The red platelets from above were recovered and recrystallized from nitromethane; m.p. 242–248°. These crystals contained chlorine but did not give a satisfactory analysis. This material could be impure V.

The orange material was obtained in pure form by extraction with 10% NaOH, filtering the solution and acidification with hydrochloric acid to a *p*H of about 5.0. The orange crystals which were recovered melted at 215°. They were identified as 2-chloro-3-hydroxy-1,4-naphthoquinone (VI) by melting point and failure of these crystals to depress the melting point of an authentic sample of VI.[6]

One gram of the 2-chloro-3-hydroxyl-1,4-naphthoquinone was heated with 0.5 gram of aniline in 5 ml. of ethanol. Crystals of 2-anilino-3-hydroxy-1,4-naphthoquinone (VII) were obtained, m.p. 185°. This compound is reported to melt at 183°.[6]

**Benzo(d)pyrido(a)benzimidazole-4,9-diacetate (VIII).**—A solution of 2.5 g. (0.01 mole) of benzo(d)pyrido(a)benzimidazole-4,9-quinone in 20 ml. of acetic anhydride and 20 ml. of acetic acid was shaken with platinum catalyst under an initial hydrogen pressure of 10 p.s.i. One mole of hydrogen was rapidly absorbed and a grayish powder was produced. The yield of this material was 2.3 g. (70%), m.p. 194°.

A sample was dried at 210° and 5 mm. pressure for 1 hr. and analyzed.

*Anal.* Calcd. for $C_{19}H_{14}N_2O_4$: N, 8.38. Found: N, 8.30.

**Hydrolysis of VIII.**—A mixture of 1 g. of III and 10 ml. of 10% sodium hydroxide was stirred in an open beaker for 1 hr. and acidified with 10 ml. of glacial acetic acid. The orange product was filtered and dried, m.p. 305–306°. The material was identical with III.

Denton, Texas

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[Contribution from the Research Department, Ciba Pharmaceutical Products, Inc.]

# Investigations in Heterocycles. III. Imidazo and Imidazolino[2,1-b]thiazolium Compounds[1]

By George deStevens and Angelina Halamandaris

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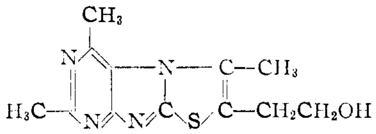
A number of polycyclic compounds containing the imidazo[2,1-b]thiazole and imidazolino[2,1-b]thiazole nucleus has been prepared for pharmacological evaluation. The essential reaction for the formation of these heterocycles is condensation between an α-haloketone and a 2-mercaptoimidazole or 2-mercaptoimidazoline. A new imidazole, 2-mercapto-4,5,6,7-tetrahydrobenzimidazole, was prepared to serve as an intermediate.

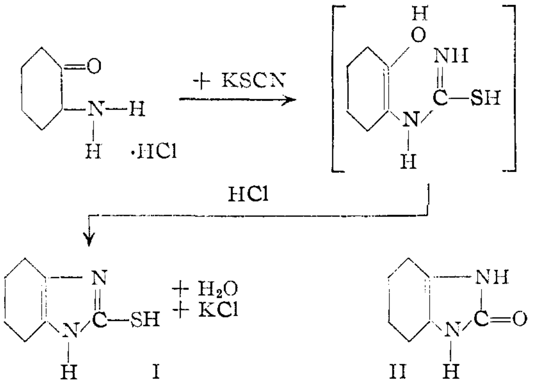
Initial studies on imidazo[2,1-b]thiazoles were carried out by Ochiai[2] who proved the structural complexity of thiochrome through condensation of 2,6-dimethyl-7-mercaptopurine with 3-chloro-5-hydroxy-2-pentanone.



Thiochrome

Analogs of this thiamine rearrangement substance were prepared by similar condensations by Andersag[3] and Westphal, Kondo and Nagasawa[4] and Matsukawa and Ban.[5] More recently Wilson and Woodger[6] reported on the synthesis and spectral properties of some imidazolino[2,1-b]thiazolium salts. Our work[7–9] in the field of thiazole chemistry prompted us to look into these systems for biological evaluation.

One of the compounds used as an intermediate was 2-mercapto-4,5,6,7-tetrahydrobenzimidazole (I), the preparation of which has not been heretofore reported. A facile synthesis of this substance was through thiocyanation of 2-aminocyclohexanone hydrochloride.[10] In passing, we would like to note that 4,5,6,7-tetrahydrobenzimidazolin-2-one[11] (II) can be prepared in about 80% yield when potassium isocyanate is allowed to react with the aforementioned aminoketone hydrochloride.



The condensation of I with α-chlorocyclohexanone gave III, with 2-bromoindanone IV and with 2-bromotetralone V.

These were highly crystalline materials and very soluble in water. The free base could easily be generated by dissolution of the salt in water followed by basification under cooling. Methylation of the free base of III with methyl iodide gave rise to IIIa The alkylated derivatives were found to be unusually unstable, decomposing in boiling ethyl alcohol.

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(1) Presented before the Division of Organic Chemistry at the 132nd Meeting of the American Chemical Society in New York City, N. Y., September, 1957.

(2) E. Ochiai, *Ber.*, **69**, 1650 (1936).

(3) H. Andersag and K. Westphal, *ibid.*, **70**, 2035 (1937).

(4) H. Kondo and F. Nagasawa, *J. Pharm. Soc. Japan*, **57**, 1050 (1937).

(5) Y. Matsukawa and S. Ban, *ibid.*, **71**, 756 (1951).

(6) W. Wilson and R. Woodger, *J. Chem. Soc.*, 2943 (1955).

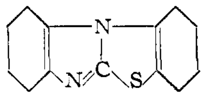
(7) G. deStevens, H. A. Luts and J. A. Schneider, This Journal, **79**, 1516 (1957).

(8) G. deStevens, A. Frutchey, A. Halamandaris and H. A. Luts, *ibid.*, **79**, 5263 (1957).

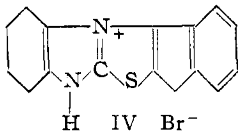
(9) G. deStevens, H. A. Luts and A. Halamandaris, *J. Org. Chem.*, **22**, in press (1957).

(10) H. E. Baumgarten and F. A. Bower, This Journal, **76**, 4561 (1954).

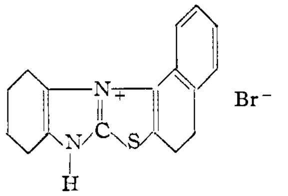
(11) The synthesis of this compound in 42% yield by an alternate route was reported recently by R. Gomper, *Ber.*, **89**, 1748 (1956).



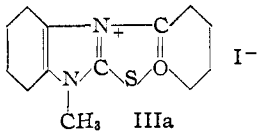
III



IV



V



IIIa

Other 2-mercapto compounds used as intermediates were 2-mercaptoimidazoline and 2-mercaptobenzimidazole. These were condensed with various α-haloketones of the acyclic and alicyclic series.

**Acknowledgment.**—We wish to thank Mr. Dorfman and his associates for the microanalytical data.

## Experimental[12]

**2-Mercapto-4,5,6,7-tetrahydrobenzimidazole (I).**—A mixture of 20.0 g. (0.13 mole) of 2-aminocyclohexanone hydrochloride[10] and 12.5 g. (0.13 mole) of potassium isothiocyanate dissolved in 100 ml. of water was heated on the steam-bath for 7 hr. A fine yellow powder began to fall out of solution within the first hour of heating. After chilling the mixture overnight, the precipitate was collected at the pump, washed well with water and air-dried. The yield of crude material (m.p. 278–282°) was 80%. Two recrystallizations from ethyl alcohol gave an analytically pure substance, m.p. 282–283°.

*Anal.* Calcd. for $C_7H_{10}N_2S$: N, 18.18; S, 20.80. Found: N, 18.12; S, 21.20.

**4,5,6,7-Tetrahydrobenzimidazolin-2-one** (II).—Five grams (0.03 mole) of 2-aminocyclohexanone hydrochloride and 2.7 g. (0.03 mole) of potassium isocyanate dissolved in 25 ml. of water were heated on the steam-bath for 7 hr. After chilling the solution overnight, the crystals were collected, washed well with water and air-dried; the yield of crude product was 82%. This was recrystallized from ethyl alcohol to give tiny white crystals, m.p. 340–341° dec.

*Anal.* Calcd. for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.52; H, 7.53; N, 20.33.

**1,2,3,4,7,8,9,10-Octahydrobenzimidazo[2,1-b]benzothiazole** (III).—A mixture of 3.0 g. (0.02 mole) of 2-mercapto-4,5,6,7-tetrahydrobenzimidazole, 2.6 g. (0.02 mole) of α-chlorocyclohexanone[13] and 20 ml. of ethyl alcohol was heated under reflux for 4 hr. The clear solution was evaporated down to approximately one-tenth its volume and then triturated well with dry ether. A semi-viscous material was obtained which resisted all attempts to crystallization. Consequently, it was dissolved in 50 ml. of water and made slightly alkaline with dilute (10%) sodium hydroxide solution. A white crystalline powder was precipitated which, after filtering and washing with water, was recrystallized from ethyl alcohol to give needles, m.p. 153–154°.

*Anal.* Calcd. for $C_{13}H_{18}N_2S{\cdot}H_2O$: N, 11.05; S, 12.75. Found: N, 10.99; S, 13.05.

The methiodide IIIa of this compound was prepared by refluxing the free base with methyl iodide in acetone. The resulting crystalline product was recrystallized by rapid dissolution in ethanol and chilling overnight, m.p. 225–226°.

*Anal.* Calcd. for $C_{14}H_{21}IN_2S$: N, 7.48; S, 8.51. Found: N, 7.35; S, 8.49.

**1,2,3,4-Tetrahydrobenzimidazo[2,1-b]8H-indenothiazolium Bromide (IV).**—Three grams (0.02 mole) of 2-mercapto-4,5,6,7-tetrahydrobenzimidazole, 4.2 g. (0.02 mole) of 2-bromoindanone[14] and 20 ml. of ethyl alcohol were heated under reflux for 3 hr. After being chilled, the clear solution was diluted with 200 ml. of dry ether with vigorous stirring. The white fluffy powder obtained was recrystallized twice by dissolving the compound in ethyl alcohol followed by the addition of an excess ether to give 45% yield of pure product, m.p. 215–216°.

*Anal.* Calcd. for $C_{16}H_{16}BrN_2S$: N, 8.08; S, 9.24. Found: N, 7.77; S, 8.90.

**1,2,3,4,7,8-Hexahydrobenzimidazo[2,1-b]-β-naphthothiazolium Bromide (V).**—A mixture of 4.2 g. (0.028 mole) of 2-mercapto-4,5,6,7-tetrahydrobenzimidazole, 6.2 g. (0.028 mole) of 2-bromotetralone[14] and 50 ml. of ethyl alcohol was refluxed for 3 hr. Work-up of the reaction mixture gave a 35% yield of product, m.p. 203–205°. It was recrystallized from ethyl alcohol–acetone (1:1) mixture.

*Anal.* Calcd. for $C_{17}H_{12}BrN_2S$: N, 7.76; S, 8.88. Found: N, 7.40; S, 8.80.

**1,2,5,6,7,8-Hexahydroimidazo[2,1-b]benzothiazolium chloride.**—A mixture of 18.5 g. (0.18 mole) of 2-mercaptoimidazoline and 24 g. (0.18 mole) of α-chlorocyclohexanone dissolved in 150 ml. of ethyl alcohol was refluxed for 24 hr. Work-up of the reaction in the usual manner gave a 44% yield of product, m.p. 158–160°

*Anal.* Calcd. for $C_9H_{13}ClN_2S$: N, 12.85, S, 14.95. Found: N, 12.51; S, 15.34.

**1,2-Dihydroimidazo[2,1-b]spiro[4·5]decenothiazolium Chloride.**—An alcohol solution of 6.2 g. (0.34 mole) of spiro-[4·5]-7-chloro-6-decanone[15] and 3.5 g. (0.034 mole) of 2-mercaptoimidazoline, after refluxing for 6 hr., was worked up in the usual manner to give a 25% yield of product, m.p. 254–255°.

*Anal.* Calcd. for $C_{13}H_{19}ClN_2S$: N, 10.35; S, 11.85. Found: N, 10.33; S, 12.17.

**2,3-Dimethylbenzimidazo[2,1-b]thiazolium Bromide.**—One-tenth molar quantities of 2-mercaptobenzimidazole and 3-bromobutanone[16] in ethyl alcohol were refluxed for 4 hr. After being chilled overnight, the product was collected and recrystallized from ethyl alcohol giving a 64% yield of product, m.p. 273–275°.

*Anal.* Calcd. for $C_{11}H_{11}BrN_2S$: N, 9.92; S, 11.32. Found: N, 9.50; S, 11.38.

The free base **2,3-dimethylbenzimidazo[2,1-b]thiazole**, m. p. 154–156°, was prepared by neutralization of a water solution of the base with 20% sodium carbonate solution.

*Anal.* Calcd. for $C_{11}H_{10}N_2S$: N, 13.85; S, 15.83. Found: N, 13.60; S, 15.78.

Treatment of the free base with methyl iodide in ethyl alcohol under reflux for 18 hr. gave a quantitative yield of **2,3,9-trimethylbenzimidazo[2,1-b]thiazolium iodide**, m.p. 303–304°.

*Anal.* Calcd. for $C_{12}H_{13}IN_2S$: N, 8.14; S, 9.32; I, 36.88. Found: N, 8.02; S, 9.64; I, 36.96.

Reaction between the free base and β-iodopropionic acid under reflux in ethyl alcohol yielded **2,3-dimethyl-9-β-carboxyethylbenzimidazo[2,1-b]thiazolium iodide**, m.p. 250–253°.

*Anal.* Calcd. for $C_{14}H_{15}IN_2O_2S$: N, 6.97; S, 7.98; I, 31.54. Found: N, 7.10; S, 8.11; I, 31.83.

SUMMIT, N. J.

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[12] All melting points are uncorrected.

[13] A. Kötz, *Ann.*, **400**, 53 (1940).

[14] A. J. Wilds, THIS JOURNAL, **67**, 1751 (1945).

[15] E. J. Corey, *ibid.*, **75**, 2301 (1953).

[16] J. Reymanant, *Chem. Zentr.*, **72**, 95 (1901).