. Calcd for $C_9H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 72.89; H, 7.33.

Semicarbazone, mp 155–156° (lit.[15] mp 157.5–158.5°).

Anal. Calcd for $C_{11}H_{15}N_3O_2$: N, 18.99. Found: N, 18.85.

Reaction of 1-Methoxy-1-phenyl-1,2-epoxypropane (Ia) with Ethylene Chlorohydrin.—The epoxy ether Ia (4.15 g, 0.25 mole) was added dropwise with stirring and cooling to 80.5 g (1.0 mole) of ethylene chlorohydrin over a period of 90 min. The temperature was maintained below 25°. After addition was complete the mixture was stirred for 15 min. The precipitate was washed with cold methanol. The yield of product was 22 g, mp 192–193° after recrystallization from pyridine. The methanol washings were added to the filtrate and the mixture distilled under vacuum to remove unreacted ethylene chlorohydrin and methanol. The residual liquid was washed with distilled water and extracted with ether. After evaporation of the ether, distillation of the residual yellow oil gave a fraction (4.6 g) boiling at 62–70° (3 mm). The melting point of the semicarbazone of this fraction (161–162.5°) indicated it to be α-methoxypropiophenone (lit.[5] mp 161–162°).

A sample of the solid product recrystallized three times from pyridine exhibited mp 195–196° dec. Thin layer chromatography of the recrystallized material (silica gel G on glass plates with benzene as the eluent) gave two spots indicating two discreet components, hereafter referred to as A and B. The major component, A, exhibited an R_f value of 0.83, and the minor component, B, exhibited and R_f value of 0.73.

Anal. Found: C, 63.46, 63.41; H, 6.45, 6.51; Cl, 15.56, 15.55; OCH_3, 13.15; mol wt, 445; C-methyl, 9.2.

After several recrystallizations from benzene (decolorizing carbon) component A [R_f 0.83, 2,5-dimethyl-3,6-diphenyl-3,6-di(β-chloroethoxy)-1,4-dioxane (III)] was obtained pure, indicated by thin layer chromatography. Proton nmr spectra obtained in $CDCl_3$ solutions on individual samples from the above stages of purification indicated increasing degrees of purity and supported the above structural assignment. The 60-Mc nmr interpretation (Figure 1b) was substantiated by a spectrum obtained at 100 Mc which indicated no variation in the value of the coupling constant for the 2,5-proton quartet and methyl doublet. Addition of deuterium oxide to the solution of the dimer in $CDCl_3$ did not alter the nmr spectrum; peak at *ca.* 2.2 ppm due to $CDCl_3$ impurities; $\lambda_{max}^{mmμ}$ 257 mμ (ε ~510); λ_{max}^{KBr} 9.25, 9.8 μ (COC).

Anal. Calcd for $C_{22}H_{28}Cl_2O_4$: C, 62.12; H, 6.16; Cl, 16.67; mol wt, 425; OCH_3, 0. Found: C, 62.35; H, 6.11; Cl, 16.58; mol wt, 410, 428; OCH_3, 10.44.

Thin layer chromatography of the material from recrystallization mother liquors gave two spots of approximately equal intensity, the R_f values of which were in agreement with those found for components A and B above. The nmr spectrum (Figure 1a) in $CDCl_3$ indicated that this material was a mixture of two similar components in approximately equal amounts. It was assumed that component B might be 2,5-dimethyl-3,6-diphenyl-3-methoxy-6-(β-chloroethoxy)-1,4-dioxane (IV).

Anal. Calcd for 45% $C_{22}H_{28}Cl_2O_4$ (III) and 55% $C_{21}H_{25}ClO_4$ (IV): C, 64.78; H, 6.45; Cl, 12.68; mol wt, 398. Found: C, 65.04; H, 6.59; Cl, 12.98; mol wt, 400 (cryoscopic, Rast).

Attempted Hydrolysis of the Dimer (III) in Alkaline Media.—A mixture of 4.7 g (0.011 mole) of III in 75 ml of 35% water in dioxane containing 10 g of KOH was refluxed for 12 hr with stirring. The unreacted dimer was recovered in 93% yield (4.4 g), mp 197–198°, undepressed upon admixture with starting material.

Acid Hydrolysis of III.—A mixture of 6.8 g (0.016 mole) of III in 40 ml of 50% dioxane–water containing 5 ml of 37% HCl was refluxed for 10 hr. The solvent was removed by distillation. The residual yellow oil was treated with 35 ml of 2% NaOH solution and extracted with chloroform. The $CHCl_3$ phase was dried (Na_2SO_4) and concentrated to a yellow oil under reduced pressure. Distillation yielded 2.9 g of yellow oil collected at 120–160° (16 mm). The distillate gave a negative Zeisel test for alkoxyl and formed a white, water-soluble compound with saturated sodium bisulfite solution; mp above 220°. It decolorized bromine in CCl_4 with the liberation of HBr and gave a negative iodoform test and a positive periodate test with an accompanying odor of benzaldehyde. The infrared spectrum exhibited prominent bands at 2.95 (OH), 5.85, 5.95 (doublet, carbonyl), and a weaker band at 6.3 μ. The semicarbazone derivative melted at 177–178° dec after three recrystallizations from 95% ethanol. The reported values for the melting point of the semicarbazone of phenylacetylcarbinol are 189° and 182–183°.[1,16]

(13) A. Favorskii, *J. Russ. Phys. Chem. Soc.*, **44**, 1339 (1912); T. I. Temnikova and N. I. Ahnashi, *J. Gen. Chem. USSR*, **23**, 1338 (1953).

(14) Melting points (corrected) were determined on a Thomas–Hoover capillary apparatus. Boiling points are uncorrected. Elemental analyses, molecular weight determinations (osmometric unless otherwise indicated), methoxyl, and C-methyl determinations are by the Microanalytical Laboratory, Department of Chemistry, University of California, Berkeley, Calif. Ultraviolet spectra were obtained on a Cary Model 11 recording spectrophotometer and infrared spectra on a Perkin-Elmer Model 21 double-beam recording spectrophotometer using potassium bromide pellets. Proton nmr spectra were obtained on a Varian Associates Model A-60 spectrometer with tetramethylsilane as internal reference and carbon tetrachloride as solvent unless otherwise noted. The nmr instrument was purchased with funds from National Science Foundation Grant G21268. Values of chemical shifts, δ, are reported in parts per million (ppm) downfield from the tetramethylsilane peak taken as zero. The 100-Mc nmr spectrum of III in $CDCl_3$ was obtained on a Varian HR-100 spectrometer through the courtesy of Dr. N. Bhacca of Varian Associates, Palo Alto, Calif. Qualitative methoxyl tests were performed by the method of Zeisel (R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, John Wiley and Sons, Inc., New York, N. Y., 1956, p 116). The authors are indebted to Mr. M. Brenoff for technical assistance and to Dr. L. A. Strait for interpretive assistance with infrared and ultraviolet spectra.

(15) K. v. Auwers, H. Lublwig, and A. Müller, *Ann.*, **526**, 143 (1936).

(16) T. I. Temnikova and E. N. Kropacheva, *J. Gen. Chem. USSR*, **21**, 183 (1951).

Anal. Calcd for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.78; H, 6.73; N, 19.99.

An additional recrystallization from absolute ethanol raised the melting point to 185–186°.

Oxidation of III.—A suspension of 1.0 g (0.0024 mole) of III in 40 ml of 30% HNO_3 was refluxed for 7 hr. The reaction mixture was chilled and the resulting precipitate was filtered and washed with water. The ether extract of the filtrate afforded additional crystalline material. The total yield of benzoic acid was 0.5 g (85%), mp 119–120°. After recrystallization from water, the melting point was 120–121°, undepressed upon admixture with an authentic sample.

Treatment of III with HCl in Chloroform. 2,5-Dimethyl-3,6-diphenyl-6-(β-chloroethoxy)-1,4-dioxene (VI).—A mixture of 1.7 g (0.004 mole) of III in 30 ml of $CHCl_3$ containing 4 drops of concentrated HCl was refluxed for 20 min. The solvent was immediately removed by evaporation in an open dish on a steam cone. Petroleum ether (bp 30–60°) was added to the residual oil, and the mixture was chilled and filtered. The product was recrystallized twice from petroleum ether; yield 1.0 g (73%), mp 107–110°. An analytical sample obtained by additional recrystallizations from the same solvent melted at 110–112°. The infrared spectrum showed no hydroxyl absorption and was identical with that of the compound obtained below by pyrolysis of III. A mixture melting point exhibited no depression. The compound gave a negative Zeisel test for alkoxyl groups. Addition of D_2O to the solution did not alter the nmr spectrum (Figure 2); λ_{max}^{hexane} 274 mμ (ε 9750); λ_{max}^{KBr} 5.98 (C=C), 9.8 μ (COC).

Anal. Calcd for $C_{20}H_{21}ClO_3$: C, 69.66; H, 6.14; Cl, 10.28; mol wt, 345. Found: C, 69.84; H, 6.21; Cl, 10.14; mol wt, 390.

Pyrolysis of III.—The dimer III (2.25 g, 0.0053 mole) was heated in an open tube in an oil bath at 200–210° for 15 min. The resulting amber-colored melt was cooled, treated with 5 ml of 95% ethanol and chilled. The crystalline material was filtered and washed with cold ethanol. The crude yield of VI was 1.3 g (72%), mp 104–108°. Two recrystallizations from 95% ethanol and one from petroleum ether yielded 0.75 g (41%) of product melting at 110.5–112°. On standing the material gradually decomposed to a yellow oil. The infrared spectrum of the oil was similar to that obtained from the acid hydrolysis product of III.

2,5-Dimethyl-3,6-diphenyl-6-(β-piperidinoethoxy)-1,4-dioxene Oxalate (VII).—A solution of 0.7 g (0.002 mole) of 2,5-dimethyl-3,6-diphenyl-6-(β-chloroethoxy)-1,4-dioxene (VI) (from treatment of III with HCl in $CHCl_3$) in 15 ml of piperidine was refluxed for 3.5 hr. The piperidine hydrochloride (130 mg) was removed by filtration, and the filtrate was evaporated to a yellow, nonerystallizable oil. The oil was dissolved in dry ether and treated with a solution of 250 mg (0.002 mole) of oxalic acid dihydrate in 95% ethanol. The precipitated salt was filtered and washed with ether. The crude yield was 0.45 g (46%). After one recrystallization from 95% ethanol, the melting point was 174–175° dec. An analytical sample obtained by further recrystallization from the same solvent melted at 174–175°dec.

Anal. Calcd for $C_{37}H_{33}NO_7$; C, 67.06; H, 6.88; N, 2.89. Found: C, 66.93; H, 6.74; N, 2.76.

2,5-Dimethyl-3,6-diphenyl-3,6-di(β-pyrrolidinoethoxy)-1,4-dioxane (VIIIa).—A solution of 1.36 g (0.0032 mole) of III in 25 ml of pyrrolidine was refluxed for 7 hr. Air draft evaporation of the pyrrolidine produced a solid which was recrystallized from hexane. The yield was 1.2 g (82%), mp 134–138°. An analytical sample obtained by further recrystallization from the same solvent melted at 138–140°; nmr (CCl_4), δ 7.3 (multiplet, phenyl), 3.89 (quartet, dioxane ring protons), 3.33 (triplet, alkoxymethylene), 2.55 (multiplet, aminomethylene), 1.5–1.8 (multiplet, methylene), 1.12 (doublet, methyl), relative intensity 10:2:4:12:8:6; λ_{max}^{KBr} 8.95, 9.2, 9.3, 9.6, 9.9 μ.

Anal. Calcd for $C_{30}H_{42}N_2O_4$: C, 72.84; H, 8.56; N, 5.66. Found: C, 73.0; H, 8.5; N, 5.8 (hygroscopic).

2,5-Dimethyl-3,6-diphenyl-3,6-di(β-piperidinoethoxy)-1,4-dioxane (VIIIb).—A solution of 1.36 g (0.0032 mole) of III in 20 ml of piperidine was refluxed for 3 hr. Chilling and filtration of the reaction mixture yielded 0.67 g (86%) of piperidine hydrochloride. The filtrate was air-draft evaporated to dryness. The residue was dissolved in hot hexane, filtered, and allowed to crystallize; yield 1.0 g (60%), mp 147–151° dec. An analytical sample obtained by several recrystallizations alternately from hexane and 95% ethanol melted at 152–154° dec. The compound gave a negative Zeisel test for alkoxyl; nmr (CCl_4), δ 7.3 (multiplet, phenyl), 3.90 (quartet, dioxane ring protons), 3.30 (triplet, alkoxymethylene), 2.40 (multiplet, aminomethylene), 1.2–1.6 (multiplet, methylene), 1.12 (doublet, methyl), relative intensity 10:2:4:12:12:6; λ_{max}^{KBr} 8.95, 9.2, 9.5, 9.7, 9.9 μ.

Anal. Calcd for $C_{32}H_{46}N_2O_4$: C, 73.53; H, 8.87; N, 5.36; mol wt, 523. Found: C, 73.17; H, 8.82; N, 5.14; mol wt, 474.

Spiranes. XI. Spiro Derivatives from 7-Methoxy-β-tetralone[1]

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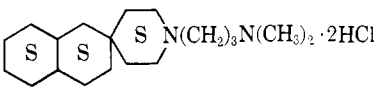
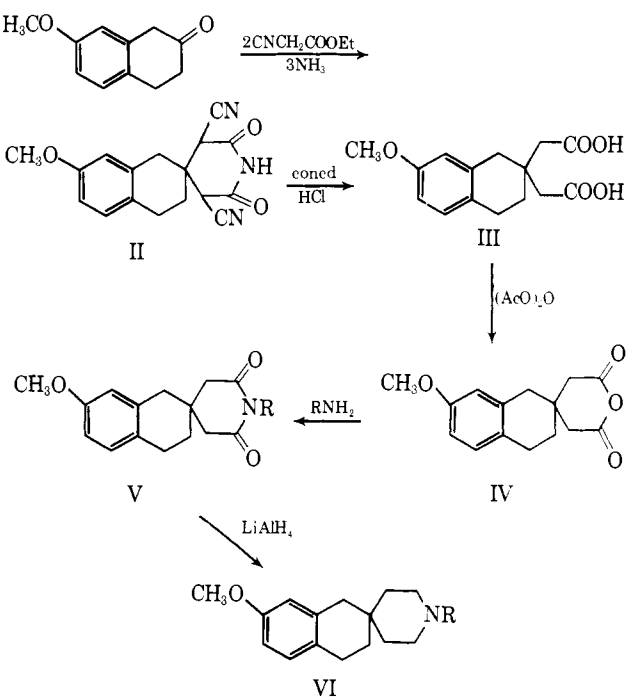
The interesting pharmacological properties displayed by spiro-*trans*-decalin-2,4′-piperidine-1′-(3-dimethylaminopropyl) dihydrochloride[2a] (I) made it desirable



I

to prepare the corresponding 7-methoxytetralin derivative VI (Scheme I). Some of these properties of I consisted of the inhibition of the KB cell line in tissue culture at <1 μg/ml and the production of dwarf offspring, marked reduction in fertility, microphthalmia in

SCHEME I



(1) Part X: L. M. Rice, E. C. Dobbs, and C. H. Grogan, *J. Med. Chem.*, **8**, 825 (1965).

(2) (a) L. M. Rice, C. F. Geschickter, and C. H. Grogan, *ibid.*, **6**, 388 (1963); (b) I. Guareschi, *Atti. Accad. Sci. Torino*, **36**, 443 (1900/1901).