dride or by dry distillation with calcium oxide yielded 2-(1′-naphthylmethyl)-cyclopentanone (II). The ultraviolet absorption spectrum of II was similar to that of 1-methylnaphthalene.

2-(2′-Naphthylmethyl)-cyclopentanone was prepared in a similar manner from β-chloromethylnaphthalene. An excellent yield of the crystalline ketone was obtained by cyclization of the intermediate α-(2′-naphthylmethyl)-adipic acid with acetic anhydride. The ketone was obtained also by acid hydrolysis of 2-carbethoxy-2-(2′-naphthylmethyl)-cyclopentanone.

Experimental[2]

α-(1′-Naphthylmethyl)-adipic Acid (I).—A mixture of 15.6 g. (0.1 mole) of 2-carbethoxycyclopentanone, sodium methoxide (prepared from 2.3 g. of sodium and dried at 100° and 20 mm.), and 150 cc. of dry benzene was refluxed for five minutes; any lumps present were crushed with a spatula. After the addition of 17.6 g. (0.1 mole) of α-chloromethylnaphthalene, the mixture was refluxed for six hours. After the removal of the benzene under reduced pressure, 40 cc. of 40% aqueous potassium hydroxide and 60 cc. of methanol were added and the solution was refluxed for eighteen hours. After being cooled and diluted with water to 300 cc., the solution was washed twice with ether and then acidified with hydrochloric acid. The substituted adipic acid, which was isolated by extraction with two 200-cc. portions of ether and removal of the ether, was triturated with 30 cc. of benzene; yield of colorless granular crystals, 15 g., m. p. 116–121°. An additional 1.17 g. of the acid (m. p. 110–118°) was obtained by further treatment of the non-crystalline portion with 40 cc. of 20% aqueous potassium hydroxide at 100° for twenty-four hours; total yield, 56%. After several recrystallizations from benzene the acid melted at 126–127.4°.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.30, H, 6.33; neut. equiv., 143. Found: C, 71.42; H, 6.37; neut. equiv., 144.

2-(1′-Naphthylmethyl)-cyclopentanone (II).—The acetic anhydride was distilled slowly from a solution of 0.5 g. of the aforementioned acid in 1.5 cc. of acetic anhydride. After the apparatus had been filled with nitrogen, the temperature was raised to 300° in the course of five minutes; the pressure was then lowered to 30 mm. in order to complete the distillation; yield of colorless liquid, 71%. **The 2,4-dinitrophenylhydrazone** (m. p. 232.2–233.2°), which was prepared in 76% yield by addition of 1 cc. of concentrated hydrochloric acid to a refluxing solution of 100 mg. of the ketone and 150 mg. of 2,4-dinitrophenylhydrazine in ethanol, crystallized in fine, yellow needles.

Anal. Calcd. for $C_{22}H_{20}N_4O_4$: C, 65.33; H, 4.99. Found: C, 65.47; H, 5.16.

When the diacid alone was distilled, the yield of ketone was low and much acid was recovered. By dry distillation of an intimate mixture of 2 g. of the diacid and 0.4 g. of powdered calcium oxide under nitrogen and redistillation of the dark distillate at 130–170° and 0.1 mm., 1.02 g. of the ketone was obtained.

2-(2′-Naphthylmethyl)-cyclopentanone.—The cyclic keto ester prepared from 11.2 g. of β-chloromethylnaphthalene and an equivalent amount of 2-carbethoxycyclopentanone was completely hydrolyzed and cleaved by refluxing with aqueous methanolic alkali for eighteen hours. Recrystallization of the crude diacid from acetone–benzene gave two crops: 12.8 g., m. p. 149–150°, and 2 g., m. p. 144–146°; total yield, 81%. The highest m. p. obtained for α-(2′-naphthylmethyl)-adipic acid was 152.3–152.8°.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.30; H, 6.33; neut. equiv., 143. Found: C, 71.50; H, 6.50; neut. equiv., 142.5.

By the procedure described for the isomer, 3.63 g. (93%) of the cyclic ketone (m. p. 57–63°) was obtained from 5 g. of the diacid and 15 cc. of acetic anhydride. The **2-(2′-naphthylmethyl)-cyclopentanone** crystallized from ether–petroleum ether in colorless glistening flakes; weight, 2.9 g. (75%), m. p. 70.3–71.3°.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.66; H, 7.19. Found: C, 85.78; H, 7.45.

A 38% yield of the ketone (m. p. 65.5–67°) was obtained when the diacid was distilled from calcium oxide and a 53% yield of ketone (m. p. 57–65°) resulted from refluxing a solution of 3.6 g. of the 2-carbethoxy-2-(2′-naphthylmethyl)-cyclopentanone in 10 cc. of acetic acid and 10 cc. of concentrated hydrochloric acid for twelve hours and evaporatively distilling the neutral product up to 180° at 0.1 mm.

The 2,4-dinitrophenylhydrazone (prepared in quantitative yield as described for the isomer except that the mixture was refluxed for five minutes and then allowed to stand for several days) crystallized in fine, short yellow needles; m. p. 138–139°, raised to 144.2–145° by recrystallization from ethanol.

Anal. Calcd. for $C_{22}H_{20}N_4O_4$: C, 65.33; H, 4.99. Found: C, 65.48; H, 4.95.

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[2] All melting points are corrected.

Derivatives of Indole-2-carboxylic Acid

BY WARREN J. BREHM

This report of work originally aimed at a synthesis of lysergic acid, but now discontinued, is prompted by Uhle's successful synthesis of 5-keto-1,3,4,5-tetrahydrobenz[cd]indole.[1] It was hoped that an abrine suitably protected at the 2-position to permit closure of the (α-methylamino)-propionic acid side-chain into the 4-position could be prepared by following the tryptophan syntheses developed by Snyder[2] or Robson.[3] The choice of the carboxypiperidide as the protective group made subsequent decarboxylation or its equivalent a necessary step. In an attempt to avoid the difficulties often attendant upon decarboxylation of indole-2-acids, 2-hydroxymethylindole was prepared. When this compound did not lose formaldehyde on treatment with base this alternate scheme had to be abandoned.

Experimental

Ethyl Indole-2-carboxylate.—Crude ethyl *o*-nitrophenylpyruvate, obtained as an oil by the method of Wislicenus and Thoma,[4] was dissolved in glacial acetic acid (35 g. of ester in 225 cc. of solvent). It was reduced with hydrogen at a pressure of 3 atm. over Adams catalyst (0.2 g.). At the end of the very rapid reduction the catalyst was filtered off and the solution diluted with water. This gave 22 g. (80%) of ethyl indole-2-carboxylate, m. p. 121–123°.

2-Hydroxymethylindole.—Lithium aluminum hydride (4.75 g.) was dissolved in 180 cc. of dry ether. With mechanical stirring a solution of 18.9 g. of ethyl indole-2-carboxylate in 250 cc. of dry ether was added dropwise at a rate sufficient to keep the solution boiling. When the addition was complete, stirring was continued for fifteen minutes, and then 100 cc. of water added slowly to decompose the excess reducing agent. The ether layer was

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(1) Uhle, THIS JOURNAL, **71**, 761 (1949).

(2) Snyder and Smith, *ibid.*, **66**, 351 (1944).

(3) Miller and Robson, *J. Chem. Soc.*, 1910 (1938).

(4) Wislicenus and Thoma, *Ann.*, **436**, 45 (1924).

separated, washed with water and dried over magnesium sulfate. The ether was boiled off and the residue twice recrystallized from benzene–hexane; 10.0 g. (68%) of colorless plates, m. p. 74–77°. Analytical sample sublimed *in vacuo*, m. p. 75–77°. *Anal.* Calcd. for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.79; H, 6.24; N, 9.52.

A solution of 1.0 g. of 2-hydroxymethylindole in 60 cc. of alcohol was treated with 3.0 g. of barium hydroxide in 60 cc. of water. The solution was heated on the steam-bath for three hours, diluted with 400 cc. of water and extracted with ether. The ether was dried over sodium sulfate. After removal of the ether and recrystallization from hexane the residue weighed 0.7 g., m. p. 76–77°. This melting point was not depressed when the sample was mixed with starting material.

2-Carboxypiperidinoindole.—(a) Ethyl indole-2-carboxylate (3.8 g.) was suspended in 50 cc. of 1 *N* sodium hydroxide and the mixture was heated on the steam-bath for one hour when complete solution had been attained. The solution was treated with charcoal, filtered and acidified with hydrochloric acid. The precipitated indole-2-carboxylic acid was filtered off, 2.9 g. (90%), m. p. 206–208°. A solution of 2.85 g. of this acid in 100 cc. of dry ether was treated with 3.0 cc. of thionyl chloride. After standing at room temperature for one hour the solvents were removed *in vacuo*. The residue was twice treated with 60 cc. of dry ether and taken to dryness to remove traces of hydrogen chloride. Finally it was dissolved in 90 cc. of dry ether, filtered and treated with 3.5 cc. of piperidine. There was an immediate precipitation of a gum which gradually crystallized. After recrystallization from ethanol–water, 0.4 g. of 2-carboxypiperidinoindole, m. p. 161–164° separated. After three recrystallizations from hexane the white needles melted at 165–166°. *Anal.* Calcd. for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.07; N, 12.27. Found: C, 73.63; H, 6.86; N, 12.45.

(b) Ethyl indole-2-carboxylate (36 g.) was suspended in 480 cc. of piperidine, and the mixture was treated with 90 cc. of glacial acetic acid. The mixture was heated to boiling, giving a complete solution, and maintained at reflux for two days. The hot solution was diluted with 200 cc. of water and filtered. The filtrate was treated with 2 liters of water to precipitate the 2-carboxypiperidinoindole, 36 g. (83%), m. p. 163–166°.

3-Dimethylaminomethylindole-2-carboxypiperidide.—A suspension of 10.0 g. of 2-carboxypiperidinoindole in 65 cc. of glacial acetic acid, 24 cc. of 25% aqueous dimethylamine and 14 cc. of 40% aqueous formaldehyde was heated on the steam-bath for one hour and then kept at room temperature overnight. After diluting the solution with 700 cc. of water it was extracted with 100 cc. of benzene. The aqueous layer was made basic with concentrated ammonium hydroxide, and the oily product was extracted into ether (one 400-cc. and three 250-cc. portions of solvent). The combined extracts were washed twice with 150 cc. of water and dried over sodium sulfate. After removal of the ether on the steam-bath the oily residue weighed 17 g. Since the theoretical yield was only 12 g. there was considerable contamination, but the material was suitable for further work as it stood.

When a small amount of this oil was heated with 10% chloroplatinic acid a crystalline chloroplatinate precipitated which contained two organic residues per atom of platinum. After recrystallization from water this melted at 208° (dec.). *Anal.* Calcd. for $C_{34}H_{46}N_6O_2$–H_2PtCl_6: C, 41.63; H, 4.93; N, 8.57; Cl, 21.69. Found: Cl, 41.60; H, 4.97; N, 8.53; Cl, 20.83.

2-Carboxypiperidinoskatylacetylaminomalonic Ester.—The 17 g. of crude 3-dimethylaminomethylindole-2-carboxypiperidide (see above) was treated with 150 cc. of xylene and the solution distilled until the distillate was no longer cloudy. The volume of the solvent was replenished, and there was added 9.6 g. of acetylaminomalonic ester (prepared according to the method of Snyder and Smith[2]) and 0.6 g. of powdered sodium hydroxide. With stirring, the mixture was heated to its boiling point while dry nitrogen was passed over the system. Bubbles appeared in the reaction mixture as soon as it became warm, and the exhaust gases became basic. This was presumably due to the evolution of dimethylamine. After twenty hours the evolution of amine had ceased, and the reaction mixture was filtered, washed with 50 cc. of water, twice with 50 cc. of 10% hydrochloric acid and again with 50 cc. of water. The xylene solution was dried over sodium sulfate. After removing the xylene *in vacuo* the residue was crystallized by boiling with ether. The insoluble crystalline residue of 2-carboxypiperidinoskatylacetylaminomalonic ester weighed 10.0 g., m. p. 146–149°; after recrystallizations from ethyl acetate–hexane, ethanol–water and ethyl acetate–isopropyl ether, m. p. 149–152°. *Anal.* Calcd. for $C_{24}H_{31}N_3O_6$: C, 63.00; H, 6.83; N, 9.18. Found: C, 63.22; H, 6.88; N, 8.77.

When this preparation was repeated the ether-insoluble residue melted at 197–200°. It was recrystallized from acetic acid–water, acetone–water and ethanol–water, m. p. 200.2–201.6°. *Anal.* Calcd. for $C_{24}H_{31}N_3O_6$: C, 63.00; H, 6.83; N, 9.18. Found: C, 63.11; H, 6.92; N, 9.17. A sample of the lower melting material, m. p. 149–152°, was recrystallized from ethanol–water and seeded with a crystal of this latter form. The product melted at 200–202°.

2-Carboxypiperidinoindole-3-aldehyde.—To a cold solution of 5.4 g. of N-methylformanilide and 3.66 cc. of phosphorus oxychloride in 35 cc. of *o*-dichlorobenzene there was added gradually 9.1 g. of 2-carboxypiperidinoindole. The resulting suspension was kept at room temperature for forty-three hours although solution was complete after fifteen hours. The solution was poured into a slurry of 30 g. of ice and 20 g. of 35% sodium hydroxide solution. The organic layer was separated, washed with 20 cc. of water and dried over sodium sulfate. The solvent was removed *in vacuo*, the residue dissolved in ethanol, and the solution diluted with water. The precipitated product was recrystallized from benzene-hexane; 6.6 g. (65%), m. p. 149–155°. Five recrystallizations from benzene–hexane gave white needles, m. p. 155.5–156.5°. *Anal.* Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.38; H, 6.09; N, 11.20.

The compound gave a red-orange 2,4-dinitrophenylhydrazone; recrystallized from dioxane, m. p. 310° (dec.). *Anal.* Calcd. for $C_{21}H_{20}N_6O_5$: C, 57.79; H, 4.62; N, 19.26. Found: C, 57.98; H, 4.48; N, 18.68.

5-(3′-α-Carboxypiperidinoindolal)-1-methylhydantoin.—A solution of 1.8 g. of 1-methylhydantoin (prepared according to the method of Miller and Robson[3]) and 2.86 g. of 2-carboxypiperidinoindole-3-aldehyde in 5 cc. of piperidine was heated under reflux for one hour. Some solid yellow material had precipitated during this period. The reaction mixture was treated with 30 cc. of hot water, made slightly acidic with acetic acid, cooled and the solid product filtered off; 3.0 g. (76%), m. p. 289–295°. After seven recrystallizations from pyridine–water the light yellow plates melted at 306–307.5° (dec.). *Anal.* Calcd. for $C_{19}H_{20}N_4O_3$: C, 64.76; H, 5.72; N, 15.90. Found: C, 65.08; H, 5.81; N, 16.03.

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Acylation of Some Thiophenes with Crotonyl Chloride[1]

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Recently Hartough, Kosak and Sardella[2] have shown that thiophene in the presence of activated montmorillonite clay may be acylated with crotonyl chloride to yield 2-crotonylthiophene.

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[1] This note consists of a report of work done under contract with the Medical Division, Chemical Corps, U. S. Army.

[2] Hartough, Kosak and Sardella, THIS JOURNAL, 69, 1014 (1947).