crystallized from a small amount of acetone to yield 6.3 g. (40%) of 5,8-dihydroxy-2-keto-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene, m.p. 241–245°.

8-Acetoxy-2-keto-5-methoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (XXII).—A mixture of 5.2 g. (0.02 mole) of 8-hydroxy-2-keto-5-methoxy-4a-methyl-2,3,4,4a,9,-10-hexahydrophenanthrene (XIX), 6 ml. of acetic anhydride and a small amount of sodium acetate was refluxed for two hours. The reaction mixture was cooled and poured into water. The water solution was extracted with ether and the ether extract was washed with aqueous sodium bicarbonate and water. The ether layer was dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure. The product, 4.2 g. (67%), m.p. 117–119°, crystallized from the concentrate. A sample was recrystallized twice from chloroform to yield the purified acetoxy compound, m.p. 120–121°.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.93; H, 6.47.

2-Keto-5,8-dimethoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (XVIII).—Twenty milligrams of 8-hydroxy-2-keto-5-methoxy-4a-methyl-2,3,4,4a,9,10-hexahydrophenanthrene (XIX) was dissolved in 1.5 ml. of 2.5 *N* sodium hydroxide solution and treated with two drops of dimethyl sulfate. The mixture was stirred for 30 minutes at room temperature and then warmed at 60° for 15 minutes. After cooling the mixture to 0°, the colorless needles were collected on a filter and recrystallized from methanol. This procedure afforded the dimethoxy compound, m.p. 120–120.5° (lit. m.p. 120–121°[4]). The dimethoxyhexahydrophenanthrene was converted to a crystalline 2,4-dinitrophenylhydrazone melting at 218–220° with sintering at 215° (lit. m.p. 219–221°, sintered at 215°[4]).

RAHWAY, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

Metabolite Analogs. IV. Preparation of Some Sulfur-containing Benzimidazoles with Substituents on the 4(7)- and 6(5)-Positions[1]

BY JOHN R. E. HOOVER[2] AND ALLAN R. DAY

RECEIVED JUNE 1, 1955

Benzimidazoles, containing in addition to a nitro or amino group, a sulfonic acid, sulfonamido, mercapto or methylmercapto grouping on the 4(7)- and 6(5)-positions, have been prepared as potential metabolite (purine, vitamin B_{12}, folic acid) inhibitors.

In a preceding communication[3] the preparations of benzimidazoles with substituents on the 4(7)- and 6(5)-positions were described. Continuing the search for benzimidazoles possessing potential antimetabolite activity (purine, vitamin B_{12}, folic acid) a number of sulfur-containing derivatives have been added to this group. These compounds, in addition to a nitro or amino group, also contain a sulfonic acid, sulfonamido, mercapto or methylmercapto grouping. To cast some light on the effect of substituent and position upon the activity, reversed isomers have been prepared, where possible, with those compounds containing the latter two of the groupings mentioned above.

4-Nitrobenzimidazole-6-sulfonic acid and its amino analog were prepared by the partial (ammonium sulfide) and complete (stannous chloride) reduction of 3,5-dinitro-4-aminobenzenesulfonic acid, followed by formation of the imidazole ring. The ring closure with 3,4,5-triaminobenzenesulfonic acid was readily accomplished in 4 *N* hydrochloric acid according to Phillips' conditions.[4] This procedure, and others using formic acid or ethyl orthoformate, failed with 3,4-diamino-5-nitrobenzenesulfonic acid, probably because of interaction between the sulfonic acid group and one of the two amino groupings required for the ring closure. Under basic conditions, *i.e.*, on heating with formamide, the imidazole ring was formed, as evidenced by analytical data and the disappearance of the N–H absorption bands in the infrared at 2.84 and 2.92 μ (the product displayed a single band at 3.12 μ).

The sulfonic acids were prepared as possible intermediates for obtaining the sulfonamides and especially the divalent sulfur derivatives. Because of the anomalous behavior of heterocyclic sulfonic acids,[5] a route involving conversion of the sulfonic acid grouping before forming the imidazole ring was utilized instead.

Treatment of 4-chloro-3,5-dinitrobenzenesulfonyl chloride with ammonia in dioxane gave the corresponding 4-amino-3,5-dinitrobenzenesulfonamide. In benzene solution, in addition to the aminosulfonamide, a product was obtained in which only one chlorine atom had been replaced. This material was identical with 4-amino-3,5-dinitrobenzenesulfonyl chloride, prepared by the action of phosphorus pentachloride on 4-amino-3,5-dinitrobenzenesulfonic acid.

The reduction of 4-amino-3,5-dinitrobenzenesulfonamide. With ammonium sulfide resulted in 3,4-diamino-5-nitrobenzenesulfonamide. Stannous chloride in hydrochloric acid reduced both nitro groups, but did not affect the sulfonamido grouping at room temperature. With 3,5-dinitro-4-aminobenzenesulfonyl chloride, the sulfur moiety was also reduced under the latter conditions giving 3,4,5-triaminothiophenol. The mercapto grouping of this compound was readily methylated under alkaline conditions by methyl iodide giving methyl 3,4,5-triaminophenyl sulfide.

Formation of the benzimidazoles from these compounds was accomplished using modifications of the Phillips procedure with the exception of 4-nitro-6-sulfonamidobenzimidazole, which was prepared by heating the corresponding diamine with anhydrous formic acid.

The synthesis of the 6-nitro-(or amino)-4-mer-

(1) This investigation was supported by a research grant (C-2189) from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) To whom inquiries should be addressed.

(3) J. R. E. Hoover and A. R. Day, THIS JOURNAL, **77**, 4324 (1955).

(4) M. A. Phillips, *J. Chem. Soc.*, 2393 (1928).

(5) J. G. Everett, *ibid.*, 2402 (1930).

capto-(or methylmercapto)-benzimidazoles was based on decomposition of the appropriate diazonium salt derived from 4-amino-6-nitrobenzimidazole. The diazonium chloride underwent double decomposition with methyl mercaptan giving a sparingly soluble salt which, on heating, decomposed smoothly to 4-methylmercapto-6-nitrobenzimidazole. Reduction of the nitro group with stannous chloride in hydrochloric acid gave 4-methylmercapto-6-aminobenzimidazole dihydrochloride which displayed a pronounced tendency to form complex salts with the solvents used for recrystallization of the material.

The preparation of 4-mercapto-6-nitrobenzimidazole utilized the diazonium salt of 4-amino-6-nitrobenzimidazole with ethylxanthic acid. This salt lost nitrogen on warming to give ethyl 6-nitrobenzimidazole-4-thiocarbonate, among other products. The thiocarbonate was hydrolyzed by dilute alkali to the mercapto derivative. This was converted to 4-mercapto-6-aminobenzimidazole dihydrochloride by the usual methods.

The results of the biological screening of the benzimidazoles and of several of the intermediates used in their preparation will be included in separate communications.

Experimental[6]

3,4-Diamino-5-nitrobenzenesulfonic Acid.—The crude potassium salt of 3,5-dinitro-4-aminobenzenesulfonic acid[7] (30 g.) was added to 500 ml. of 2 *N* ammonium hydroxide, previously saturated with hydrogen sulfide. The mixture was stirred for one hour at room temperature and then made strongly acid with concentrated hydrochloric acid. The yellow solid (28.3 g.) which was obtained after cooling the acidified mixture was twice extracted with hot water (400 ml.) and, after treatment with decolorizing charcoal, the extracts were cooled. The yellow needles (11.12 g.) which separated decomposed explosively at 330°.

Anal. Calcd. for $C_6H_7N_3O_5S$: C, 30.90; H, 3.03; N, 18.02. Found: C, 30.77; H, 2.86; N, 18.25.

3,4,5-Triaminobenzenesulfonic Acid.—The white tin double salt (18.70 g.), which separated during the addition of 13.46 g. (0.05 mole) of potassium 4-amino-3,5-dinitrobenzenesulfonate to 60 g. of anhydrous stannous chloride in 200 ml. of concentrated hydrochloric acid, was removed and decomposed in dilute hydrochloric acid solution with hydrogen sulfide. The decomposition took place slowly. An equal volume of absolute alcohol was added to the clear filtrate, giving white needles (6.82 g., 57%) of 3,4,5-triaminobenzenesulfonic acid monohydrochloride, which decomposed at 302–304° (with bubbling). Purification was accomplished by recrystallization from 1 *N* hydrochloric acid. The final melting point ranged from 306 to 310°, depending on the rate of heating. Attempts to recrystallize the material from hot water resulted in a chloride-free product which melted above 330° and was only slightly soluble in hot water. It was much more prone to oxidation on standing in air and could be converted to the hydrochloride by recrystallization from 1 *N* hydrochloric acid.

Anal. Calcd. for $C_6H_{10}N_3O_3SCl$: C, 30.06; H, 4.21 N, 17.53. Found: C, 30.07; H, 4.18; N, 17.47.

4-Nitrobenzimidazole-6-sulfonic Acid.—A suspension of 2.33 g. (0.01 mole) of 3,4-diamino-5-nitrobenzenesulfonic acid in 25 ml. of formamide was heated in an oil-bath at 150° for one hour. The mixture was cooled and, after adding an equal volume of absolute alcohol, ether was added to complete precipitation. The tan product (2.66 g.) was dissolved in hot 2 *N* hydrochloric acid and the mixture was cooled, giving 1.91 g. (79%) of yellow crystals which decomposed above 370°. The product was purified by recrystallization from hot water.

Anal. Calcd. for $C_7H_5N_3O_5S$: C, 34.57; H, 2.07; N, 17.28. Found: C, 34.66; H, 1.96; N, 17.28.

4-Aminobenzimidazole-6-sulfonic Acid.—Using a modification of the Phillips reaction, 5.07 g. (0.025 mole) of 3,4,5-triaminobenzenesulfonic acid monohydrochloride was heated under reflux with two ml. of formic acid in 30 ml. of 2 *N* hydrochloric acid for one hour. A white crystalline product (4.59 g., 86%) separated on cooling to 5°. It decomposed above 370° and was recrystallized from hot water for analytical purposes.

Anal. Calcd. for $C_7H_7N_3O_3S$: C, 39.43; H, 3.31; N, 19.71. Found: C, 39.21; H, 3.55; N, 19.62.

3,5-Dinitro-4-aminobenzenesulfonyl Chloride. a. From 3,5-Dinitro-4-Chlorobenzenesulfonyl Chloride.—Anhydrous ammonia was passed into a hot solution of 6.02 g. (0.02 mole) of 3,5-dinitro-4-chlorobenzenesulfonyl chloride[8] in 100 ml. of benzene. The mixture was filtered while hot and the residue, which consisted of 1.47 g. of 3,5-dinitro-4-aminobenzenesulfonamide (m.p. 216–219°), was washed with hot benzene. An excess of petroleum ether (30–60°) was added to the filtrate giving 2.66 g. (48%) of yellow crystals, m.p. 147–151°. According to infrared spectra and mixed melting points, this material was identical with that prepared from 3,5-dinitro-4-aminobenzenesulfonic acid. It was converted quantitatively to 3,5-dinitro-4-aminobenzenesulfonamide by ammonia in dioxane.

b. From Potassium 3,5-Dinitro-4-aminobenzenesulfonate.—The potassium salt of 3,5-dinitro-4-aminobenzenesulfonic acid[7] (40 g.), phosphorus pentachloride (40 g.) and phosphorus oxychloride (80 ml.) were heated under reflux for one hour. The solution was cooled and poured over crushed ice. After one hour, the yellow crystals (33 g., m.p. 149–150°) were removed and recrystallized from hot benzene giving 25 g. of light yellow product melting at 155–157°.

Anal. Calcd. for $C_6H_4N_3O_6SCl$: C, 25.60; H, 1.43; N, 14.92; S, 11.39. Found: C, 25.49; H, 1.43; N, 15.16; S, 11.16.

3,5-Dinitro-4-aminobenzenesulfonamide.—A solution of 3,5-dinitro-4-chlorobenzenesulfonyl chloride (60.2 g., 0.2 mole) in hot dioxane (500 ml.) was treated for 30 minutes with dry ammonia. The hot mixture was filtered and the residue was washed with a small amount of the warm solvent. The filtrate and washings were poured into excess water and cooled, giving yellow crystals (43.5 g., 83%) melting at 217–221°. Purification was accomplished by dissolving the material in dioxane and precipitating it with petroleum ether, m.p. 221–223°.

Anal. Calcd. for $C_6H_6N_4O_4S$: C, 27.48; H, 2.31; N, 21.37. Found: C, 27.54; H, 2.32; N, 21.43.

3,4-Diamino-5-nitrobenzenesulfonamide.—A procedure similar to that used to prepare the corresponding sulfonic acid was applied to 20.96 g. (0.08 mole) of 3,5-dinitro-4-aminobenzenesulfonamide. The red crystals which separated from the cooled reaction mixture (not acidified) melted at 260–262°. The material was purified by dissolving it in warm 4 *N* hydrochloric acid and neutralizing the charcoal-treated solution with ammonium hydroxide; yield 13.81 g. (57%), m.p. 269–271°. For analytical purposes a sample was recrystallized from hot water, in which it is sparingly soluble.

Anal. Calcd. for $C_6H_8N_4O_4S$: C, 31.03; H, 3.47; N, 24.13. Found: C, 31.03; H, 3.57; N, 24.12.

3,4,5-Triaminobenzenesulfonamide Dihydrochloride.—By slowly adding 2.62 g. (0.01 mole) of 3,5-dinitro-4-aminobenzenesulfonamide to 12 g. of stannous chloride in 40 ml. of concentrated hydrochloric acid at room temperature and cooling the reaction mixture to 5°, 2.07 g. (75%) of white needles, m.p. 260° (with decomposition), was obtained. The product was purified by dissolving it in water and adding several volumes of concentrated hydrochloric acid; m.p. 263° (with decomposition).

Anal. Calcd. for $C_6H_{12}N_4O_2SCl_2$ C, 26.19; H, 4.40; N, 20.36. Found: C, 26.29; H, 4.52; N, 20.17.

On treatment with formic acid, this material gave 4-amino-6-sulfonamidobenzimidazole, identical with that prepared by reducing the 4-nitro-6-sulfonamido derivative.

(6) The microanalyses were performed by Dr. Harry W. Galbraith, Knoxville, Tenn.

(7) F. D. Gunstone and S. H. Tucker, *J. Appl. Chem.*, **2**, 204 (1952).

(8) F. Ullmann and E. Kuhn, *Ann.*, **366**, 104 (1909).

4-Nitro-6-sulfonamidobenzimidazole.—A solution of 11.61 g. (0.05 mole) of 3,4-diamino-5-nitrobenzenesulfonamide in 50 ml. of formic acid (98–100%) was refluxed for one hour and then evaporated to dryness on the steam-bath. The resulting deep yellow residue (10.55 g., 87%) decomposed at 247–251°. Recrystallization from water gave 8.12 g. (67%) of orange-yellow material, m.p. 260–262° (with decomposition).

Anal. Calcd. for $C_7H_6N_4O_4S$: C, 34.70; H, 2.50; N, 23.13; S, 13.24. Found: C, 34.94; H, 2.47; N, 23.15; S, 13.43.

4-Amino-6-sulfonamidobenzimidazole Hydrochloride.—Following the gradual addition of 2.42 g. (0.01 mole) of 4-nitro-6-sulfonamidobenzimidazole to 5.70 g. of stannous chloride in 20 ml. of concentrated hydrochloric acid, the reaction mixture was heated on the steam-bath for ten minutes and an equal volume of absolute alcohol was added to the cooled solution. The white crystals which separated (2.32 g., 93%) decomposed at 329°. After several recrystallizations from water containing a little hydrochloric acid, the material decomposed at 333°.

Anal. Calcd. for $C_7H_9N_4O_2SCl$: C, 33.81; H, 3.65; N, 22.53; S, 12.89. Found: C, 33.97; H, 3.41; N, 22.34; S, 12.76.

3,4,5-Triaminothiophenol Dihydrochloride.—3,5-Dinitro-4-aminobenzenesulfonyl chloride (14.08 g., 0.05 mole) was reduced in a manner similar to that applied to the corresponding sulfonamide, using 100 g. of stannous chloride (85.4 g. is 0.45 mole) and 100 ml. of concentrated hydrochloric acid. The reaction mixture, which was initially cooled in an ice-bath, was warmed on the steam-bath for 15 minutes after the addition was completed. Concentrated hydrochloric acid (one-half volume) was added to the cooled mixture whereupon crystallization began. After 24 hours, the light yellow crystals (8.87 g., 73%) were removed, washed first with an alcohol–ether mixture (1:1), then with ether and dried, m.p. above 360°. This was dissolved in a minimal amount of hot water, decolorized with charcoal and treated with two volumes of concentrated hydrochloric acid. Cooling overnight gave 7.65 g. of white platelets.

Anal. Calcd. for $C_6H_{11}N_3SCl_2$: C, 31.58; H, 4.86; N, 18.42; S, 14.06. Found: C, 31.74; H, 4.77; N, 18.40; S, 13.96.

Methyl 3,4,5-Triaminophenyl Sulfide.—Methyl iodide (2.1 ml.) was added dropwise, with shaking, to a cooled solution of 3,4,5-triaminothiophenol dihydrochloride (6.84 g., 0.03 mole) in 48 ml. of 2 *N* sodium hydroxide. White crystals separated from the basic solution. The material was washed with cold water and dried *in vacuo;* yield 3.03 g. (60%), m.p. 106–110°. Several precipitations from ethyl acetate solution using petroleum ether gave white plates melting at 115–117°. The material displayed a strong tendency to oxidize to colored products on standing in air.

Anal. Calcd. for $C_7H_{11}N_3S$: C, 49.67; H, 6.55; N, 24.83; S, 18.95. Found: C, 49.69; H, 6.55; N, 24.85; S, 18.80.

4-Amino-6-mercaptobenzimidazole Dihydrochloride.—A solution of 2.28 g. (0.01 mole) of 3,4,5-triaminothiophenol dihydrochloride in 0.75 ml. of formic acid and 10 ml. of 2 *N* hydrochloric acid was heated for one hour at 100° and cooled. Two volumes of absolute alcohol were added to the reaction mixture, followed by ether to a definite turbidity (final volume, approximately 125 ml). The resulting white needles (2.09 g., 89%) melted at 292–293° (with decomposition). After repeatedly dissolving the product in water and precipitating it with excess concentrated hydrochloric acid it decomposed at 293°.

Anal. Calcd. for $C_7H_9N_3SCl_2$: C, 35.30; H, 3.81; N, 17.65; S, 13.47. Found: C, 35.10; H, 3.97; N, 17.49; S, 13.27.

Picrate.—The picrate crystallized from water, in which it is sparingly soluble, as yellow needles which decomposed explosively around 280°.

Anal. Calcd. for $C_{13}H_{10}N_6O_7S$: C, 39.60; H, 2.55; N, 21.31; S, 8.13. Found: C, 39.78; H, 2.77; N, 21.47; S, 7.98.

4-Amino-6-methylmercaptobenzimidazole Dihydrochloride.—The S-methyl derivative was prepared by a procedure similar to that used for the free mercapto compound, using 1.69 g. (0.01 mole) of methyl 3,4,5-triaminophenyl sulfide in 10 ml. of 4 *N* hydrochloric acid and 0.7 ml. of formic acid; yield 1.82 g. (72%), m.p. 246–249° (with decomposition). After several recrystallizations by adding ether to the product dissolved in absolute alcohol, the white crystals melted at 248–250°.

Anal. Calcd. for $C_8H_{11}N_3SCl_2$: C, 38.10; H, 4.40; N, 16.66; S, 12.72. Found: C, 38.21; H, 4.52; N, 16.60; S, 12.49.

Picrate.—The picrate (from water), after purification by adding water to a solution of the material in cellosolve at room temperature, melted at 248–249° (with decomposition).

Anal. Calcd. for $C_{14}H_{12}N_6O_7S$: C, 41.17; H, 2.96; N, 20.58; S, 7.85. Found: C, 41.04; H, 2.87; N, 20.60; S, 7.61.

4-Mercapto-6-nitrobenzimidazole.—A stirred suspension of 21.46 g. (0.01 mole) of 4-amino-6-nitrobenzimidazole hydrochloride[3] in 750 ml. of 1 *N* hydrochloric acid was cooled to 5° and 6.90 g. of sodium nitrite, dissolved in 50 ml. of water, was added in one portion. Stirring was continued until all of the material had gone into solution. To this was added 16.02 g. of purified potassium ethyl xanthogenate dissolved in a little water. The yellow crystals which formed were filtered in a cooled Büchner funnel and suspended in 400 ml. of water. The suspension was heated slowly and finally allowed to boil for 15 minutes. On cooling, the reaction mixture was neutralized with sodium bicarbonate solution, giving 20.2 g. of orange product (after washing with water and drying *in vacuo*). It displayed an indefinite melting point.

The dried material, obtained from decomposition of the diazonium salt, was placed in a Soxhlet extraction apparatus and thoroughly extracted with 500 ml. of ethyl acetate, leaving an unidentified residue (8.0 g.) which decomposed explosively at 216°. The orange to red ethyl acetate solution was passed through a charcoal–celite (1:1) column and the resulting light yellow solution was evaporated to dryness. The sirup which remained was stirred with petroleum ether, giving 7.0 g. of crude, light orange ethyl 6-nitrobenzimidazole-4-thiocarbonate with an indefinite melting point in the vicinity of 85°.

The crude thiocarbonate (7.0 g.) was refluxed for 30 minutes with 100 ml. of 2 *N* sodium hydroxide. The resulting dark red solution was treated with a small excess of concentrated hydrochloric acid. After the evolution of carbon oxysulfide from the warm acidified mixture had ceased, a slight excess of 2 *N* sodium hydroxide was added and the *p*H of the charcoal treated solution was then adjusted to 4.5–5. Light orange 4-mercapto-6-nitrobenzimidazole (3.22 g., 17%) separated, m.p. 180–185°. The material was purified by dissolving it in 50% alcohol and filtering the charcoal-treated solution into a flask immersed in ice-water. Slower cooling gave a semi-colloidal product. The light orange material obtained by rapid cooling sintered strongly above 188° and decomposed at 210° (with bubbling).

Anal. Calcd. for $C_7H_5N_3O_2S$: C, 43.07; H, 2.58; S, 16.43. Found: C, 43.21; H, 2.40; S, 16.67.

Picrate.—The picrate crystallized from alcohol as light yellow needles, m.p. 156–157° (with decomposition).

Anal. Calcd. for $C_{13}H_8N_6O_9S$: C, 36.80; H, 1.90; S, 7.56. Found: C, 36.98; H, 1.96; S, 7.51.

4-Mercapto-6-aminobenzimidazole Dihydrochloride.—4-Mercapto-6-nitrobenzimidazole (1.95 g., 0.01 mole) was reduced with stannous chloride (6 g.) and hydrochloric acid (20 ml.) in the usual manner. The tin double salt (2.20 g.) so obtained was decomposed by hydrogen sulfide in 20 ml. of 2 *N* hydrochloric acid and the dihydrochloride was precipitated by adding 50 ml. of absolute alcohol, 50 ml. of dioxane and then ether to a final volume of 500 ml. The white crystals (0.70 g., 29%) which separated decomposed at 287–289°. Purification was accomplished by repeated solution in a minimal amount of 4 *N* hydrochloric acid followed by addition of absolute alcohol and ether. The decomposition point was unchanged by this treatment.

Anal. Calcd. for $C_7H_9N_3SCl_2$: C, 35.30; H, 3.81; N, 17.64; S, 13.47. Found: C, 35.29; H, 4.08; N, 17.63; S, 13.29.

Picrate.—The light yellow picrate, obtained from the hydrochloride in water, melted initially at 124–128°. After

repeated recrystallization from water, it was converted to a light orange crystalline product which melted at 225–227° (with decomposition).

Anal. Calcd. for $C_{13}H_{10}N_6O_7S$: C, 39.60; H, 2.55; N, 21.31; S, 8.13. Found: C, 39.35; H, 2.73; N, 21.11; S, 8.00.

4-Methylmercapto-6-nitrobenzimidazole.—A cooled solution of the diazonium chloride of 4-amino-6-nitrobenzimidazole, prepared from 5.37 g. (0.025 mole) of the hydrochloride according to the procedure just described, was treated with 1.8 ml. of methyl mercaptan. After several minutes the light yellow diazonium salt separated. The reaction mixture was heated rapidly on the steam-bath until the evolution of nitrogen had ceased. The resulting light orange-yellow solution, after treatment with charcoal, was neutralized with sodium carbonate giving 2.73 g. (52%) of 4-methylmercapto-6-nitrobenzimidazole, m.p. 248–254°. Recrystallization from 80% alcohol gave 1.38 g. of fine yellow crystals, m.p. 277–278°.

Anal. Calcd. for $C_8H_7N_3O_2S$: C, 45.93; H, 3.37; N, 20.08; S, 15.33. Found: C, 45.77; H, 3.25; N, 19.84; S, 15.51.

Picrate.—The picrate crystallized from alcohol as yellow needles melting at 229–231°. Attempts to recrystallize this material from water resulted in regeneration of the free benzimidazole. A serious amount of dissociation occurred on repeated recrystallization from both 50 and 95% alcohol. A sample, purified for analysis by recrystallization from 50% alcohol containing a small amount of picric acid, analyzed as the hemipicrate.

Anal. Calcd. for $C_8H_7N_3O_2S \cdot {}^1/_2C_6H_3N_3O_7$: C, 40.80; H, 2.65; N, 19.46. Found: C, 40.10; H, 2.56; N, 18.61, 19.33.

4-Methylmercapto-6-aminobenzimidazole Dihydrochloride.—4-Methylmercapto-6-nitrobenzimidazole (2.01 g., 0.01 mole) was reduced at 5° with stannous chloride (5.80 g.) and hydrochloric acid (20 ml.) in a manner similar to the preceding reductions. Decomposition of the tin double salt (2.84 g.) which separated, by hydrogen sulfide in 1 *N* hydrochloric acid, and treatment of the filtrate with excess acetone gave white crystals (0.61 g., 21%), m.p. 287–290°. Purification was accomplished by dissolving the product in 5 ml. of water and, after treatment with charcoal, adding 50 ml. of absolute alcohol followed by benzene to definite turbidity. After crystallization began, more benzene was added to complete the precipitation. The product obtained in this manner retained a half mole of solvent of crystallization which was not removed by drying at 100° *in vacuo*. The benzene was released upon solution of the material in water.

Anal. Calcd. for $C_8H_{11}N_3SCl_2 \cdot {}^1/_2C_6H_6$: C, 45.36; H, 4.85; N, 14.43; S, 11.01; Cl, 24.35. Found: C, 45.28; H, 4.85; N, 14.70; S, 11.13; Cl, 23.82.

Picrate.—The picrate crystallized from water as light yellow needles melting at 220–222°. After repeated recrystallization from water, the material was transformed to a deep yellow crystalline product melting at 251–252°.

Anal. Calcd. for $C_{14}H_{12}N_6O_7S$: C, 41.17; H, 2.96; N, 20.58. Found: C, 41.00; H, 3.02; N, 20.35.

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[CONTRIBUTION FROM THE BEN MAY LABORATORY FOR CANCER RESEARCH AND THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF CHICAGO]

Hormone Analogs. I. Preparation of Intermediate Ketones for the Synthesis of Stilbestrol Analogs[1,2]

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RECEIVED MAY 3, 1955

Certain 4-arylhexan-3-ones, useful for the synthesis of stilbestrol analogs, have been prepared by ethylation of the corresponding 1-arylbutan-2-ones which in turn are obtained conveniently from aromatic aldehydes, either by the glycidic ester condensation with ethyl α-bromobutyrate followed by saponification and decarboxylation, or by the amine-catalyzed condensation with 1-nitropropane followed by reduction and hydrolysis. Substitution of ethyl phenylbromoacetate for ethyl bromobutyrate in the glycidic ester process leads to a substituted desoxybenzoin, also a useful intermediate for the preparation of stilbestrol analogs.

In addition to the characteristic effects on their specific target tissues, the different types of steroid sex hormones possess the ability to inhibit or antagonize certain of the physiological actions of one another as well as to diminish the secretory activity of the pituitary gland.[3] These phenomena of inhibition and antagonism find clinical application in cases where chemical regulation of the endocrine balance is desired. In general it has been the potent members of each class of hormones which have been employed in this way, and their administration often is accompanied by undesirable side effects which arise from the primary hormonal actions of these materials. Therefore it would be of practical as well as of theoretical interest if compounds could be discovered which possess little or no primary hormonal activity, but which still have the ability to modify or regulate endocrine balance.

Whereas extensive studies have been carried out concerning the relation of molecular structure to primary hormonal activity, relatively little is known about the structural requirements for antagonism and pituitary inhibition. Accordingly an investigation has been undertaken in this Laboratory of compounds closely related in structure to the active hormones to determine whether antagonistic and pituitary-inhibiting properties depend on the same molecular features as the primary hormonal activity.

One class of substances being studied in this regard consists of compounds related in structure to stilbestrol, a synthetic estrogenic hormone which exhibits the characteristic physiological actions, both hormonal and inhibitory, of the natural steroid estrogens. A general method has been developed by which one or both of the aromatic

(1) Presented in part before the Division of Organic Chemistry, 123rd Meeting of the American Chemical Society, Los Angeles, Calif., March, 1953.

(2) This investigation was supported in part by a grant from the American Cancer Society as recommended by the Committee on Growth of the National Research Council.

(3) C. W. Emmens and A. S. Parkes, *Vitamins and Hormones*, **5**, 233 (1947); R. Courrier, *ibid.*, **8**, 179 (1950); H. Burrows, "Biological Actions of Sex Hormones," 2nd ed., Cambridge University Press, 1949; G. Pincus and K. V. Thimann, "The Hormones," Academic Press, Inc., New York ,N. Y. ,Vol. I, 1948, ch. 12, Vol. II, 1950, ch. 1, 2, 6.