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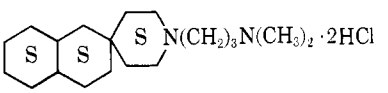
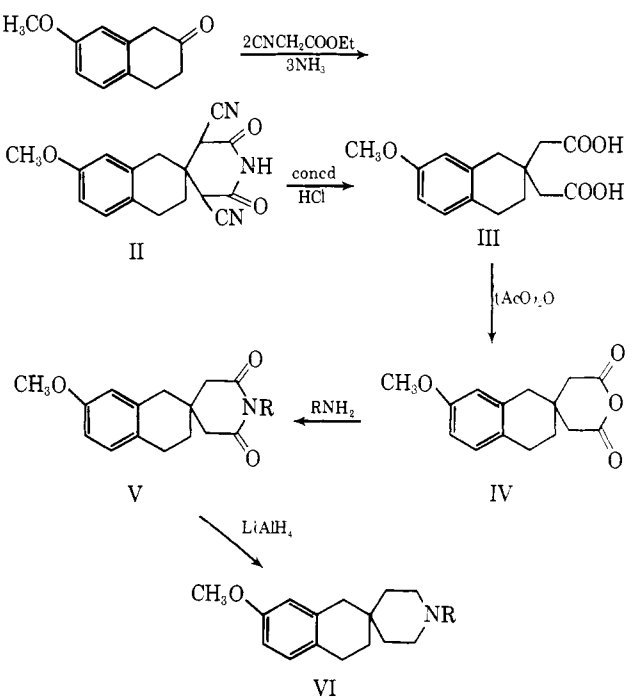
The interesting pharmacological properties displayed by spiro-*trans*-decalin-2,4′-piperidine-1′-(3-dimethylaminopropyl) dihydrochloride[2a] (I) made it desirable



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



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the F_3, and loss of tails in the F_4 generation of Sprague–Dawley strain rats.[3]

Condensation of 7-methoxy-β-tetralone with ethyl cyanoacetate in the Guareschi reaction[2] gave II in low yield (20–35%) and the ammonium salt of II was obtained only after the addition of a large excess of ether to the reaction mixture. Attempted hydrolysis of II by the usual procedure, employing 60–70% sulfuric acid, to the corresponding *gem*-diacetic acid III gave largely decomposition and intractable tars. However, it was found that prolonged refluxing of the imide II with a large excess of concentrated hydrochloric acid smoothly hydrolyzed II to III in fair yield. The desired *gem*-diacetic acid III was converted to the corresponding anhydride IV, which was obtained as a glass; without further purification IV was converted directly to the imide V. The imide V was isolated in pure state by vacuum distillation. Reduction of V with lithium aluminum hydride in the usual manner gave the desired base VI, which was isolated as the dihydrochloride.

A comparison of the two compounds for inhibitory effects (ED_{50} in μg ml) on the growth of KB cells in culture gave the following results: I, <1.0, 2.8, <1.0, 0.63; VI, 2.5, 2.6. The inhibitory effects on the growth of this cell line were of the same order of magnitude, although I seems to be the more potent. The 7-methoxytetraline analog (VI) of I is at present undergoing tests to determine its effects, if any, on the fertility and offspring of Sprague–Dawley rats. These results will be published later.

Experimental Section

Elemental microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y., and the Microanalytical Laboratory of the National Institutes of Health. All melting points were determined on a Thomas–Hoover capillary-type melting point apparatus and are corrected.

3,4-Dihydro-7-methoxynaphthalenespiro-2(1H),4'-piperidine-3',5'-dicyano-2',6'-dione (II).—A solution of 125 g (0.68 mole) of 7-methoxy-β-tetralone, of 96.5% purity by a vapor phase chromatogram, in 160 g of ethyl cyanoacetate was prepared and cooled to 0°. This solution was mixed with 450 ml of absolute alcohol that had previously been saturated with anhydrous NH_3 at 0°. After the mixture had been allowed to stand in the refrigerator for 3 weeks at 5°, it was diluted with 1500 ml of anhydrous ether and allowed to stand an additional 2 days. The precipitate was filtered, washed with anhydrous ether, and dried. It was dissolved in boiling water (approximately 5 l.), filtered, and acidified with 400 ml of concentrated HCl. The mixture was placed in the refrigerator overnight and the precipitate was filtered, washed with water, and dried at 90° for several days. It weighed 41.5 g (20%). Recrystallization from ethyl acetate gave analytical material, mp 233.5–234.5°.

Anal. Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.59. Found: C, 66.26; H, 4.93; N, 13.68.

7-Methoxytetralin-2,2-diacetic Acid (III).—The imide II (25 g, 0.08 mole) was refluxed in a 5-l. flask with 1500 ml of concentrated HCl for 52 hr. After 36–40 hr of refluxing the imide had all dissolved and a clear solution was obtained. On cooling, a first crop of 11 g was obtained. The filtrate was concentrated to 400 ml and, on cooling, yielded an additional crop of 4 g. Both crops melted at 198–201°. The combined crops (15 g, 60%) were dissolved in $KHCO_3$ solution, decolorized three times with carbon and acidified with 10% HCl. The product (13 g) melted at 201–202°, unchanged on recrystallization from water.

Anal. Calcd for $C_{15}H_{19}O_5$: C, 64.74; H, 6.52. Found: C, 64.71; H, 6.43.

Examination of the infrared spectrum showed no OH absorption and indicated that the methoxyl group was intact.

3,4-Dihydro-7-methoxynaphthalenespiro-2(1H),4'-piperidine-2',6'-dione-1'-(3-dimethylaminopropyl) (V).—The diacetic acid III (11 g, 0.04 mole) was refluxed for 5 min with 25 ml of acetic anhydride. The acetic anhydride was stripped off *in vacuo* and the crude anhydride cooled. It became a viscous glassy material. 3-Dimethylaminopropylamine (5 g) was added and the mixture refluxed until a clear melt was obtained. The melt was heated at 180° for 1 hr and vacuum distilled. The product was obtained as a glass, bp 226–233° (0.1 mm) (7 g, 51%) based on the diacid III.

Anal. Calcd for $C_{29}H_{25}N_2O_3$: C, 69.74; H, 8.19; N, 8.13. Found: C, 69.52; H, 8.47; N, 9.02.

The **imide methiodide** was formed in alcohol and melted at 206–208°, and at 211–213° after recrystallization from alcohol.

Anal. Calcd for $C_{21}H_{31}IN_2O_3$: I, 26.09. Found: I, 26.38.

3,4-Dihydro-7-methoxynaphthalenespiro-2(1H),4'-piperidine-1'-(3-dimethylaminopropyl) Dihydrochloride (VI).—The imide V (5 g, 0.014 mole), dissolved in 50 ml of tetrahydrofuran (THF), was added to a solution of 5 g of $LiAlH_4$ in 250 ml of THF and stirred and refluxed for 1 hr. After decomposition with water, filtering, and stripping the solvent, it was apparent that part of the product was contained in the inorganic cake. The cake was extracted twice with boiling ethyl acetate. These extracts and the orginal filtrate were combined and dried (Na_2SO_4). After filtering the Na_2SO_4, the addition of alcoholic HCl precipitated the product (4 g, 71%), mp 275–279°. Two recrystallizations from ethanol–methanol–ether raised the melting point to 284–287° dec.

Anal. Calcd for $C_{25}H_{44}Cl_2N_2O$: C, 61.68; H, 8.80; Cl, 18.21; N, 7.19. Found: C, 61.46; H, 8.85; Cl, 18.19; N, 7.39.

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1-Amino-2-(4-imidazolyl)cyclopropanecarboxylic Acid[1a]

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The inhibition of specific histidine decarboxylase,[2] or other less specific enzymes which decarboxylate histidine as a source of intracellular histamine,[3–5] has long been regarded as a potentially favorable alternative to the therapeutic competition with histamine by histamine antimetabolites. Among inhibitors of specific histidine decarboxylase, which have been found of particular interest, are α-hydrazinohistidine,[2] 4-bromo-3-hydroxybenzyloxyamine,[2] and α-methylhistidine.[5,6] It had previously been observed, in other pharmacodynamic types, that replacement of a metabolically

(1) (a) Supported in part by Grant GM-01-001882 from the Institute of General Medicine, National Institutes of Health, U. S. Public Health Service. (b) Du Pont Teaching Fellow, 1963–1964; NASA trainee, 1965–1966.

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