solvents had been distilled under reduced pressure, a white solid, m.p. 166.5–167.4°, remained.

*Anal.* Calcd. for $C_{15}H_{23}O_3N_3$: C, 61.41; H, 7.90; N, 14.32. Found: C, 61.46, 61.60; H, 7.83, 7.86; N, 13.86, 13.89.

XI did not react in a refluxing solution of acetic anhydride. The starting material was recovered after 4 hr. of heating in the acetic anhydride solution.

*Acknowledgment.* The author is indebted to L. J. Lohr and R. W. Warren, who prepared the infrared and ultraviolet spectra and assisted in their interpretation.

GIBBSTOWN, N. J.

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, UNION CARBIDE CHEMICALS COMPANY]

# 3-Indolepropionic Acid

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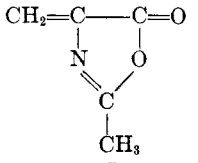
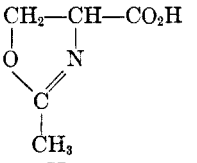
3-Indolepropionic acid has been prepared in 56% yield by the reaction of indole with acrylic acid in the presence of acetic anhydride.

3-Indolepropionic acid has, over a period of years, been the subject of many investigations concerning its plant growth regulating properties. More recently, its use as a starting material for the synthesis of lysergic acid has been described.[1] There are various procedures by which 3-indolepropionic acid may be synthesized, and, until the present investigation, the most convenient of these consisted of the hydrolysis of 3-indolepropionitrile obtained from the reaction of indole and acrylonitrile.[2]

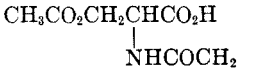
The reaction of acrylic acid with indole at 130° is reported to give a quantitative yield of 1-indolepropionic acid.[2] α-Acetamidoacrylic acid, however, reacts with indole in the presence of acetic anhydride to give acetyltryptophan.[3]



I



II

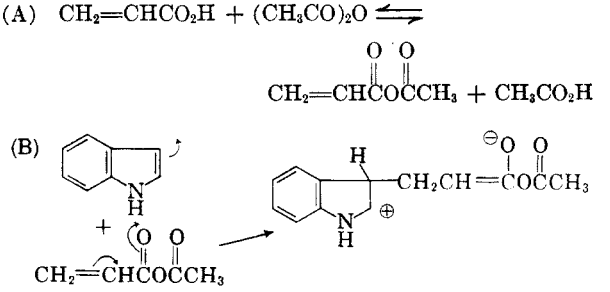


III

When acrylic acid and indole were allowed to react in acetic acid solution containing acetic anhydride, 3-indolepropionic acid could be isolated in 56% yield from the reaction mixture. The quantity of anhydride necessary for the reaction to take place was not critically investigated, but it was found that 0.20 equivalent (based on indole) was not sufficient. For convenience, at least two equivalents were usually employed, one equivalent being somewhat less satisfactory.

The role of acetic anhydride in the reaction still remains uncertain. Snyder and MacDonald[3] suggested that α-acetamidoacrylic acid is possibly converted by the anhydride present into an intermediate azlactone (I), oxazoline (II), or diacetylserine (III). On the basis of model experiments, these intermediates were rejected as unlikely, and no other explanations were presented. I and II are not possible intermediates in the present synthesis of 3-indolepropionic acid. III is considered improbable, as acetic acid would not be expected to add to acrylic acid under the reaction conditions.

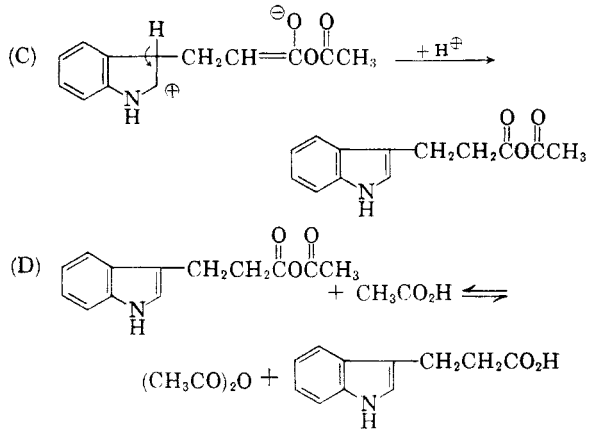
A mechanism consistent with the addition of both acrylic acid and α-acetamidoacrylic acid to the 3-position of indole places the anhydride in the role of forming a mixed anhydride with the acrylic acid. This mixed anhydride, or an acryloyl cation produced by its dissociation, is the reactive species that adds to the 3-position (Equations A–D).



(1) E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, D. E. Morrison, R. G. Jones, and R. B. Woodward, *J. Am. Chem. Soc.*, **78**, 3087 (1956). E. C. Kornfeld, G. B. Kline, and E. J. Fornefeld, U. S. Patent **2,796,419**.

(2) W. Reppe and H. Ufer, German Patent **698,273**; French Patent **48,570**, addition to French Patent **742,358**.

(3) H. R. Snyder and J. A. MacDonald, *J. Am. Chem. Soc.*, **77**, 1257 (1955); U. S. Patent **2,810,727**.



The equilibrium represented in (A) is apparently an over-simplification, as the seemingly excessive amount of acetic anhydride that is necessary for the reaction to proceed satisfactorily is not anticipated. Other factors therefore must predominate, and it is speculated that the quantity of acetic acrylic anhydride present at any one time is small. The possibility of (B) being a slow reaction and the equilibrium of (D) not being readily attained is considered to be of minor importance.

As would be expected on the basis of the proposed mechanism, acrylic anhydride and indole in acetic acid solution react to give 3-indolepropionic acid. Also, methyl acrylate and acrylonitrile are unreactive toward indole in the presence of acetic acid and acetic anhydride under the above reaction conditions.

## EXPERIMENTAL[4]

*3-Indolepropionic Acid:* (a). *By the reaction of indole, acrylic acid and acetic anhydride.* A solution of 60 g. (0.51 mole) of indole in 240 ml. of acetic acid containing 100 ml. (1.0 mole) of acetic anhydride and 80 g. (1.1 moles) of acrylic acid was heated at 90° for 3 hr. The reaction mixture was allowed to stand overnight at 25° and then all volatile material quickly removed by distillation under reduced pressure. A dark viscous residue remained which was added to a solution of 60 g. (1.5 moles) of sodium hydroxide in 500 ml. of water without external cooling. The mixture was then allowed to cool and the insoluble material removed by filtration. Acidification of the filtrate with concentrated hydrochloric acid precipitated 3-indolepropionic acid. The product was isolated by filtration and dried to give 54 g. (56%) of light-tan material, m.p. 128–131°. A sample was crystallized from water as long nearly-colorless needles, melting point and mixed melting point with an authentic sample prepared by the hydrolysis of 3-indolepropionitrile, 135–136°, lit.,[5] m.p. 133–134°.

(b). *By the reaction of indole, acrylic anhydride, and acetic acid.* Twenty-three grams (0.20 mole) of indole, 25 g. (0.20 mole) of acrylic anhydride, and 100 ml. of acetic acid were allowed to react according to the above procedure to give 17 g. (45%) of 3-indolepropionic acid, m.p. 124–126°. The infrared spectrum of this material is identical to the infrared spectrum of an authentic sample of 3-indolepropionic acid.

*Acknowledgment.* The authors wish to thank Mr. C. R. McClure for his able assistance.

SOUTH CHARLESTON, W. VA.

(4) All melting points are corrected.

(5) A. Ellinger, *Chem. Ber.*, **38**, 2884 (1905).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND THE LABORATORY OF PHARMACEUTICAL CHEMISTRY, UNIVERSITY OF NEW MEXICO]

# Cinnoline Chemistry. V. 4-Mercaptocinnolines and Related Compounds[1,2]

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4-Mercaptocinnoline, 6,7-dimethoxy-4-mercaptocinnoline and a number of alkyl and heterocyclic derivatives of these compounds have been prepared for antitumor screening. 4,6,7-Trimethoxycinnoline and 4-ethoxy-6,7-dimethoxycinnoline were also prepared. The infrared spectra of most of these compounds were determined.

The antileukemic activity of 6-mercaptopurine prompted the preparation of the mercaptocinnolines and related compounds. 4-Mercaptocinnoline (I) was prepared by the action of thiourea on 4-chlorocinnoline. The intermediate, which precipitated from the methanolic solution, was assumed to be the thiouronium salt and was readily converted into 4-mercaptocinnoline by heating with sodium hydroxide solution. 6,7-Dimethoxy-4-mercaptocinnoline (II) was prepared in the same manner. 4-Mercaptocinnoline was prepared in nearly quantitative yield by allowing phosphorus pentasulfide to react with 4-hydroxycinnoline in dry pyridine solution. 6,7-Dimethoxy-4-mercaptocinnoline was prepared in somewhat poorer yield in the same manner. 4-Methylmercaptocinnoline (III) was prepared by allowing I to react with methyl iodide in alkaline solution. 6,7-Dimethoxy-4-methylmercaptocinnoline (IV) was prepared in a similar fashion.

4-Bicinnolyl sulfide (V) was prepared by allowing

(1) Paper IV in this series, R. N. Castle, D. B. Cox, and J. F. Suttle, *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 135 (1959).

(2) This investigation was supported in part by Grant CY-4327 from the National Cancer Institute, Public Health Service. Presented before the Division of Medicinal Chemistry, 136th Meeting of the American Chemical Society, September 1959, Atlantic City.