measurements emphasize the attractiveness of this method for research in the pharmaceutical sciences.

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Convenient Synthesis of 3-(γ-Aminopropyl)-5-ethoxyindole

By HUBERT W. MURPHY

3-(γ-Aminopropyl)-5-ethoxyindole has been synthesized from *p*-phenetidine and α-methyl-acetoacetate. This method involves fewer intermediates, with new and better methods for their purification.

THE PREPARATION of this indole in low yield by the use of the Japp-Klingmann reaction has been reported (1). A simpler and more satisfactory synthesis has been developed to prepare larger quantities. By this reaction the desired 4-ethoxyphenylhydrazone was prepared from 4-ethoxybenzenediazonium chloride and ethyl α-methyl-acetoacetate. The crude hydrazone was cyclized by heating in absolute alcohol containing 10% concentrated sulfuric acid to produce 5-ethoxy-2-carbethoxyindole in 40% yield. Saponification with methanolic potassium hydroxide gave an 82% yield of 5-ethoxy-2-carboxyindole. The latter was decarboxylated to furnish 5-ethoxyindole in 80% yield. 5-Ethoxyindole was reacted with acrylonitrile under pressure to yield about 80% of crude 5-ethoxy-3-indolepropionitrile. This can be crystallized from isopropanol before being reduced; however, it was found more expedient to reduce the crude nitrile. Reduction of the crude product furnished a mixture containing both primary and secondary amines from which the pure γ-(5-ethoxy-3-indolyl)-propylamine was separated by crystallization as a Schiff base from acetone. The yield, based on 5-ethoxyindole, was about 20%.

The structure of the isopropylidene was firmly established by infrared absorption: N—H 3.20; N=C, 6.01; aryl ring, 6.14, 6.27, and 6.69; and ethoxy, 8.03 and 9.56 μ. The assigned structure was supported by the nuclear magnetic resonance pattern. The isopropylidene derivative was converted practically quantitatively to an amine salt by hydrolyzing the Schiff base with a dilute aqueous solution of a strong acid.

This Schiff base can also be used as a starting material for the preparation of secondary amines (2). The ease with which the Schiff base is formed under alkaline conditions with acetone is remarkable. Since tryptamine and acetone readily furnish a similar Schiff base, this may be characteristic of 3-indolylamines.

A dicarboxylic acid was isolated from the acetone filtrate remaining from the crystallization of 5-ethoxy-2-carbethoxyindole. This acid is believed to be α-(5-ethoxy-2-carboxy-3-indolyl)-acrylic acid. Structure assignment has been made on the basis of titration data, ultraviolet and infrared absorption, nuclear magnetic resonance studies, melting point, and elemental analysis. The difference in pKa′ values (ΔpKa′, 1-2) in 66% dimethylformamide was 3.6 pH units for this acid. This is about halfway between that for succinic acid, representing an acid with free rotation of the carboxyl groups, and *o*-phthalic acid, an acid with somewhat limited rotation. It is distinctly different from maleic acid, an acid with restricted rotation. This is strong evidence against the alternative quinoline dicarboxylic acid structure. Infrared

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and ultraviolet absorption spectra are consistent with the proposed structure. All hydrogen atoms can be accounted for by a careful comparative study of the nuclear magnetic resonance patterns of the free acid and its dimethyl ester.

Mixtures of 5-ethoxy-2-carboxyindole and this indole acrylic acid melt between the melting points of the pure compounds (179 and 221°, respectively). This may account for the different melting points that have been reported for 5-ethoxy-2-carboxyindole. Rydon and Siddappa (3) reported 202-203°, and Hoshino and Kotake (4) reported 204°. The mechanism by which this acrylic acid is produced is not known. It appears improbable that it results from an impurity in the initial reactants, since both were carefully purified and characterized before use.

EXPERIMENTAL[1]

5-Ethoxy-2-carbethoxyindole (I).—In a 4-L. beaker provided with a thermometer, mechanical stirrer, and an ice bath were placed 1400 Gm. of crushed ice, 180 Gm. (1.31 moles) of freshly distilled *p*-phenetidine, and 320 ml. of concentrated hydrochloric acid; this mixture was cooled to 4°. A solution of 89.6 Gm. of sodium nitrite in 320 ml. of water was added dropwise at such a rate that the temperature remained below 4°. Toward the end of the diazotization, the hydrochloride of *p*-phenetidine, which had precipitated, dissolved; a clear yellow solution was obtained. The completion of the diazotization was determined with starch-iodide test paper.

About 70 ml. cold 40% potassium hydroxide solution (320 Gm. in 800 ml. distilled water) was added, while stirring vigorously, to a mixture of 1600 Gm. of crushed ice and 190 Gm. (1.31 moles) of freshly distilled ethyl α-methyl-acetoacetate. About 140 ml. of the *p*-ethoxybenzene diazonium chloride solution was then added slowly, making sure that alkali was always present in excess. Vigorous stirring was provided to prevent the formation of localized areas of appreciable acidity. The remaining potassium hydroxide and *p*-ethoxybenzene diazonium chloride solutions were added in small quantities with sufficient crushed ice to keep the temperature of the reaction mixture near 0°.

The reaction mixture was stirred for an additional half hour and was then acidified by the addition of 256 ml. of concentrated hydrochloric acid in 1300 Gm. of crushed ice. A viscous red oil separated which was extracted from the aqueous phase by two 1200-ml. portions of benzene followed by a 1000-ml. portion of chloroform. The benzene and chloroform extracts were combined and filtered through a sintered-glass filter overlaid with 260 Gm. of anhydrous potassium carbonate. The filtrate was concentrated *in vacuo* at 30° and the residue was heated to 80° *in vacuo* for 2 hours to remove the last traces of volatile matter.

A mixture of 1600 ml. of absolute ethanol and 160 ml. of concentrated sulfuric acid, which had been cautiously mixed, was added to the residual oil and the solution obtained was refluxed gently for 3 hours. The alcohol was then removed at 5 mm. Hg without heating.

The residue was dissolved in 2 L. of chloroform and 1 L. of distilled water. The acidic aqueous layer was separated and discarded. The chloroform phase was washed with two 1-L. portions of distilled water, a 750-ml. portion of a 3% solution of sodium bicarbonate, and then with three more 750-ml. portions of distilled water. After drying the chloroformic phase with 200 Gm. of anhydrous sodium sulfate, the chloroform was removed at reduced pressure. The residue was dissolved in hot acetone. After filtration, acetone was removed from the filtrate at 5 mm. Hg to a volume of about 500 ml. The crystals which separated on cooling were collected and washed with about 70 ml. of cold acetone. The air-dried crystals weighed 120 Gm., m.p. 152°. Yield, 40% based on *p*-phenetidine.

Anal.—Calcd. for $C_{13}H_{15}NO_3$: N, 6.01. Found: N, 6.08.

5-Ethoxy-2-carboxyindole (II).—The ethyl ester (I) was added slowly to a solution of 100 Gm. of potassium hydroxide dissolved in 800 ml. of methanol. The mixture was stirred and heated gently until all the large particles had been dispersed. After stirring for an additional hour, the insoluble product was collected on a sintered-glass filter and washed with about 100 ml. of cold methanol then with 300 ml. of cold ether. The potassium salt was dissolved in about 1 L. of distilled water, filtered, and the filtrate was acidified to a pH of 2.2 with concentrated hydrochloric acid. The acidic mixture was cooled in the refrigerator; the acid which crystallized was collected and washed with about 150 ml. of cold distilled water.

This acid was purified by dissolving it in basic solution (pH 9.0) decolorized with 4 Gm. of carbon and 5 Gm. of talc. This mixture was heated to 70°, filtered, and the cooled filtrate acidified with hydrochloric acid (pH 2.2). The crystalline acid was collected as before and dried *in vacuo*. The yield was 83.0 Gm. (79% of theory), m.p. 179°. The pKa′ in 66% dimethylformamide was 6.4 and an apparent molecular weight of 205 (theory 205) was determined.

Anal.—Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.63; H, 5.63; N, 6.53.

5-Ethoxyindole (III).—To a 50-ml. distilling flask containing 300 mg. of bronze powder, 30 Gm. of 5-ethoxy-2-carboxyindole (II) was added. The flask and its contents were heated in a silicone oil bath at 222° for 20 minutes to complete decarboxylation. The residue was distilled at reduced pressure (b.p. 162° at 4 mm., 194° at 11 mm. Hg) to furnish 18.0 Gm. (76.5% of theory) of 5-ethoxyindole.

Anal.—Calcd. for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.38; H, 6.75; N, 8.80.

5-Ethoxy-3-cyanoethylindole (IV).—This was prepared by a modification of a method described by Terent'ev, *et al.* (5). In a 100-ml. round-bottomed flask was placed 16.12 Gm. (0.1 mole) of 5-ethoxyindole (III), 21.2 Gm. of freshly distilled acrylonitrile, 10 ml. of thiophene-free benzene, 0.3 Gm. of glacial acetic acid, 0.2 Gm. of cupric acetate, and 70 mg. of boric acid. The flask was provided with a

[1] All melting points and boiling points reported are uncorrected.

ground-glass stopper and placed in a steel autoclave. About 50 ml. of benzene was placed in the autoclave. The mixture was heated under pressure for 6 hours at 180–190°, then allowed to cool. The flask was carefully removed from the autoclave and most of the contents dissolved in about 500 ml. of ether. The ether extract was washed with four 500-ml. portions of distilled water containing 15 ml. of glacial acetic acid, dried with 40 Gm. of anhydrous potassium carbonate, and decolorized with 2 Gm. of carbon. The ether was removed from the filtrate at reduced pressure to furnish 17.5 Gm. of gummy residue. This residue was dissolved in about 40 ml. of warm isopropanol and then chilled at −10° overnight. The crystals that separated were collected, washed rapidly with about 10 ml. of cold ether (−10°), and solvent removed *in vacuo*. Yield, 3.4 Gm., m.p. 89°. An additional 1.1 Gm. of product was obtained from the filtrate for a total yield of about 20%.

Anal.—Calcd. for $C_{13}H_{14}N_{2O}$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.74; H, 6.43; N, 12.81.

3-(γ-Isopropylideneaminopropyl)-5-ethoxyindole (V).—Two grams of 5-ethoxy-3-cyanoethylindole (IV) dissolved in 100 ml. of methanol, a mixture of 30 ml. of liquid ammonia, and 20 ml. of methanol, and 5 Gm. of Raney nickel catalyst which had been moistened with methanol were combined in a stainless steel bomb. The bomb was heated to 90° under hydrogen at 1500 p.s.i. for 4 hours with constant agitation. After cooling, the catalyst was removed by filtration and the ammonia and methanol removed with a stream of air in a hood. The residue was taken up in a mixture of 200 ml. of ether and 300 ml. of distilled water to which 10 ml. of concentrated nitric acid had been added. The aqueous portion was separated and washed twice with ether; it was decolorized with 1.25 Gm. of carbon. The filtrate was cooled and transferred to a separator and 250 ml. of ether and sufficient 40% sodium hydroxide solution to adjust the pH to 9.5 were added. The ether phase was separated and the alkaline aqueous portion was extracted with two more 150-ml. portions of ether. The ether extracts were combined, washed with four 250-ml. portions of distilled water, and dried and decolorized by adding 30 Gm. of anhydrous potassium carbonate and 2 Gm. of carbon. After filtration, the ether was removed from the filtrate at reduced pressure. The residue was dissolved in about 25 ml. of acetone and the product crystallized from the cooled solution. Yield, 1.14 Gm. (47% of theory), m.p. 128°.

Anal.—Calcd. for $C_{16}H_{22}N_{2O}$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.36; H, 8.81; N, 11.07.

It was not necessary to isolate crystalline 5-ethoxy-3-cyanoethylindole (IV). The crude gummy residue obtained, as described, was reduced to furnish the amine. Thus 17.4 Gm. of crude product from the acrylation procedure was reduced by the method described for the purified cyanoethylindole and gave 5.7 Gm. (22% based on 5-ethoxyindole) of the isopropylidene compound.

γ-(5-Ethoxy-3-indolyl)propylamine Hydrochloride (VI).—One gram of 3-(γ-isopropylideneaminopropyl)-5-ethoxyindole (V) was dissolved in 39 ml. of 0.1 *N* hydrochloric acid and the mixture filtered through an asbestos pad. The filtrate was frozen and dried from the frozen state to furnish 975 mg. of the desired hydrochloride, m.p. 196°.

α-(5-Ethoxy-2-carboxy-3-indolyl)acrylic Acid (VII).—The acetone was removed at reduced pressure from the filtrate and washings obtained after collecting the 5-ethoxy-2-carbethoxyindole (I); the residue was dissolved in 400 ml. of ethanol containing 22 Gm. of sodium hydroxide. This alcoholic solution was warmed to 50°, then allowed to stand at room temperature for 24 hours. A very small amount of precipitate separated which was removed with difficulty by filtration. The filtrate stood an additional 24 hours at room temperature, but no more precipitate appeared. The alcohol was removed at reduced pressure, and the residue was dissolved in about 600 ml. of distilled water. This aqueous solution was partially decolorized by several treatments with carbon. The filtrate was acidified (pH 2.2) with concentrated hydrochloric acid and chilled. The acidic product was collected and washed with cold distilled water. It was recrystallized from 150 ml. of methanol. Yield: 3.0 Gm., m.p. 221°.

A second crop was obtained by concentrating the methanolic filtrate. Yield: 1.5 Gm., m.p. 221°.

Anal.—Calcd. for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09; O, 29.06. Found: C, 60.71; H, 4.89; N, 5.13; O, 28.68.

The pKa′ values in 66% dimethylformamide were 5.8 and 9.4, and in water, 3.9 and 5.3. The calculated molecular weight from titration was 282 (theory 275).

The dimethyl ester was prepared from absolute methanol with sulfuric acid catalyst in the usual manner in almost quantitative yield, m.p. 150.5°.

Anal.—Calcd. for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.15; H, 5.89; N, 4.59.

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