Cyclohexane-1,3-bis(methylamine).—*m*-Xylylenediamine (13.6 g.) was hydrogenated in ethanol solution with ruthenium dioxide catalyst (272 mg.) at 200° and a pressure of 105.45 kg./cm.^{2} (1500 p.s.i.). The theoretical amount of hydrogen was taken up in 12 hr. Removal of the catalyst by filtration and fractional distillation of the filtrate yielded an oil (11.4 gm.), b.p. 120° (15 mm.). A dihydrochloride salt was prepared with ethereal HCl. It was crystallized from ethanol–ether and had m.p. 252–254°.

Anal. Calcd. for $C_8H_{20}Cl_2N_2$: Cl, 32.95; N, 13.02. Found: Cl, 32.16; N, 12.91.

Dimethyl Cyclohexane-*trans*-1,4-dicarbamate.—Sodium methoxide (from 2.7 g. of sodium) in methanol (60 ml.) was added slowly to a refluxing mixture of cyclohexane-*trans*-1,4-dicarboxamide[10] (5.0 g., 0.294 mole) in methanol (400 ml.), followed by bromine (4.7 g.). The additions of sodium methoxide and bromine were repeated three times using the same quantities as above. After refluxing for 4 hr., the solution was filtered, and the filtrate was concentrated to dryness and triturated with water. Filtration yielded the crude dicarbamate. It was crystallized from acetone to yield pure material (5.8 g., 85.8%), m.p. 259–260°. This compound has previously been prepared from *trans*-cyclohexane-1,4-diamine and methylchloro carbonate and reported to have m.p. 264°.[11]

Dimethyl cyclohexane-*cis*-1,4-dicarbamate was prepared as described above from cyclohexane-*cis*-1,4-dicarboxamide[10] in 60% yield, m.p. 138–140° (ether–hexane), lit.[11] m.p. 139–140°.

Cyclohexane-*trans*-1,4-diamine.—Dimethyl cyclohexane-*trans*-1,4-dicarbamate (1.3 g.) was refluxed for 6 hr. with 50 ml. of concentrated HCl. Removal of the acid *in vacuo* and trituration of the residue with acetone yielded the dihydrochloride (1.0 g., 94.5%). A sample crystallized from methanol had m.p. >300.°

Anal. Calcd. for: $C_6H_{16}Cl_2N_2$: Cl, 37.89; N, 14.98. Found: Cl, 37.87; N, 14.94.

The free base was obtained from the salt in the usual manner. It is very volatile and water soluble. It had m.p. 69–71°, lit. m.p.[12] 72–73° (obtained in *ca.* 12% yield by the action of sodium azide on the corresponding diacid).

Cyclohexane-*cis*-1,4-diamine.—The dihydrochloride salt of the title compound was obtained from the corresponding dicarbamate as described above, in 61% yield, m.p. >310° (MeOH–ether).

Anal. Calcd. for $C_6H_{16}Cl_2N_2$: Cl, 37.89; N, 14.98. Found: Cl, 37.68; N, 14.68.

This free base, an oil, was not characterized, but was used crude.

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A Convenient Synthesis of 5-Hydroxy-2-methyltryptophan

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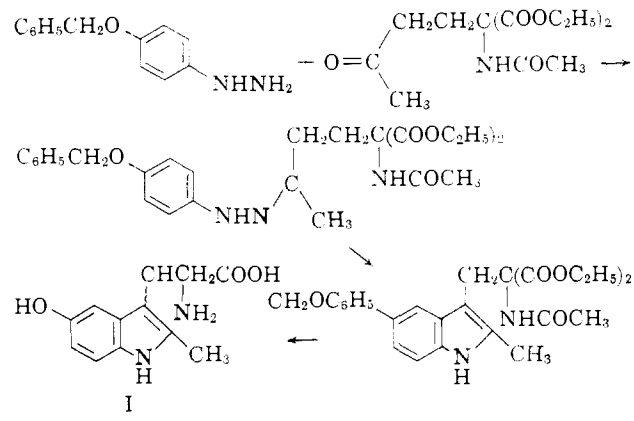
Pentamalli,[2] in a recent article on the synthesis of potential antagonists of serotonin (5-hydroxytryptamine),[3] described the preparation from gramine intermediates of 5-hydroxy-2-methyltryptophan (I), a compound which we synthesized several years ago by an adaptation of the Warner–Moe tryptophan synthesis.[4] It should be noted, on the other hand, that all attempts to prepare 2-methyl-5-methoxytryptophan[5] by a Warner–Moe synthesis failed at the first step, *i.e.*, hydrazone formation, and it became necessary to prepare it from a gramine intermediate.[6]



Experimental[7]

Diethyl Acetamido(5-benzyloxy-2-methyl-3-indolylmethyl)-malonate.—Methyl vinyl ketone (13.5 ml., 0.166 mole) was added dropwise during 20 min. to a cooled (−10 to +3°), efficiently stirred slurry of 29.0 g. (0.134 mole) of diethyl acetamidomalonate, 0.15 g. of sodium methoxide, and 75 ml. of absolute ethanol. The mixture was stirred for 2 hr. at −10 to +3°, treated with 29.0 g. (0.135 mole) of *p*-benzyloxyphenylhydrazine[8] and 3.7 ml. of glacial acetic acid, heated at 50–55° in an atmosphere of nitrogen, and stored at room temperature overnight. The mixture was diluted to 500 ml. with water, treated with 20 ml. of H_2SO_4 with vigorous stirring, and refluxed for 3 hr.[9] The reaction mixture was cooled in an ice bath, and stored overnight in the refrigerator. The precipitate (m.p. 185° dec.) was filtered off, washed with water, and dried *in vacuo;* yield 49.6 g. (79.6%), m.p. 199–200° after recrystallization from isopropyl alcohol.

Anal. Calcd. for $C_{26}H_{30}N_2O_6$: C, 66.92; H, 6.48; N, 6.01. Found: C, 66.66; H, 6.87; N, 5.90.

DL-5-Benzyloxy-2-methyltryptophan.—A mixture of 40.0 g. (0.0857 mole) of diethyl acetamido(5-benzyloxy-2-methyl-3-indolylmethyl)malonate and 400 ml. of 10% NaOH solution was refluxed for 10 hr., filtered hot, cooled, acidified to pH 3 with 6 *N* HCl, and stored overnight in the refrigerator. The precipitate of acetamido(5-benzyloxy-2-methyl-3-indolylmethyl)malonic acid was removed by filtration, washed with water, and dried *in vacuo;* yield 35.0 g. (99%), m.p. 148–149°. After reprecipitation from 0.1 *N* $NaHCO_3$ solution with 0.1 *N* HCl and washing with water, the preparation melted at 150–151°.

Anal. Calcd. for $C_{22}H_{22}N_2O_6$: N, 6.77. Found: N, 6.62.

The malonic acid (30.0 g., 0.0732 mole) was refluxed with stirring for 24 hr. with 200 ml. of water, diluted with 100 ml. of 10% NaOH, refluxed for an additional 24 hr., filtered hot, cooled, and acidified with acetic acid. The voluminous precipitate was filtered off, washed with water, and dried; yield 16.7 g. (70.4%), m.p. 248–250° dec. It melted at 257–259° after recrystallization from 50% ethanol.

Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.33; H, 6.22; N, 8.64. Found: C, 70.06; H, 6.20; N, 8.10.

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DL-5-Hydroxy-2-methyltryptophan.—A solution of 16.5 g. (0.0705 mole) of crude (m.p. 248–250°) DL-5-benzyloxy-2-methyltryptophan in 250 ml. of 0.5 *N* NaOH was hydrogenated [initial pressure 4.22 kg./cm.² (60 lb./p.s.i.)] in the presence of 10 g. of 10% palladium on charcoal.[10] Hydrogenation stopped after 0.268 kg./cm.² of hydrogen had been absorbed (theoretical uptake, 0.288 kg./cm.²). The solution was filtered and evaporated *in vacuo*, and the residue was dissolved in water. The resulting solution was adjusted, to pH 5.86 with 6 *N* HCl, filtered to remove SiO_2, and evaporated to dryness. The residue was slurried twice with ice water (5-ml. portions) and recrystallized from 50% ethanol; yield 3.07 g. (15.8%), m.p. 292–293°.

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.03; N, 11.96.

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The Synthesis of Disalicyl Alcohols

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Salicyl alcohol is used as an antipyretic and as a local anesthetic.[1] It is possible that the related compounds which we report might possess similar potential uses. Clemmensen and Heitman[2] have shown that 5,5′-methylenedisalicylic acid can be prepared by the condensation of formaldehyde and salicylic acid. In this investigation, the dimethyl ester of this acid has been reduced to its corresponding alcohol with $LiAlH_4$. It is shown that the efficiency of the reduction is related to the nature of the bridging group. A significant increase in yield was realized when a modification of the procedure was used to synthesize 5,5′-isopropylidenedisalicyl alcohol.

Experimental[3,4]

5,5′-Isopropylidenedisalicylic Acid.—A mixture of 32 g. (0.23 mole) of salicylic acid, 7.73 g. (0.133 mole) of acetone, and 180 g. of 60% sulfuric acid was heated under gentle reflux for 10–12 hr. with constant stirring. It was then allowed to cool and was filtered, and the residue was washed with cold water and air dried. Unchanged salicylic acid was removed by adding the powdered product to boiling water, with constant stirring, filtering while hot, and allowing the residue to dry in air. Purification was effected by dissolving the crude product in an excess of hot 95% ethanol, treating with Norit, filtering, and reprecipitating with cold water. The tan material was dried in a vacuum desiccator ($CaCl_2$); yield 11 g. (30.2%), m.p. 287–289°.

Anal. Calcd. for $C_{17}H_{16}O_6$: C, 64.60; H, 5.07. Found: C, 64.90; H, 5.35.

Dimethyl 5,5′-Isopropylidenedisalicylate.—This dimethyl ester was prepared by the Fischer–Speier[5] method. The product was isolated in the usual manner and recrystallized from absolute methanol. Fifty grams of acid gave 18 g. (33.3%) of pure ester, m.p. 98–99°.

5,5-Isopropylidenedisalicyl Alcohol.—A solution of 4.0 g. (0.1 mole) of $LiAlH_4$ in 225 ml. of absolute ether was made by stirring the slurry for 4 hr. The reaction mixture was protected from atmospheric moisture by attaching $CaCl_2$ tubes to all openings. Then a solution of 12.0 g. (0.035 mole) of dimethyl 5,5′-isopropylidenedisalicylate in 120 ml. of absolute ether was added through the dropping funnel at a rate which produced gentle reflux. After the addition, the reaction was gently heated at reflux temperature for 12 hr. and allowed to cool. The excess $LiAlH_4$ was decomposed by the cautious addition of water. The contents of the reaction flask were then added to a mixture of crushed ice and concentrated H_2SO_4, stirred for 10 min., and filtered. This residue was combined with the residue obtained by evaporating the dried ether layer of the filtrate. These solids were then repeatedly recrystallized from hot water until long white needles of the desired pure alcohol were obtained; yield 5.0 g. (25%), m.p. 146–147°.

Anal. Calcd. for $C_{17}H_{20}O_4$: C, 70.83; H, 6.94. Found: C, 70.85; H, 6.79.

5,5′-Methylenedisalicyl Alcohol.—This alcohol was prepared by the $LiAlH_4$ reduction of its dimethyl ester according to the procedure outlined above for the isopropylidene alcohol. The crude product was recrystallized from hot water to give glistening, pale gray plates; yield 2.0 g. (8%), m.p. 166–167°.

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.23; H, 6.15. Found: C, 69.25; H, 6.20.

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Aromatic Fluorine Compounds. XIII. Substituted N-Phenylglycine Ethyl Esters and Hydrazides[1]

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Data on the herbicidal and medicinal properties of halogenated N-arylglycine esters and hydrazides are limited to a few compounds. In 1949 when the plant growth regulating properties of maleic hydrazide[2] were reported, N-(2,4-dichlorophenyl)-glycine[3] was found also to have herbicidal properties. The first biological data on fluorinated arylglycine derivatives appeared about a decade later. Tuberculostatic tests[4] were reported on N-(4-fluorophenyl)glycine, its ethyl ester, and its hydrazide. Tomato leaf curvature data[5] appeared in 1959 on N-(3-trifluoromethylphenyl)glycine and N-(3-trifluoromethyl-4-chlorophenyl)-glycine and their amides.

A large number of fluorine, other halogen, and methyl derivatives of N-phenylglycine was prepared as part of a program[6] on the synthesis of fluorinated herbicides and medicinals. Tables I and II summarize the physical data on 31 glycine ethyl esters and 28 glycine hydrazides, respectively.

Experimental[7]

N-Phenylglycine Ethyl Esters.—These compounds with substitution in the phenyl group were prepared by condensing the appropriately substituted primary anilines with ethyl chloroacetate.[4,8]

To a well-stirred mixture of 114 g. (0.75 mole) of sodium acetate trihydrate and 50–75 ml. of ethanol was added 0.5 mole of the appropriate aniline and 62 g. (0.5 mole) of ethyl chloroacetate. The reaction mixture was refluxed gently with stirring for 24–48

(1) This research was supported in part by contract with the U. S. Army Biological Laboratories, Fort Detrick, Frederick, Md., through the University of Illinois. The research was the responsibility of the Illinois State Geological Survey.

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