tated oil was extracted with ether. The solvent was removed, and the residue dissolved in hot petroleum ether (60–75°) Crystalline β-phenylpropionic acid (1.4 g., 93.4%) separated from the cold solution; mixed m. p. with an authentic sample 48–49°.[13]

Anal. Calcd. for $C_9H_{10}O_2$: neut. equiv., 150.2. Found: neut. equiv., 150.7.

The amide, prepared from the acid chloride and ammonia, melted at 99–100°,[14] after recrystallization from water, and then from petroleum ether (60–75°); mixed m. p. 99–100°.

By the process described above, except that less catalyst was used (28.5 g. of Raney nickel for 0.01 mole of the acid), 1.9 g. of thianaphthene-2-acetic acid was converted into 1.4 g. (85%) of γ-phenylbutyric acid; m. p. 51–52°[15] without recrystallization.

Anal. Calcd. for $C_{10}H_{12}O_2$: neut. equiv., 164.2. Found: neut. equiv., 164.9.

The amide melted at 84–85°[16] after recrystallization from water.

By use of the above procedure, 1.9 g. of thianaphthene-3-acetic acid and 34 g. of Raney nickel yielded 1.6 g. (98%) of oily β-phenylbutyric acid.

Anal. Calcd. for $C_{10}H_{12}O_2$: neut. equiv., 164.2. Found: neut. equiv., 164.1.

The oily acid was converted to its acid chloride, and the latter treated with ammonia water; the amide melted at 104–105°[17] after recrystallization from water.

The anilide melted at 136–137°[18] after recrystallization from acetone–petroleum ether (60–75°).

Summary

The preparation of 3-chloromethylthianaphthene, thianaphthene-2- and thianaphthene-3-acetic acid has been described.

3-Chloromethylthianaphthene was converted into N,N-dimethyl-N′-(2-pyridyl)-N′-(3-thianaphthenylmethyl)-ethylenediamine hydrochloride.

From thianaphthene-2- and thianaphthene-3-acetic acid, the corresponding 2-(thianaphthenylmethyl)-imidazolines were obtained.

Sulfur can be removed from thianaphthenecarboxylic and thianaphtheneacetic acids with the formation, in high yields, of phenyl-substituted propionic and butyric acids, respectively.

ANN ARBOR, MICHIGAN RECEIVED MAY 19, 1948

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[13] Merz and Weith (*Ber.*, **10**, 758 (1877)) reported 47°.

[14] Weerman and Jongkees (*Rec. trav. chim.*, **25**, 241 (1906)) found 99°.

[15] Semmler (*Ber.*, **39**, 728 (1906)) found 52°.

[16] Willgerodt and Merck (*J. prakt. Chem.*, [2] **80**, 197 (1909)) reported 84.5°.

[17] Kohler and Reimer (*Am. Chem. J.*, **33**, 353 (1905)) reported 105°.

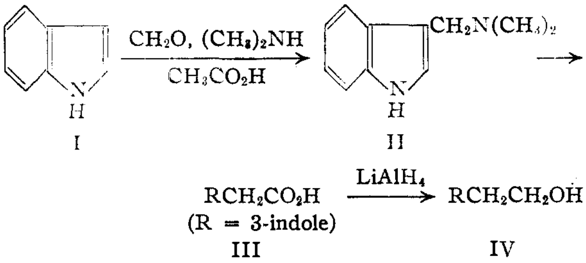
[18] Eijkman (*Chem. Weekblad*, **5**, 657; *Chem. Centr.*, **79**, II, 1100 (1908)) found the same melting point.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Preparation of 3-Indoleacetic Acid; A New Synthesis of Tryptophol

BY H. R. SNYDER AND FREDERICK J. PILGRIM[1]

In a recently reported synthesis of *dl*-homotryptophan,[2] tryptophol [β-(3-indole)-ethanol, IV] was employed as an intermediate. In connection with that work it was of interest to develop a method of preparation of tryptophol more convenient than any previously described. A new synthesis has been accomplished as indicated in the accompanying diagram.



$$RCH_2CO_2H \xrightarrow{LiAlH_4} RCH_2CH_2OH$$

Tryptophol has been previously prepared by the method of Oddo and Cambieri,[2,3] which consists in the treatment of indole-magnesium bromide with ethylene oxide; by the method of Jackson,[4] which involves the Bouveault–Blanc reduction of 3-indoleacetic ester (prepared by treatment of indolemagnesium iodide with chloroacetonitrile,[5] hydrolysis of 3-indoleacetonitrile and subsequent esterification of 3-indoleacetic acid); and by the treatment of indolemagnesium iodide with ethylene chlorohydrin.[6]

Gramine (β-dimethylaminomethylindole, II) was prepared from indole (I) by the method of Kühn and Stein.[7] When gramine was treated with a boiling aqueous alcoholic solution of sodium cyanide for eighty hours, the reaction product was found to be a readily separable mixture of sodium 3-indoleacetate (80%) and 3-indoleacetamide (20%). The amide was smoothly converted to 3-indoleacetic acid (III) in high yield by hydrolysis with sodium hydroxide solution. The over-all yield of III from gramine (II) was nearly 90%. The treatment of dialkylaminomethyl derivatives of indole with sodium cyanide to produce 3-indoleacetic acid has been previously reported by Kühn and Andersag[8] but no experimental details of this work are available.

3-Indoleacetic acid was readily reduced to the

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[1] Present address: Chas. Pfizer and Co., Inc., Brooklyn 6, N. Y.

[2] Snyder and Pilgrim, THIS JOURNAL, **70**, 1962 (1948).

[3] Oddo and Cambieri, *Gazz. chim. ital.*, **69**, 19 (1939).

[4] Jackson, *J. Biol. Chem.*, **88**, 659 (1930).

[5] Majima and Hoshino, *Ber.*, **58**, 2042 (1925).

[6] Hoshino and Shimodaira, *Ann.*, **520**, 19 (1935).

[7] Kühn and Stein, *Ber.*, **70**, 567 (1937).

[8] Described in Department of Commerce reports of German technological developments by Dr. W. Salzer (P. B. 706).

corresponding alcohol, tryptophol (IV), by the excellent method of Nystrom and Brown.[9] An ether solution of III was treated with lithium aluminum hydride, suspended in ether, to give IV in good yield (65%).

Experimental

3-Indoleacetic Acid (III).—Gramine (II) was prepared by the Mannich reaction on indole (I) according to the method of Kühn and Stein.[7] A mixture of 25.0 g. of gramine (II), 35.2 g. of sodium cyanide, 280 ml. of 95% ethyl alcohol and 70 ml. of water was boiled for eighty hours. To the cooled reaction mixture was added 350 ml. of water. The solution was treated with Norite, filtered, concentrated under reduced pressure until all the alcohol had been removed, cooled to 5° and filtered. The solid on the funnel (7.0 g., m. p. 145–150°) was recrystallized from alcohol and ether to give 5.0 g. of 3-indoleacetamide, m. p. 149–151°. A sample of the amide, prepared for analysis by recrystallization from absolute alcohol and petroleum ether, was found to melt at 153°. The amide has been previously reported to melt at 150–151°.[10,6]

Anal. Calcd. for $C_{10}H_{10}N_2O$: N, 16.09: Found: N, 15.94.

The reaction mixture, after removal of amide by filtration, was concentrated under reduced pressure to a volume of approximately 300 ml. and cooled to 10°. Dropwise addition of cold, concentrated hydrochloric acid (hood!) to the vigorously stirred solution caused precipitation of crude, slightly pink 3-indoleacetic acid. The crude material was filtered and dried at 70°; yield 20.0 g. (79.5%) of product melting at 158–161°. This material was recrystallized from ethylene dichloride containing a small amount of alcohol to give pure 3-indoleacetic acid (III), m. p. 167–168°; yield 17.4 g. (69.2%). A sample of III, recrystallized from ethylene dichloride was found to melt at 168–169° (lit. m. p. 164.5–165°).[5]

A solution consisting of 1.0 g. of 3-indoleacetamide (m. p. 149–151°), 1.2 g. of sodium hydroxide and 8.0 ml. of water was boiled for four hours. The cooled (5°) solution was treated with Norite, filtered and made strongly acidic (*p*H about 1.5) with concentrated hydrochloric acid. The 3-indoleacetic acid which precipitated was collected on a Büchner funnel and dried at 70°. The yield of product, melting at 167–168°, was 0.95 g. (95%). On the basis of this experiment the over-all yield of pure III from gramine (II) was 88%.

In one experiment the alkaline solution of 3-indoleacetic acid was treated with acid to adjust the *p*H to about 4.5 (instead of 1.5). The product which precipitated proved to be a mixture of III and the sodium salt of III. In those cases where the *p*H was adjusted to about 1.5 the product was found to be only III.

β-(3-Indole)-ethanol (Tryptophol) (IV).—To a rapidly stirred suspension of 1.4 g. of lithium aluminum hydride in 100 ml. of anhydrous ether was added a solution of 5.0 g. of III in 300 ml. of anhydrous ether at such a rate that gentle reflux was maintained. The reaction mixture was stirred for fifteen minutes after the addition was completed. The excess lithium aluminum hydride was decomposed by the dropwise addition of a few milliters of water. The reaction mixture was treated with 60 ml. of 10% sodium hydroxide solution (added dropwise), and the ether layer was separated; the aqueous layer was filtered, and the filtrate was extracted with 100 ml. of ether. The combined ether solutions were evaporated under reduced pressure. The residual oil did not readily crystallize and was distilled to give 3.0 g. of tryptophol (IV), b. p. 174° (2 mm.); yield 65.2%. Some decomposition of the product occurred during the distillation. On standing the oily product crystallized to give solid material melting at 57–58°; the mixed m. p. with an authentic sample of IV, prepared by another method,[3] was 57–58°.

Summary

Tryptophol [β-(3-indole)-ethanol] has been prepared *via* the sequence: indole, gramine, 3-indoleacetic acid, tryptophol. Detailed experimental conditions are given for the preparation of 3-indoleacetic acid from gramine.

URBANA, ILLINOIS RECEIVED JULY 12, 1948

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(9) Nystrom and Brown, THIS JOURNAL, **69**, 1197 (1947); **69**, 2548 (1947).

(10) Baker and Happold, *Biochem. J.*, **34**, 657 (1940).

[CONTRIBUTION FROM THE CHEMOTHERAPY DIVISION, STAMFORD RESEARCH LABORATORIES, AMERICAN CYANAMID COMPANY]

Chemical Studies on Polymyxin.[1] I. Isolation and Preliminary Purification

BY R. G. SHEPHERD, P. G. STANSLY, R. WINTERBOTTOM, J. P. ENGLISH, C. E. FELLOWS, N. H. ANANENKO AND G. L. GUILLET

In a previous report[2] describing the chemotherapeutic properties of polymyxin, the isolation of the antibiotic mixture from the fermentation liquor of *Bacillus polymyxa* was briefly described. The procedure employed was based on charcoal adsorption, elution with acid methanol, and precipitation of the hydrochloride salt with acetone. To facilitate investigation of this antibiotic, the present communication describes its isolation and purification in detail. Some of the properties of polymyxin are also summarized. The preparation of polymyxins which are homogeneous with respect to biological activity and the identity of the constituents are reported in a separate paper.[3]

Experimental

The method of assay used in these isolation studies and the definition of the "unit" of activity have been reported earlier.[4] The assay error of any single determination has been estimated to be ±15%. Except as otherwise stated, the various comparative experiments were carried out on 100–500 cc. quantities of fermentation liquor prepared

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(1) Polymyxin is a generic term for the antibiotics (first isolated from *B. polymyxa* filtrates) which have the closely related biological and chemical characteristics described elsewhere (refs. 2 and 3). This paper was presented before the Division of Biological Chemistry at the American Chemical Society meeting in Chicago on April 20, 1948.

(2) Stansly, Shepherd and White, *Bull. Johns Hopkins Hosp.*, **81**, 43 (1947).

(3) Bell, *et al.*, *Ann. N. Y. Acad. Sci.*, **51**, in press (1948).

(4) Stansly and Schlosser, *J. Bact.*, **54**, 585 (1947).