uct that could be isolated was the benzimidazolylpropionic acid. Since this is a new compound its preparation is included. Method A was used, but in this case the polyphosphoric acid was preheated to 150° and after adding the diamine the mixture was kept at this temperature for five hours. On cooling the reaction mixture and diluting with water a tar formed from which no identifiable product could be obtained. The filtrate from the tar was neutralized and the yellow product which formed was removed and washed with water. It was recrystallized from ethanol–water with the aid of decolorizing carbon, yield 45%, m.p. 240–242°.

Anal. Calcd. for $C_{10}H_5N_3O_4Cl$: C, 44.52; H, 2.99; N, 15.58; Cl, 13.15. Found: C, 44.68; H, 3.12; N, 15.62; Cl, 13.26.

Preparation of Bis-benzimidazolylbutanes. 1,4-Bis-(2-benzimidazolyl)-butane.—This compound was made earlier by Shriner and Upson from *o*-phenylenediamine and adipic acid. It was made in this work, by both methods A and B to get samples for the screening program. The yields were around 40% by both methods.

1,4-Bis-(6-amino-2-benzimidazolyl)-butane.—1,4-Bis-(6-nitro-2-benzimidazolyl)-butane (3.8 g., 0.01 mole) was added to 20 ml. of 4 *N* hydrochloric acid and 0.5 g. of 5% palladium-on-alumina added. When the hydrogenation was complete, 50 ml. of 4 *N* hydrochloric acid was added and the solution warmed. The catalyst was removed and the dihydrochloride separated from the filtrate on cooling. It was recrystallized from 4 *N* hydrochloric acid. Method B was followed from this point.

1,4-Bis-(7-nitro-5-chloro-2-benzimidazolyl)-butane.—This compound was prepared by method A. The temperature was kept at 130° for five hours. The crude product was extracted with hot 10% sodium bicarbonate solution, dried and recrystallized from ethylene glycol.

1,4-Bis-(7-amino-5-chloro-2-benzimidazolyl)-butane.—This bis-benzimidazole was prepared from 3-nitro-5-chloro-*o*-phenylenediamine by reducing it in 4 *N* hydrochloric acid over palladium-on-alumina. The filtrate from the catayst was refluxed with adipic acid for ten hours as in the preparation of 1,2-bis-(7-amino-5-chloro-2-benzimidazolyl)ethane.

Preparation of Bis-benzimidazolylhexanes.—Suberic acid was the starting organic acid for this series.

Bis-benzimidazolyloctanes were prepared from sebacic acid and the appropriate diamines.

1,8-Bis-(6-chloro-2-benzimidazolyl)-octane.—In this case, 1 ml. of concentrated sulfuric acid was added to the polyphosphoric acid and the reaction mixture was stirred for five hours at 150°.

Preparation of Bis-benzimidazolyl-1,2-ethanediols.—The starting materials were tartaric acid and *o*-phenylenediamines.

1,2-Bis-(6-ethoxy-2-benzimidazolyl)-1,2-ethanediol was prepared from 3-amino-4-nitrophenetole and *d*-tartaric acid by the procedure described for making 1,2-bis-(6-ethoxy-2-benzimidazolyl)-ethane.

1,2-Bis-(6-nitro-2-benzimidazolyl)-1,2-ethanediol was recrystallized from ethylene glycol–water with the aid of decolorizing carbon.

Preparation of 2,2′-(Thiodiethylene)-bis-benzimidazole.—This compound was prepared from *o*-phenylenediamine and 3,3′-dithiopropionic acid.[10]

2,2′-*o*-Phenylenebis-(6-chlorobenzimidazole) was prepared from 4-chloro-*o*-phenylenediamine and phthalic anhydride. The crude product was washed with hot 95% ethanol. The residue (43% yield) was recrystallized from N-dimethylformamide.

Preparation of Ethyl N-Benzimidazolylthiocarbamate.—2-Aminobenzimidazole (13.3 g.) was mixed with 40 ml. of carbon disulfide and 30 ml. of absolute ethanol. The reaction mixture was refluxed on a steam-bath for 50 hours and the product was isolated and purified as described by Crippa, *et al.*[8] The analytical data indicated that the compound was a thiocarbamate rather than the bis derivative reported in reference 8. The yield was 40%, m.p. 202°.

Anal. Calcd. for $C_{10}H_{11}N_3SO$: C, 54.27; H, 5.01; N, 19.00; S, 14.50. Found: C, 54.54; H, 5.15; N, 19.09; S, 14.64.

(10) The 3,3′-dithiopropionic acid was obtained from the American Cyanamid Co.

PHILADELPHIA, PENNA.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTH TEXAS STATE COLLEGE]

Benzo[d]pyrido[a]benzimidazole-4,9-quinone

BY PRICE TRUITT, JAMES ERWIN COOPER, III,[1] AND FRANK M. WOOD, JR.[2]

RECEIVED MAY 25, 1957

The reaction of 2-aminopyridine and 2-acetamido-3-chloro-1,4-naphthoquinone gave the title compound. The same substance was obtained from the reaction of 2-aminopyridine and 2,3-dichloro-1,4-naphthoquinone.

2-Acetamido-3-chloro-1,4-naphthoquinone reacts readily with primary amines to yield 2-acetamido-3-alkyl(aryl)amino-1,4-naphthoquinones.[3,4]

Since Calandra and Adams[5] had reported that the reaction of 2-aminopyridine and 2,3-dichloro-1,4-naphthoquinone yielded a product described as 2-(2-pyridylamino)-3-chloro-1,4-naphthoquinone, it seemed reasonable that 2-aminopyridine should react with 2-acetamido-3-chloro-1,4-naphthoquinone to give 2-acetamido-3-(2-pyridylamino)-1,4-naphthoquinone. When 2-acetamido-3-chloro-1,4-naphthoquinone (I) and 2-aminopyridine (II) were heated together in refluxing butanol, an orange product (III), m.p. 306°, was obtained. It did not contain chlorine. Again, when the 2-acetamido-3-chloro-1,4-naphthoquinone was replaced in the reaction with 2-chloroacetamido-3-chloro-1,4-naphthoquinone, an orange product (III) was obtained, m.p. 306°. It did not contain chlorine. A mixed melting point determination proved that the two substances melting at 306° were identical.

The reaction of 2-aminopyridine (II) and 2,3-dichloro-1,4-naphthoquinone (IV) in refluxing ethanol did indeed give 2-chloro-3-(2-pyridylamino)-1,4-naphthoquinone (V), m.p. 275–276°, as Calandra and Adams indicated.[5]

A suspension of V in glacial acetic acid gave III when heated and cooled.

A solution of I and II were refluxed for 12 hr. in methanol and VI was obtained as orange crystals, m.p. 215°, along with unidentified red platelets. VI was identified as 2-chloro-3-hydroxy-1,4-naphthoquinone.[6] These workers reported VI to melt at 215+°. VI reacted with aniline to yield VII, m.p. 185°. 2-Anilino-3-hydroxy-1,4-naphthoquinone is reported to melt at 183°.[6]

(1) National Science Predoctoral Fellow, 1954–1955.

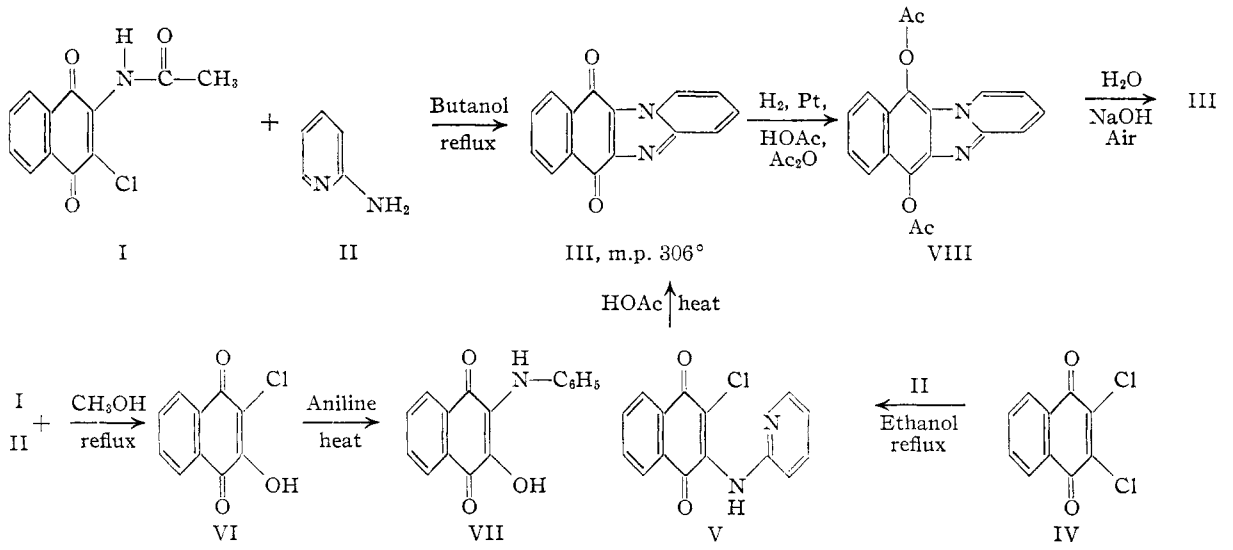
(2) Research Fellow of Parke, Davis & Co., 1950–1953.

(3) K. Fries and K. Billig, *Ber.*, **58**, 1128 (1925).

(4) J. R. E. Hoover and A. R. Day, THIS JOURNAL, **76**, 1148 (1954).

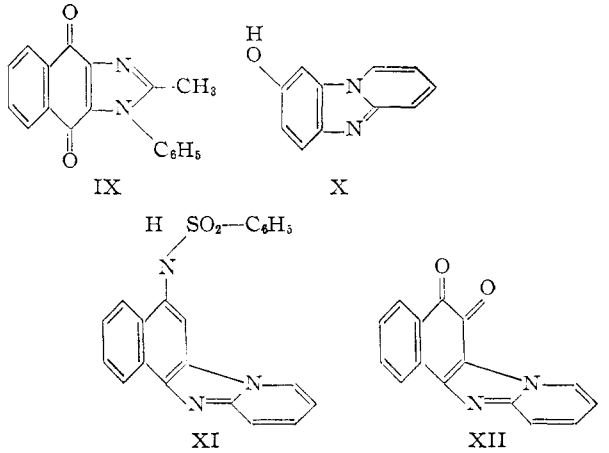
(5) J. C. Calandra and E. C. Adams, *ibid.*, **72**, 4804 (1950).

(6) T. Zincke and C. Gerland, *Ber.*, **20**, 3222 (1887).



The reduction of III with hydrogen and platinum in acetic anhydride and acetic acid gave a grayish powder, VIII, which analyzed correctly for 4,9-diacetoxybenzo(d)pyrido(a)benzimidazole which fluoresced blue in alcohol solution. Hydrolysis of VIII with 10% sodium hydroxide solution while exposed to air oxidation gave III.

Analytical data are consistent with a structure corresponding to III. A number of compounds of this general type have been prepared and are very stable. Fries and Billig[3] obtained IX by heating 2-acetamido-3-aniline-1,4-naphthoquinone in alcoholic sodium hydroxide solution.



Schmid and Czerny[7] obtained 6-hydroxy-1',2',-1,2-pyridobenzimidazole (X) by heating *p*-benzoquinone with 2-aminopyridine. When this compound was acetylated, it fluoresced blue in alcohol solution. They were unable to carry out the same reaction with 1,4-naphthoquinone.

Adams and Pomerantz[8] reported the synthesis of 5-benzenesulfonamidobenzo(e)pyrido(a) benzimidazole (XI), which has a ring structure isomeric with III.

Thus, the structure III seems entirely justified except for the possibility of structure XII. Since the compound shown as III does not react with *o*-phenylenediamine, which is known to react with 1,2-quinones,[9] structure XII is ruled out.

In an attempt to determine if the reaction proceeded through the amino group or through the ring nitrogen of the 2-aminopyridine, 2-acetamidopyridine was refluxed with 2-acetamido-3-chloro-1,4-naphthoquinone and also with 2,3-dichloro-1,4-naphthoquinone in several solvents. In no case was a reaction observed. This indicates that the amino group initiated the reaction probably by initial displacement of the acylamido group.

Experimental

2-Chloro-3-(2-pyridylamino)-1,4-naphthoquinone (V).—A mixture of 20 g. (0.092 mole) of 2,3-dichloro-1,4-naphthoquinone and 8.4 g. (0.089 mole) of 2-aminopyridine was allowed to react in 50 ml. of refluxing ethanol. The solution was red after 1 hr., and a brown material began to form by the end of the second hour of reflux. After 3 hr. the mixture was cooled and filtered. The yield was 23 g. (91%) of brown solid which melted at 276–278°. 2-Chloro-3-(2-pyridylamino)-1,4-naphthoquinone was reported to melt at 276–278°.[5]

Benzo(d)pyrido(a)benzimidazole-4,9-quinone (III). Procedure A.—A mixture of 5 g. (0.02 mole) of 2-acetamido-3-chloro-1,4-naphthoquinone,[3] 3.5 g. (0.038 mole) of 2-aminopyridine and 40 ml. of *n*-butanol was heated under reflux. The mixture immediately became red and soon dissolved to form a red solution. An orange precipitate began to form after 3 hr. The heating was continued for 1 more hr.

The mixture was cooled, filtered and the solid recrystallized from glacial acetic acid. The yield was 2.4 g. (50%) of bright orange needles, m.p. 306°.

Anal. Calcd. for $C_{15}H_8N_2O_2$: C, 72.57; H, 3.23; N, 11.19. Found: C, 72.61; H, 3.39; N, 11.22.

It was necessary to dry this compound at 210° and 5 mm. pressure for 10 minutes to obtain a satisfactory analysis.

Procedure B.—A suspension of 0.2 g. of 2-chloro-3-(2-pyridylamino)-1,4-naphthoquinone in 5 ml. of acetic acid was warmed until solution was complete. When the solution was cooled, orange crystals formed, m.p. 306°. These crystals did not depress the melting point of III from procedure A.

Reaction of 2-Chloro-3-(2-acetamido)-1,4-naphthoquinone with 2-Aminopyridine in Methanol.—A mixture of 7.8 g. (0.035 mole) of 2-chloro-3-acetamido-1,4-naphthoquinone and 3.3 g. (0.035 mole) of 2-aminopyridine was refluxed in 75 ml. of methanol for 12 hr. A yield of 6.8 g. of a mixture of orange needles and red platelets was obtained.

(7) L. Schmid and H. Czerny, *Monatsh.*, **83**, 31 (1952).

(8) R. Adams and S. H. Pomerantz, THIS JOURNAL, **76**, 705 (1954).

(9) O. N. Witt, *Ber.*, **20**, 575 (1887).

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

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

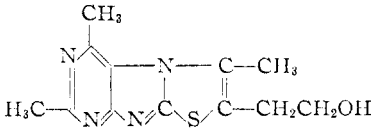
Investigations in Heterocycles. III. Imidazo and Imidazolino[2,1-b]thiazolium Compounds[1]

BY GEORGE DESTEVENS AND ANGELINA HALAMANDARIS

RECEIVED JUNE 14, 1957

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.

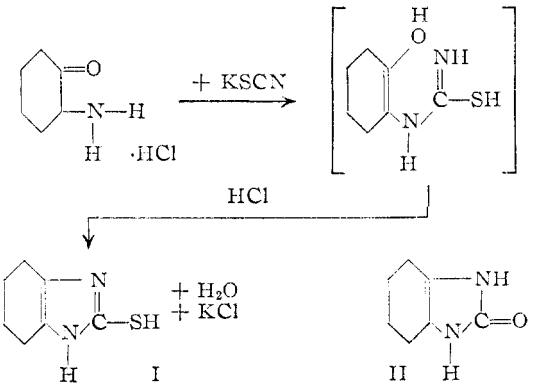
Initial studies on imidazo[2,1-b]thiazoles were carried out by Ochiai[2] who proved the structural complexity of thiochrome through condensation of 2,6-dimethyl-7-mercaptopurine with 3-chloro-5-hydroxy-2-pentanone.



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.

(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).