ligroin afforded 0.2 g. (30%) of material melting at 121.4–122°.

Anal. Calcd. for $C_{15}H_{14}$: C, 92.75; H, 7.26. Found: C, 92.72; H, 7.24.

Attempts to prepare a pure picrate were unsuccessful, the best sample sintering at 121° and melting over the range 127–130°. The **trinitrobenzene derivative** crystallized from ethanol in orange needles; m. p. 147–148°.

Anal. Calcd. for $C_{21}H_{17}O_6N_3$: C, 61.91; H, 4.21. Found: C, 61.98; H, 4.50.

Other Trials.—3-Methylacenaphthene (10 g.) was condensed with N-methylformanilide under the conditions used in the reaction with acenaphthene. Steam distillation gave 8.0 g. (68%) of a mixture of aldehydes, m. p. 67–100°, but no satisfactory method of separation was found. 3-Methylpyrene[5] (9 g.) was submitted to the reaction in *o*-dichlorobenzene solution at the steam-bath temperature, and the reaction mixture when processed through the bisulfite addition product yielded 7.5 g. (73%) of a mixture of aldehydes, m. p. 98–108°, but this again proved intractable. The semicarbazone mixture did not seem favorable for fractionation and the regeneration proceeded poorly. Extensive fractionation of the aldehyde mixture from alcohol and from benzene-ligroin afforded only a small amount of possibly homogeneous orange needles; m. p. 138–140°.

Anal. Calcd. for $C_{17}H_{10}O$: C, 88.50; H, 4.99. Found: C, 88.60; H, 4.95.

Summary

The reaction of aromatic hydrocarbons with N-methylformanilide to give aldehydes is limited to substances having a particularly reactive nuclear position and not too sensitive to be destroyed by the condensing agent (phosphorus oxychloride). Acenaphthene has been formylated by this method and the product utilized for the synthesis of 3,4-aceperinaphthane.

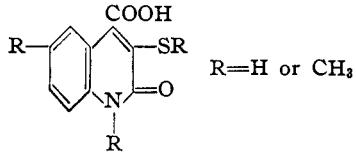
CONVERSE MEMORIAL LABORATORY
CAMBRIDGE, MASSACHUSETTS RECEIVED APRIL 1, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

The Synthesis from Rhodanine-oxindoles of Keto and Mercapto Derivatives of Cinchoninic Acid[1]

BY RUFUS VERNON JONES[2] AND HENRY R. HENZE

Although the preparation of derivatives of ketocinchoninic acids has been studied to a considerable extent, little attention has been directed to the synthesis of mercapto derivatives of the type



In fact, only two examples of this type have been reported, namely, the unsubstituted keto-mercapto acid and its 1-methyl derivative, prepared, respectively, by the alkaline hydrolysis of the appropriate rhodanine-($\Delta^{5,3'}$)-oxindole.[3]

We have resynthesized these two rhodanine-oxindoles and, in addition, have prepared the 5-methyl and the 1,5-dimethyloxindole analogs, by condensation of rhodanic acid and appropriate derivatives of isatin, in order to study their conversion into keto and mercapto derivatives of cinchoninic acid. A comparison of behavior upon hydrolysis of rhodanine-($\Delta^{5,3'}$)-oxindole and its 5-methyl homolog was of special interest since it had been shown[4] that the closely related hydantoin-(5,3')-oxindole and its 5'-methyl homolog had formed markedly different products on alkaline hydrolysis, in that the former yielded 1,2-dihydro-2-ketocinchoninic acid and the latter 5-methyloxindole.

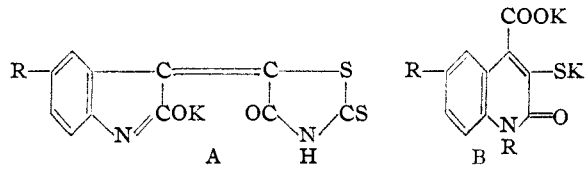
In the present investigation, rhodanine-($\Delta^{5,3'}$)-oxindole and three methyl derivatives were hydrolyzed by alkali to form derivatives of 1,2-dihydro-2-keto-3-mercaptocinchoninic acid. The behavior of these compounds toward further hydrolysis, methylation and reduction was studied. It was found that rhodanine-($\Delta^{5,3'}$)-oxindole and its 5'-methyl homolog by treatment with one molecular proportion of potassium hydroxide are converted into mono-potassium salts of the type (A) which can be hydrolyzed to regenerate the oxindoles but cannot be methylated. With an excess of alkali, rhodanine-($\Delta^{5,3'}$)-oxindole was converted into the dipotassium salt of 1,2-dihydro-2-keto-3-mercaptocinchoninic acid, and the three methyl derivatives formed analogous dipo-

(1) Presented before the Division of Organic Chemistry at the 99th meeting of the American Chemical Society at Cincinnati, Ohio, April 9–11, 1940.

(2) From the Ph.D. dissertation of R. V. Jones, June, 1937. Present address of R. V. J., East Texas State Teachers College, Commerce, Texas.

(3) (a) Gränacher and Mahal, *Helv. Chim. Acta*, **6**, 467 (1923); (b) Gränacher and Kouniniotis, *ibid.*, **11**, 1241 (1928).

(4) Henze and Blair, THIS JOURNAL, **55**, 4624 (1933).



tassium salts of type (B). The latter upon acidification form the corresponding 1,2-dihydro-2-keto-3-mercaptocinchoninic acid derivatives. These, in turn, when treated with dimethyl sulfate were converted into 1,2-dihydro-2-keto-3-methylmercaptocinchoninic acid analogs.

Experimental

Rhodanine-($\Delta^{5,3'}$)-1'-methyloxindole (II).—This compound was synthesized in a manner similar to rhodanine-($\Delta^{5,3'}$)-oxindole (I),[5] by heating for five hours at 140° a solution of 30 g. (0.185 mole) of 1-methylisatin,[6] 24.6 g. (0.185 mole) of rhodanine, 30 g. (0.36 mole) of fused sodium acetate, 400 cc. of glacial acetic acid and 4 cc. of acetic anhydride. Upon cooling, dark red crystalline plates separated which, after drying, weighed 51 g. (99% yield). This compound is virtually insoluble in the common organic solvents and does not melt or decompose at 300°. It yields a positive test with Feigl's reagent, (=C=C—SH⇌ =CH—C=S),[7] and dissolved in alkaline solution but is not reprecipitated unchanged upon acidification.

Anal. Calcd. for $C_{12}H_8N_2O_2S_2$: N, 10.14; S, 23.20. Found: N, 9.76; S, 23.31.

Rhodanine-($\Delta^{5,3'}$)-5'-methyloxindole (III).—Prepared in the same manner as the above but from 5-methylisatin, this compound possesses a copper-brown color with a metallic luster and is very sparingly soluble in ordinary organic solvents. Its physical and chemical behavior is similar to that of the 1'-isomer.

Anal. Calcd. for $C_{12}H_8N_2O_2S_2$: S, 23.20. Found: S, 22.82.

Rhodanine-($\Delta^{5,3'}$)-1',5'-dimethyloxindole (IV).—Prepared as above from 1,5-dimethylisatin[8] in 76% yield, the compound is a satin-black colored, fluffy solid with physical and chemical properties like those of the monomethyl analogs.

Anal. Calcd. for $C_{13}H_{10}NO_2S_2$: N, 9.65. Found: N, 9.83.

The same compound was obtained in 69% yield by condensing 1,5-dimethylisatin and rhodanine in ethyl alcohol solution using diethylamine as the catalyst.

Methylation of Rhodanine-($\Delta^{5,3'}$)-oxindoles.—In an attempt to convert (I) into (II), the former (0.05 mole) was mixed with dimethyl sulfate (0.05 mole) in alcoholic solution made basic with potassium hydroxide, and then was heated with an equal quantity of dimethyl sulfate for one hour. The solution was acidified and the solid which separated was purified and then melted at 216–217° with decomposition. Analysis proved the material to be **1,2-dihydro-2-keto-3-methylmercaptocinchoninic acid** (XIII), indicating that mere methylation had not occurred.

Anal. Calcd. for $C_{11}H_9NO_3S$: N, 5.95. Found: N, 5.94.

When compound I was treated with two equivalents of dimethyl sulfate in a 5% alcoholic solution, addition of 25% potassium hydroxide solution produced a red precipitate. The latter was filtered, dissolved in excess of the same alkaline solution and, upon acidification with hydrochloric acid, hydrogen sulfide was evolved. From the solution was obtained light yellow crystals melting at 345° (cor.); mixed with an authentic sample of **1,2-dihydro-2-ketocinchoninic acid** (XVII), the mixture melted unchanged.

Attempted methylation of I, suspended in methanol, by means of dimethyl sulfate and alcoholic potash for two hours at 100° was unsuccessful and I was recovered unchanged. The monopotassium salt of I was refluxed for fifteen hours with methyl iodide, but without reaction.

Likewise, no apparent change occurred when the monopotassium salt of III was suspended in dry ether and heated for several hours with dimethyl sulfate in an attempt to form IV. Even when this salt was heated for eighty hours at 100° with dimethyl sulfate, instead of methylation, hydrolysis and desulfurization produced **1,2-dihydro-2-keto-6-methylcinchoninic acid** (XVIII); m. p. 235–236° (cor.).

Anal. Calcd. for $C_{11}H_9NO_3$: N, 6.90. Found: N, 6.96.

Potassium Hydroxide on Rhodanine-($\Delta^{5,3'}$)-oxindoles.—To a well-stirred alcoholic suspension of I was added one equivalent of potassium hydroxide and the mixture was heated for one hour. The suspended, dark colored material became red and then was but slightly soluble in alcohol, ether or water. Suspended in water the salt rapidly hydrolyzed (accelerated by acid) to regenerate I. The red solid does not melt or decompose at 300°, is a monopotassium salt, and gives a positive test with the Feigl reagent.[7]

Anal. Calcd. for $C_{11}H_5KN_2O_2S_2$: N, 9.26. Found: N, 8.94.

Addition of three equivalents of potassium hydroxide to an alcoholic suspension of I caused a change of color, first to a deep red, and after a while to yellow. The mixture was boiled for one hour, cooled and filtered, yielding a canary yellow, crystalline solid. The latter is extremely soluble in water but is only slightly so in absolute alcohol or ether. The salt gave a positive Feigl test.[7] A 3% solution yields precipitates of characteristic color with many cations; these cannot be distinguished from those produced by the dipotassium salt of **1,2-dihydro-2-keto-3-mercaptocinchoninic acid** (V).

Anal. Calcd. for $C_{10}H_5K_2NO_3S$: S, 10.78. Found: S, 10.43.

A solution of this dipotassium salt in water at 0° was acidified yielding an orange colored amorphous precipitate. After drying, the product (81% yield) was recrystallized from toluene as feathery, orange crystals melting at 165–

(5) Andreasch, *Monatsh.*, **38**, 138 (1917).

(6) Heller, *Ber.*, **40**, 1300 (1907); an easier method of preparing N-methylisatin involves conversion of N-methylaniline into methylisonitrosoacetanilide and warming the latter with concentrated sulfuric acid at 40–50°.

(7) Feigl, *Mikrochemie*, **XV**, (N. F. IX), 1 (1934).

(8) Hegel [*Ann.*, **232**, 217 (1885)] reported m. p. 148°; we found m. p. 150–152° (cor.).

166° (cor.). These data are in exact agreement with that reported for **1,2-dihydro-2-keto-3-mercaptocinchoninic acid**[9] (VI).

Anal. Calcd. for $C_{10}H_7NO_3S$: neut. equiv., 110.6; N, 6.33. Found: neut. equiv., 109.5; N, 6.36.

Unsuccessful attempts were made to synthesize VI from isatin (a) with thioglycolic acid in alcohol refluxed with diethylamine and (b) with thioglycolic acid heated in glacial acetic acid containing acetic anhydride and fused sodium acetate.

Boiling the dipotassium salt (V) with glacial acetic acid caused the separation of elementary sulfur and from the solution was obtained a curdy, light yellow mass. After solution in alkali, acidification yielded material (62%) melting at 345° (cor.). This material was mixed with an authentic sample of **1,2-dihydro-2-ketocinchoninic acid**[10] (XVII) and the melting point remained unchanged.

The 1-methyl, 5-methyl and 1,5-dimethyl derivatives of rhodanine-($\Delta^{5,3'}$)-oxindole appear to be more readily hydrolyzed by action of potassium hydroxide solution and are converted into the dipotassium salts of the corresponding methylated 1,2-dihydro-2-keto-3-mercaptocinchoninic acids (VII), (IX) and (XI). These salts do not appear to decompose at 300°.

Anal. Dipotassium salt from rhodanine-($\Delta^{5,3'}$)-1'-methyloxindole (VII). Calcd. for $C_{11}H_7K_2NO_3S$: N, 4.50; S, 10.29. Found: N, 4.64; S, 9.85.

This salt was converted in 79% yield by acidification into **1,2-dihydro-2-keto-3-mercapto-1-methylcinchoninic acid** (VIII), m. p. 145° (cor.) (dec.).[11]

Anal. Calcd. for $C_{11}H_9NO_3S$: N, 5.96. Found: N, 5.73.

A monopotassium salt was obtained by interaction of rhodanine-($\Delta^{5,3'}$)-5'-methyloxindole (III) and one equivalent of potassium hydroxide in alcohol. The red salt is hydrolyzed readily by hot water, regenerating the original oxindole derivative.

Anal. Calcd. for $C_{12}H_7KN_2O_2S_2$: N, 8.92; S, 20.40. Found: N, 8.87; S, 20.10.

When the oxindole derivative III is allowed to stand in the cold with alcoholic potassium hydroxide solution, or more rapidly by warming, canary yellow needle-like crystals of a dipotassium salt (IX) are obtained in 90% yield. The compound is very soluble in water, yielding a solution neutral to phenolphthalein, but is rather sparingly soluble in 95% alcohol.

Anal. Calcd. for $C_{11}H_7K_2NO_3S$: C, 42.42; H, 2.27; N, 4.50; S, 10.29. Found: C, 42.04; H, 3.01; N, 4.47; S, 10.40.

From a chilled, aqueous solution of this salt (IX), acidification caused separation (93% yield) of an orange colored solid, so finely divided as to be filtered with extreme difficulty. It is quite soluble in alcohol, acetone and ethyl acetate, but is best recrystallized from glacial acetic acid as a bright red product; m. p. 193–196° (cor.) (dec.). **1,2-Dihydro-2-keto-3-mercapto-6-methylcinchoninic acid** (X) is rather insoluble in cold water but is decomposed by continued contact with boiling water.

Anal. Calcd. for $C_{11}H_9NO_3S$: neut. equiv., 117.6; N, 5.96; S, 13.63. Found: neut. equiv. (phenolphthalein), 117.6; N, 6.01; S, 13.75.

Compound IV was heated with slightly more than two equivalents of potassium hydroxide in water (20% solution); the black compound became red in color and dissolved. Upon dilution of the solution with ethyl alcohol a yellow, crystalline dipotassium salt (XI) separated and was filtered and dried (90% yield). This salt is extremely soluble in water and is quite hygroscopic.

Anal. Calcd. for $C_{12}H_9K_2NO_3S$: N, 4.30; S, 9.85. Found: N, 4.32; S, 10.03.

This salt (XI) upon acidification formed the corresponding **1,2-dihydro-2-keto-3-mercapto-1,6-dimethylcinchoninic acid** (XII) in 87% yield. Out of toluene, the orange-brown feathery crystals melt with decomposition at 157–159° (cor.).

Anal. Calcd. for $C_{12}H_{11}NO_3S$: neut. equiv., 124.6; N, 5.62; S, 12.86. Found: neut. equiv., 125.1 (phenolphthalein); N, 5.79; S, 12.66.

In order to further characterize X, 2 g. of the latter was heated with 1.2 g. of benzyl chloride, 5 g. of sodium hydroxide and 50 cc. of alcohol until solution was complete. On cooling, sodium chloride separated and was removed by filtration. The filtrate was diluted with a large volume of water, boiled to remove much of the alcohol, again cooled, extracted with ether, and upon acidification there was precipitated **1,2-dihydro-2-keto-3-benzylmercapto-6-methylcinchoninic acid;** purified by crystallization from diluted alcohol it melts with decomposition above 200°.

Anal. Calcd. for $C_{18}H_{15}NO_3S$: N, 4.31. Found: N, 4.29.

Following the method of Johnson, Pfau and Hodge,[12] 11 g. of chloroacetic acid was dissolved in 20 cc. of water, 5 g. of X was added and the mixture was boiled for one hour. The black, suspended material was removed and dissolved in alcohol with separation of elementary sulfur. Dilution of the filtrate caused precipitation of **1,2-dihydro-2-keto-6-methylcinchoninic acid** (XVIII). The latter was recrystallized from 80% alcohol and melted with decomposition at 235–236°. The acid is insoluble in water, but is fairly soluble in alcohol, ether and glacial acetic acid.

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.47; N, 6.90. Found: C, 65.21; H, 4.61; N, 6.88.

Formation of 1,2-Dihydro-2-keto-3-methylmercaptocinchoninic Acids.—A solution of 60 g. (0.22 mole) of the yellow dipotassium salt V in 200 cc. of water was cooled to 0° and treated with 60 g. (0.475 mole) of dimethyl sulfate with subsequent addition of 20% potassium hydroxide solution as needed to maintain the mixture alkaline to litmus. A yellow precipitate was filtered and recrystallized from boiling water. The solid did not melt at 300° and yielded a negative test with the Feigl reagent.[7]

Anal. Calcd. for $C_{11}H_9KNO_3S$: S, 11.73. Found: S, 11.57.

Upon acidifying the filtrate from this potassium salt, or a cold aqueous solution of the salt, bright yellow leaflets

(9) Gränacher and Kouniniotis, ref. 3b.

(10) Borsche and Jacobs, *Ber.*, **47**, 362 (1914).

(11) Gränacher and Kouniniotis, ref. 3b, report m. p. 146–150° (dec.). The temperature of decomposition of this acid is greatly influenced by the rate of heating during the m. p. determination.

(12) Johnson, Pfau and Hodge, THIS JOURNAL, **34**, 1041 (1912).

were obtained which could be recrystallized from dilute alcohol. Thus purified, **1,2-dihydro-2-keto-3-methylmercaptocinchoninic acid** (XIII) melts with decomposition at 219–220° (cor.).

Anal. Calcd. for $C_{11}H_9NO_3S$: neut. equiv., 235.3; N, 5.95; S, 13.63. Found: neut. equiv. (phenolphthalein), 238.9; N, 5.98; S, 13.84.

In the same manner, (VII) was converted into **1,2-dihydro-2-keto-3-methylmercapto-1-methylcinchoninic acid** (XIV), melting with decomposition at 229–230° (cor.).

Anal. Calcd. for $C_{12}H_{11}NO_3S$: neut. equiv., 249.3; N, 5.62. Found: neut. equiv. (phenolphthalein), 245.4; N, 5.87.

From the dipotassium salt (IX) there was prepared a monopotassium salt which was recrystallized from 80% alcohol.

Anal. Calcd. for $C_{12}H_{10}KNO_3S$: N, 4.88; S, 11.16. Found: N, 5.00; S, 11.16.

A sample of this monopotassium salt was dissolved in water and treated with cold, dilute hydrochloric acid causing separation of a glistening yellow solid. After recrystallization from dilute alcohol, **1,2-dihydro-2-keto-3-methylmercapto-6-methylcinchoninic acid** (XV) was obtained as an orange crystalline material melting with decomposition at 221–222° (cor.).

Anal. Calcd. for $C_{12}H_{11}NO_3S$: neut. equiv., 249.3; N, 5.62. Found: neut. equiv. (phenolphthalein), 246.2; N, 5.57.

Dimethyl sulfate converted the dipotassium salt XI into a monopotassium salt which did not melt at 300° and which did not give a positive test with Feigl reagent.[7]

Anal. Calcd. for $C_{13}H_{12}KNO_3S$: N, 4.65. Found: N, 4.35.

This salt upon acidification yielded yellow, crystalline material. Recrystallized from dilute alcohol, **1,2-dihydro-2-keto-3-methylmercapto-1,6-dimethylcinchoninic acid** (XVI) melts with decomposition at 224–225° (cor.).

Anal. Calcd. for $C_{13}H_{13}NO_3S$: neut. equiv., 263.3; N, 5.32. Found: neut. equiv. (phenolphthalein), 258.0; N, 5.61.

Reduction of 1,2-Dihydro-2-keto-3-methylmercaptocinchoninic Acids.—Six grams of XIII, 5 g. of red phosphorus and 50 cc. of hydriodic acid (sp. gr. 1.7) were refluxed for seven hours at 150°. After removal of the phosphorus by filtration and most of the acid by steam distillation, the solution was made alkaline with potassium hydroxide and then faintly acidic with hydrochloric acid; upon cooling, light yellow crystals (2 g. or 41% yield) were obtained. A mixture of this material with an authentic sample of **1,2,3,4-tetrahydro-2-ketocinchoninic acid** (XIX)[13] melted at 215–216° (cor.).

Anal. Calcd. for $C_{10}H_9NO_3$: N, 7.33. Found: N, 7.16.

Three grams of XIV was heated with 25 cc. of hydriodic acid and 2 g. of red phosphorus for eight hours at 150°, a gas with mercaptan-like odor being evolved. The gum which formed could not be caused to crystallize, but did not contain sulfur.

From heating a sample of XV with concentrated hydriodic acid for ten hours at 150° there was obtained white needles of **1,2,3,4-tetrahydro-2-keto-6-methylcinchoninic acid** (XX) melting at 219–220° (cor.). This melting point was not altered by mixture with an authentic sample.[14]

Anal. Calcd. for $C_{11}H_{11}NO_3$: N, 6.86. Found: N, 6.74.

Two attempts were made to reduce 1,2-dihydro-2-keto-3-methylmercapto-1,6-dimethylcinchoninic acid (XVI) with hydriodic acid alone or with red phosphorus; in neither case was it possible to secure a crystalline product.

Summary

The preparation of ketomercaptocinchoninic acids from rhodanine-($\Delta^{5,3'}$)-oxindoles has been studied. As a result it has been possible to synthesize examples of 1,2-dihydro-2-keto-3-methylmercaptocinchoninic acids, a type not previously reported in the chemical literature.

(13) Hill, Schultz and Lindwall [THIS JOURNAL, **52**, 773 (1930)] reported m. p. 217–218°.

(14) Henze and Blair, ref. 4.

AUSTIN, TEXAS RECEIVED DECEMBER 8, 1941

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Hydantoins Containing a Tetrahydropyranyl Substituent[1]

BY HENRY R. HENZE AND ROBERT L. MCKEE

Until quite recently, the clinical utilization of hydantoin derivatives had been limited wholly to the use of ethylphenylhydantoin (Nirvanol)[2] in the treatment of convulsions of the type of St. Vitus dance. However, the sodium salt of diphenylhydantoin (Dilantin)[3] has come now to be considered as virtually a specific for control of epileptic seizures. Treatment with this substituted hydantoin does not effect a cure of epilepsy, hence the necessity for further research seeking additional anticonvulsants.

A few hydantoin derivatives containing an alkoxy substituent[4] have been prepared in this Laboratory and shown elsewhere to possess vary-

(1) Presented before the Medicinal Division of the American Chemical Society at Memphis, April, 1942.

(2) Swiss Patent 72,561 (Sept. 16, 1916).

(3) (a) Putnam and Merritt, *Science*, **85**, 526 (1937); (b) Merritt and Putnam, *J. Am. Med. Assoc.*, **111**, 1068 (1938); (c) Putnam, *ibid.*, **112**, 2190 (1939).

(4) (a) Rigler with Henze, THIS JOURNAL, **58**, 474 (1936); (b) Speer with Henze, *ibid.*, **61**, 3376 (1939); (c) Rogers and Henze, *ibid.*, **62**, 1758 (1940).