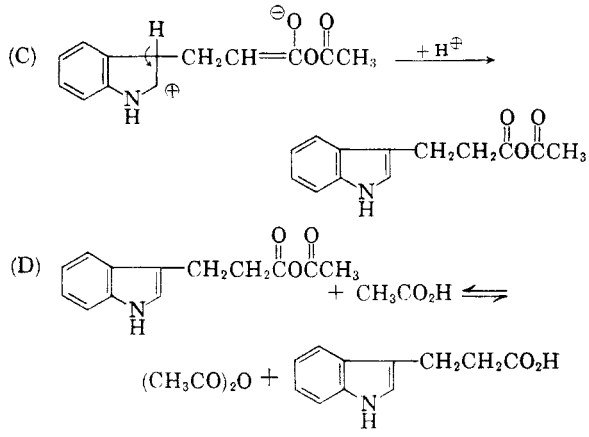


The equilibrium represented in (A) is apparently an over-simplification, as the seemingly excessive amount of acetic anhydride that is necessary for the reaction to proceed satisfactorily is not anticipated. Other factors therefore must predominate, and it is speculated that the quantity of acetic acrylic 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).

[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]

RAYMOND N. CASTLE, HELEN WARD, NOEL WHITE, AND KIKUO ADACHI

Received July 16, 1959

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

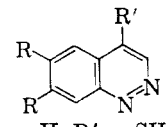
(1) Paper IV in this series, R. N. Castle, D. B. Cox, and J. F. Suttle, *J. Am. Pharm. Assoc., Sci. Ed.*, **48**, 135 (1959).

(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.

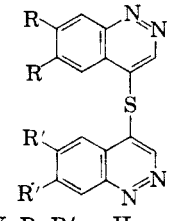
4-mercaptocinnoline to react with 4-chlorocinnoline in the presence of sodium methoxide in methanol solution. 4,4′-Bis(6,7-dimethoxycinnolyl) sulfide (VI) and 4-cinnolyl 4′-(6′,7′-dimethoxycinnolyl) sulfide (VII) were prepared by a similar procedure. 4-Cinnolyl 2-quinoxalyl sulfide (VIII) and 4-(6,7-dimethoxycinnolyl) 2-quinoxalyl sulfide (IX) were prepared similarly by allowing 2-chloroquinoxaline to react with the appropriate mercaptocinnolines.

4,6,7-Trimethoxycinnoline (X) was prepared by allowing sodium methoxide in dry methanol to react with 4-chloro-6,7-dimethoxycinnoline. 6,7-Dimethoxy-4-ethoxycinnoline (XI) was prepared in a similar manner from sodium ethoxide and 4-chloro-6,7-dimethoxycinnoline.

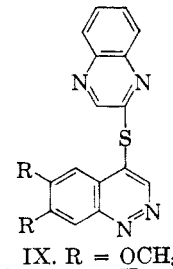
Evidence for the constitution of these compounds was obtained from the methods of synthesis and from the infrared spectra.



I. R = H, R′ = SH
II. R = OCH_3, R′ = SH
III. R = H, R′ = SCH_3
IV. R = OCH_3, R′ = SCH_3
X. R, R′ = OCH_3
XI. R = OCH_3, R′ = OC_2H_5



V. R, R′ = H
VI. R, R′ = OCH_3
VII. R = H, R′ = OCH_3



IX. R = OCH_3
VIII. R = H

EXPERIMENTAL

The analyses were by Weiler and Strauss, Oxford, and by the Tanabe Seiyaku Company, Ltd., Tokyo.[3] The melting points are uncorrected.

4-Mercaptocinnoline. A mixture of 1.1 g. of 4-chlorocinnoline and 1.0 g. of thiourea dissolved in 8 ml. of dry methanol was warmed and swirled for about 10 min. The mixture became a yellow semisolid mass which was dissolved by the addition of more absolute methanol. After filtration and vacuum evaporation, fine yellow crystals separated, m.p. 146–148°. This material was heated for 35 min. on a steam bath with 4 ml. of 2.5*N* sodium hydroxide solution. The cooled solution was acidified with dilute acetic acid and the orange-yellow semisolid mass filtered, m.p. 188–192°, yield 0.7 g. A sample for analysis was recrystallized from glacial acetic acid, m.p. 200–201°.

Anal. Calcd. for $C_9H_6N_2S$: C, 59.23; H, 3.73; N, 17.27. Found: C, 58.97; H, 3.81; N, 16.99.

Ten grams of 4-hydroxycinnoline and 60 g. of phosphorus pentasulfide were added to 650 ml. of dry, freshly distilled C. P. pyridine. This mixture was refluxed for 5 hr., and then the excess pyridine was removed by vacuum distillation until near dryness. About 400 g. of crushed ice was added to the cooled residue and the mixture was allowed to stand for 0.5 hr. After 2 hr. heating on the steam bath, the deep red solution was allowed to stand overnight in the refrigerator. Deep red needles (9.8 g.) separated, m.p. 191–198°. A sample purified for analysis by repeated solution in ammonium hydroxide and precipitation with acetic acid melted at 203–205°. The mixed melting point with the sample described above was 202–205°.

Anal. Calcd. for $C_9H_6N_2S$: C, 59.23; H, 3.73. Found: C, 58.77; H, 3.99.

6,7-Dimethoxy-4-mercaptocinnoline. One gram of thiourea and 1.1 g. of 4-chloro-6,7-dimethoxycinnoline were dissolved in 10 ml. of dry methanol and the solution refluxed on the steam bath for 7 min. At this time a solid began to separate which amounted to 1.1 g., m.p. 175–179° crude. This product was heated for 40 min. on a steam bath with 7 ml. of 2.5*N* sodium hydroxide solution. After cooling the solution was acidified with dilute acetic acid. One gram of yellow powder was obtained, m.p. 211–213°. A sample for analysis was prepared by recrystallization from glacial acetic acid, m.p. 216–217°.

Anal. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.54. Found: C, 54.16; H, 4.39.

A mixture of 7.0 g. of 6,7-dimethoxy-4-hydroxycinnoline and 30.0 g. of phosphorus pentasulfide in 325 ml. of dry, freshly distilled C. P. pyridine was refluxed for 4 hr. The pyridine was removed by distillation in vacuum on a steam bath and the residue was taken nearly to dryness. About 200 g. of crushed ice and water was added and the mixture was allowed to stand overnight, then heated 2 hr. on a steam bath. After standing 24 hr. in the refrigerator the crystalline product amounted to 6.4 g., m.p. 213–215°. A purified sample melted at 216–217° alone and when admixed with the analytical sample described above.

4-Methylmercaptocinnoline. To a solution of 1.62 g. (0.01 mole) of 4-mercaptocinnoline in 50 ml. of 10% sodium hydroxide solution was added 1.42 g. (0.01 mole) of methyl iodide. The mixture was stirred an additional 0.5 hr. at 25°, whereupon a greenish crystalline solid separated. The solid was extracted into about 100 ml. of chloroform. This solution was dried over magnesium sulfate and the residue obtained by evaporation. The residue was dissolved in ether and the insoluble impurities were removed by filtration. Upon evaporation 1.1 g. (63%) of yellow needles melting at 93–95° were obtained. An analytical specimen was obtained by crystallization from cyclohexane, m.p. 98°.

When the above procedure was repeated using the same quantities of materials except that two molar proportions of methyl iodide were used, the yield was 1.3 g. (74%) of product melting at 93–95°.

Anal.: Calcd. for $C_9H_8N_2S$: C, 61.35; H, 4.62; N, 15.90. Found: C, 61.60; H, 4.55; N, 15.85.

6,7-Dimethoxy-4-methylmercaptocinnoline. To a solution of 1.0 g. of 6,7-dimethoxy-4-mercaptocinnoline in 25 ml. of 10% sodium hydroxide solution was added 0.7 g. (one molar equivalent) of methyl iodide. The mixture was stirred at 25° for 0.5 hr. At this time a solid separated which was extracted into chloroform and dried over magnesium sulfate. The dried filtrate was subjected to chromatography through alumina, using chloroform as the eluent. A yield of 0.38 g. (37%) of yellow crystals was obtained, m.p. 205–210°.

(3) The authors are indebted to Drs. S. Yamada and K. Abe for their kindness in providing certain of these analyses.

An analytical sample prepared by crystallization from benzene melted at 215–217°.

Anal. Calcd. for $C_{11}H_{12}N_2O_2S$: C, 55.93; H, 5.12; N, 11.86. Found: C, 56.00; H, 5.34; N, 11.64.

4,4'-Bicinnolyl sulfide. A solution of 2.0 g. of 4-chlorocinnoline, 2.0 g. of 4-mercaptocinnoline and 0.67 g. of sodium methoxide in 35 ml. of dry methanol was refluxed for 1.75 hr. The product, 3.5 g. (97%), separated from the hot solution, m.p. 180–181°. A sample purified for analysis by crystallization from ethanol melted at 181°.

Anal. Calcd. for $C_{16}H_{10}N_4S$: C, 66.21; H, 3.47; N, 19.31. Found: C, 66.07; H, 3.51; N, 18.90.

4,4'-Bis(6,7-dimethoxycinnolyl) sulfide. A solution of 1.4 g. of 4-chloro-6,7-dimethoxycinnoline, 1.4 g. of 6,7-dimethoxy-4-mercaptocinnoline, and 0.34 g. of sodium methoxide in 23 ml. of dry methanol was refluxed for 2.5 hr., whereupon the solid product separated from the hot solution. There was obtained 2.4 g. of crude product, m.p. 210–215°. An analytical sample was prepared by crystallization from a large volume of ethanol, m.p. 220–225°.

Anal. Calcd. for $C_{20}H_{18}N_4SO_4$: C, 58.52; H, 4.42; N, 13.65. Found: C, 58.70; H, 4.62; N, 13.34.

4-Cinnolyl 4'-(6',7'-dimethoxycinnolyl) sulfide. A solution of 2.8 g. of 4-chloro-6,7-dimethoxycinnoline, 2.0 g. of 4-mercaptocinnoline, and 0.67 g. of sodium methoxide in 45 ml. of dry methanol was refluxed for 3.5 hr., at which time a solid product separated amounting to 4.24 g., m.p. 193°. The analytical sample was crystallized from ethanol, m.p. 193°.

Anal. Calcd. for $C_{18}H_{14}N_4O_2S$: C, 61.70; H, 4.03; N, 15.99. Found: C, 61.62; H, 4.29; N, 15.70.

4-Cinnolyl 2-quinoxalyl sulfide. A solution of 1.5 g. of 2-chloroquinoxaline, 1.5 g. of 4-mercaptocinnoline and 0.5 g. of sodium methoxide in 26 ml. of dry methanol was refluxed for 8.5 hr. Only 0.25 g. of product was obtained, which after purification by crystallization from ethanol melted at 153–154°, pale yellow needles.

Anal. Calcd. for $C_{16}H_{10}N_4S$: C, 66.21; H, 3.47; N, 19.31. Found: C, 66.02; H, 3.69; N, 18.97.

4-(6,7-Dimethoxycinnolyl) 2-quinoxalyl sulfide. A solution of 1.5 g. of 2-chloroquinoxaline, 2.1 g. of 6,7-dimethoxy-4-mercaptocinnoline, and 0.5 g. of sodium methoxide in 26 ml. of dry methanol was refluxed for 2.25 hr. The solid product amounted to 1.85 g., m.p. 210°. A sample purified for analysis by crystallization from ethanol melted at 210°.

Anal. Calcd. for $C_{18}H_{14}N_4O_2S$: C, 61.70; H, 4.03; N, 15.99. Found: C, 61.33; H, 4.18; N, 16.30.

4,6,7-Trimethoxycinnoline. A solution of 1.0 g. of 4-chloro-6,7-dimethoxycinnoline and 0.5 g. of sodium methoxide in 30 ml. of absolute methanol was refluxed for 2.5 hr. The solution was allowed to cool and stand overnight whereupon 0.74 g. (76%) of product separated, m.p. 210° dec. An analytical sample was prepared by crystallization from methanol, m.p. 210° dec.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49. Found: C, 59.74; H, 5.76.

4-Ethoxy-6,7-dimethoxycinnoline. A solution of 1.0 g. of 4-chloro-6,7-dimethoxycinnoline and 0.5 g. of sodium ethoxide in 30 ml. of absolute ethanol was refluxed for 2 hr. Some solid product separated during the heating period and additional material separated on standing overnight at room temperature. Upon purification of the nonhomogeneous solid by repeated crystallization from ethanol, 0.15 g. of 4-chloro-6,7-dimethoxycinnoline was recovered together with 0.3 g. of product, m.p. 185–187°.

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.95. Found: C, 61.67; H, 6.17; N, 11.90.

Infrared spectra were determined on all compounds except 4-ethoxy-6,7-dimethoxycinnoline and 4-cinnolyl-4'-(6',7'-dimethoxycinnolyl) sulfide. All these compounds show the characteristic cinnoline absorption band[1] in the 6.3 μ region, although the absorption is weak in some instances. These spectra were determined as Nujol mulls on the Perkin-Elmer Infracord.

ALBUQUERQUE, N. M.

[CONTRIBUTION FROM THE BOUND BROOK LABORATORIES, AMERICAN CYANAMID COMPANY]

Some Carboxaldazines and *s*-Triazoles of the Anthraquinone Series

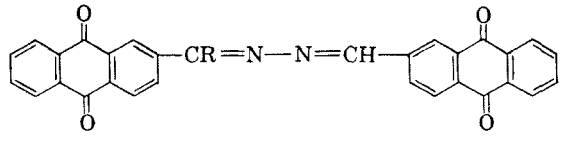
ERWIN KLINGSBERG

Received October 15, 1959

2-Anthraquinonecarboxaldazine (I) reacts with chlorine to give the α-monochloro derivative (II) or 2-cyanoanthraquinone (VI), depending on conditions. 1,1'-Dichloro-2-anthraquinonecarboxaldazine (XI) behaves similarly. II reacts with amines to give aminoaldazines or triazoles.

The present paper describes the results of an investigation into the preparation and reactions of certain chlorinated anthraquinonecarboxaldazines, undertaken with a view to the synthesis of anthraquinonyltriazoles.[1]

Stollé,[2,3] found that benzaldazine takes up one or two atoms of chlorine, according to conditions, to give the monochloro derivative $C_6H_5CCl{:}N{-}N{:}CHC_6H_5$ or the dichloro derivative $C_6H_5CCl{:}N{-}N{:}CClC_6H_5$. The behavior of 2-anthraquinonecarboxaldazine (I) is somewhat different. While it



	R =
I	H
II	Cl
III	NH_2
IV	NHMe
V	NMe_2

does react with chlorine in nitrobenzene at 100–140° to give the monochloro derivative (II), a second atom of chlorine could not be introduced. When the reaction temperature was raised to 160–165°, a poor yield of unidentified product was obtained.

(1) E. Klingsberg, *J. Am. Chem. Soc.* **80**, 5786 (1958).
(2) R. Stollé, *J. Prakt. Chem.* **85**, 386 (1912).
(3) R. Stollé and Fr. Helwerth, *Ber.*, **47**, 1132 (1914).