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Imidazo[4,5-d]pyridazines. III.

The Synthesis of 2-Phenylimidazo[4,5-d]-pyridazines (1).

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Based upon an analogy with "Dyrenium", (6-phenyl-2,4,7-triaminopteridine) (I), 4,7-diamino-2-phenylimidazo[4,5-d]pyridazine (II) has been prepared. This compound has been found to possess diuretic activity. In addition a number of other substituted 2-phenylimidazo[4,5-d]pyridazines have been prepared.

The diuretic activity (3) of "Dyrenium" (6-phenyl-2,4,7-triaminopteridine) (I) prompted the synthesis of 4,6-diamino-2-phenylimidazo[4,5-d]pyridazine (II). A search of the published literature on imidazo-[4,5-d]pyridazines (4) revealed the absence of any 2-phenylimidazo[4,5-d]pyridazines.

For the synthesis of the 2-phenylimidazo[4,5-d]-pyridazines, diethyl 2-phenylimidazole-4,5-dicarboxylate (III) prepared by a modification of the method of Fargher and Pyman (5) was selected as the starting material. Compound III was converted smoothly in 80% yield into the dihydrazide (IV) on treatment with ethanolic hydrazine. Compound IV was cyclized into 4,7-dihydroxy-2-phenylimidazo[4,5-d]pyridazine (VIII) in 94% yield by heating with 10% hydrochloric acid solution. 2-Phenylimidazo[4,5-d]pyridazine-4,7-dithiol (VII) was prepared in 95% yield by allowing VIII to react with phosphorus pentasulfide in boiling pyridine solution. Compound VII was readily converted into 4,7-bis-(methylthio)-2-phenylimidazo-[4,5-d]pyridazine (VI) by reaction with two moles of methyl iodide in alkali at room temperature. Amination of an ethanolic solution of VI in a rocking autoclave afforded 4,7-diamino-2-phenylimidazo-[4,5-d]pyridazine in 71% yield.

Nucleophilic displacement of the methylthio groups of VI with hydrazine gave 4,7-dihydrazino-2-phenylimidazo[4,5-d]pyridazine, isolated as the monohydrochloride (V). This was characterized by conversion into IX with two moles of benzaldehyde. When VI was allowed to react with ethanolic methylamine in a rocking autoclave, 4,7-bis-(methylamino)-2-phenylimidazo[4,5-d]pyridazine (XIII) was obtained in quantitative yield.

Compound VII could be mono- or dialkylated into XI and X respectively depending upon the amount of alkyl halide employed.

4,7-Dichloro-2-phenylimidazo[4,5-d]pyridazine (XII) was prepared in 75% yield by allowing VIII to react with boiling phosphorus oxychloride. Attempts to convert XII into II by amination in a rocking autoclave were unsuccessful. Glacial acetic acid hydrolysis of XII afforded 4(7)-chloro-7(4)-hydroxy-2-phenylimidazo[4,5-d]pyridazine (XV) in quantitative yield. Compound XV was readily dechlorinated with hydrogen in the presence of palladium on charcoal to yield 77% of 4-hydroxy-2-phenylimidazo[4,5-d]-pyridazine (XIV). Compound XII was catalytically dechlorinated to 2-phenylimidazo[4,5-d]pyridazine (XVI) in 74% yield.

The novel nucleophilic displacement of halogen by phosphorus pentasulfide in pyridazines (6) and cinnolines (7) has been reported from this laboratory. 2-Phenylimidazo[4,5-d]pyridazine-4,7-dithiol (VII) was obtained in 96% yield by allowing 4,7-dichloro-2-phenylimidazo[4,5-d]pyridazine (XII) to react with phosphorus pentasulfide in boiling pyridine solution. This constitutes almost quantitative replacement of both halogen atoms in an additional heterocyclic ring system.

In a preliminary screen for diuretic effect in rats hydrated with 25 ml./kg. of 0.9% sodium chloride solution, 4,7-diamino-2-phenylimidazo[4,5-d]pyridazine (II) increased water excretion above control values by 43% at 15 mg./kg. and 58% at 30 mg./kg. (8).

EXPERIMENTAL

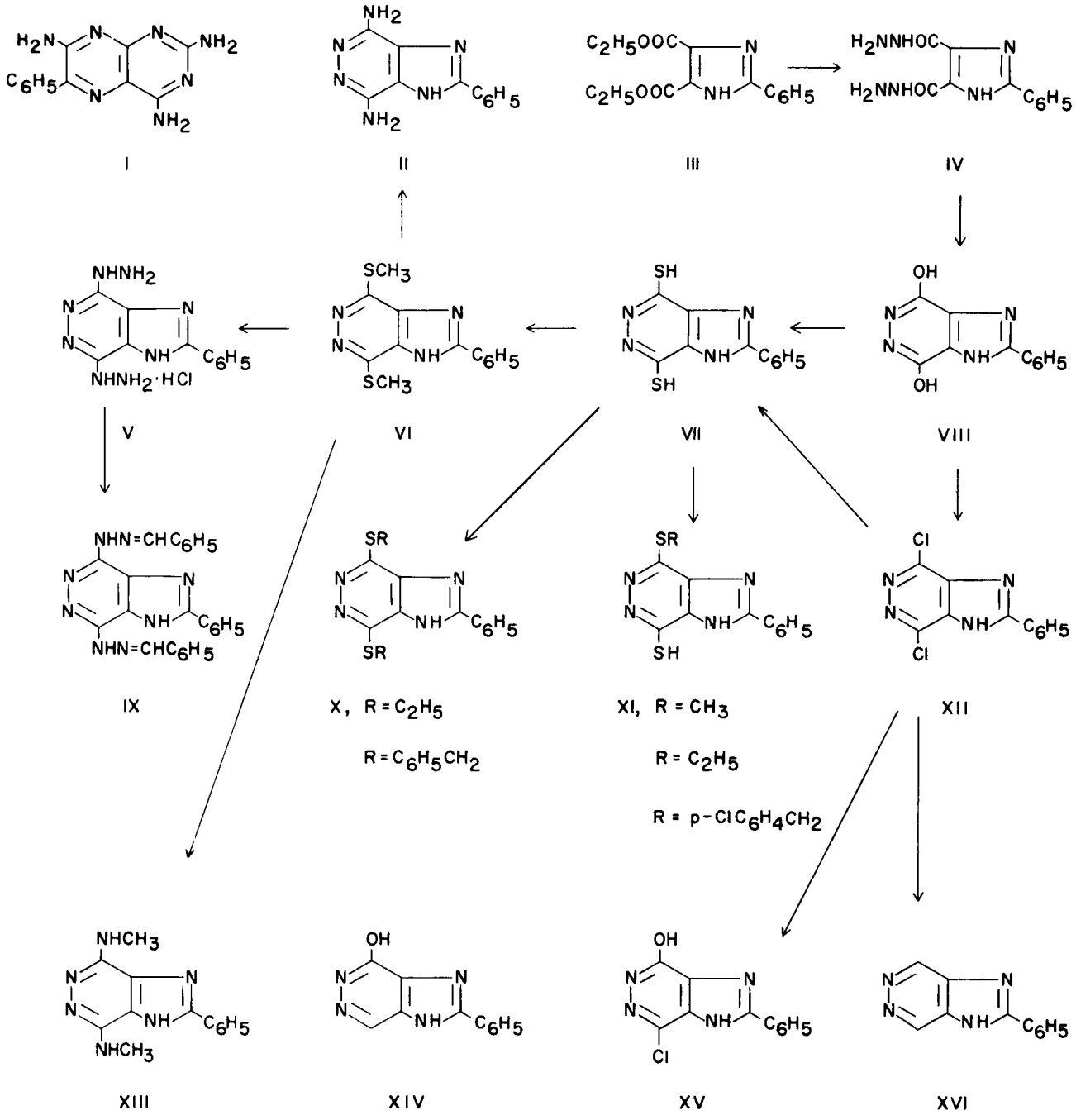
2-Phenylimidazole-4,5-dicarboxylic Acid.

The procedure of Fargher and Pyman (5) was modified as follows in order to increase the yield of 2-phenylimidazole-4,5-dicarboxylic acid from 19% to 60%.

One mole of tartaric acid (150 g.) was partially dissolved in a mixture of 324 ml. each of concentrated and fuming nitric acids. Concentrated sulfuric acid (600 ml.) was added gradually to the solution while stirring and maintaining a temperature of 38-43° with a water bath. Towards the last of the addition, white crystalline tartaric acid dinitrate began to separate.

After thorough chilling, the dinitrate was filtered as dry as possible on a Büchner funnel lined with pyrex wool. The dry cake was transferred in portions to two liters of crushed ice, stirring to dissolve each portion. The cold (-5°) mixture was further chilled to -10° and neutralized with concentrated ammonium hydroxide (400-600 ml.) at -5° to -10° (1 hour).

Ammonium hydroxide (300 ml.) was added to the neutral solution followed by one mole of freshly distilled benzaldehyde (106 g.). The mixture was stirred vigorously at 0° for 7 hours. After 3-4 hours the solid cream-colored 2-phenylimidazole-4,5-dicarboxylic acid began to separate. The cold mixture was neutralized with concentrated hydrochloric acid. The product was collected and air-dried yielding 139 g. (60%), m.p. 265-270° with effervescence. The reported m.p. was 271° with effervescence (5).



2-Phenylimidazole-4,5-dicarboxylic Acid Dihydrazide (IV).

Crude 2-phenylimidazole-4,5-dicarboxylic acid (139 g., 0.6 mole) was suspended in absolute ethanol (1.8 liters) and the suspension saturated with dry hydrogen chloride at room temperature with stirring for 8 hours. The solution was filtered and the filtrate evaporated under reduced pressure on the steam bath until only a brown sludge remained. At this point, the diethyl ester (III) could be obtained by recrystallization from aqueous ethanol yielding white needles, m.p. 190° (10).

The crude ester was dissolved in absolute ethanol (600-700 ml.) and 95% hydrazine (77 g., 2.4 moles) added to the chilled solution followed by refluxing for 2 hours. The granular cream-colored dihydrazide was collected, washed with cold ethanol and air-dried, yielding 125 g. (80%) of crude product. The product was soluble in pyridine, hot dilute hydrochloric acid, cold potassium hydroxide solution and difficultly soluble in water and ethanol. Recrystallization from 95% ethanol gave a pure white powder, m.p. above 360°.

U. V. λ max (95% C_2H_5OH): 206 (ε, 22,600); 273 mμ (ε, 22,100). Infrared cm^{-1}; 3220 (m), 1640 (w), 1530 (m), 1110 (w), 953 (m), 920 (w), 778 (m), 722 (w), 690 (s) (9).

Anal. Calcd. for $C_{11}H_{12}N_6O_2$: C, 50.76; H, 4.65; N, 32.29. Found: C, 50.94; H, 4.74; N, 32.04.

4,7-Dihydroxy-2-phenylimidazo[4,5-d]pyridazine (VIII).

2-Phenylimidazole-4,5-dicarboxylic acid dihydrazide (V) (19.5 g., 0.075 mole) was dissolved in 300 ml. of hot 10% hydrochloric acid (moist dihydrazide from the previous reaction may be used) and the solution refluxed for 1 hour. The relatively pure product was collected, washed with water and air-dried, yielding 15.9 g. (94%). The product was soluble in pyridine, dilute potassium hydroxide solution, hot glacial acetic acid, and relatively insoluble in water and ethanol. Recrystallization from aqueous pyridine gave a white powder, m.p. 390°.

U. V. λ max (95% C_2H_5OH): 206 (ε, 28,000); 256 mμ (ε, 23,000). Infrared cm^{-1}; 1640 (m), 1550 (m), 1280 (w), 1130 (w), 1080 (w), 960 (w), 815 (w), 683 (m).

Anal. Calcd. for $C_{11}H_8N_4O_2$: C, 57.89; H, 3.53; N, 24.56. Found: C, 58.38; H, 4.10; N, 24.60.

2-Phenylimidazo[4,5-d]pyridazine-4,7-dithiol (VII). Method 1.

To a solution of 4,7-dihydroxy-2-phenylimidazo[4,5-d]pyridazine (VIII) (22.8 g., 0.1 mole) in 350 ml. of dry freshly distilled pyridine was added 133.4 g. of phosphorus pentasulfide in portions with stirring and cooling. The mixture was refluxed with stirring for 1 hour. Cooling yielded yellow crystals of excess phosphorus pentasulfide which were removed. The excess pyridine was removed from the dark filtrate by distillation under reduced pressure to about one-third of the original volume. Water (about 50 ml.) was added cautiously to the residue and the mixture heated on the steam bath for 1 hour. After the evolution of hydrogen sulfide had subsided, the hot solution was filtered with suction, cooled, and acidified with 10% hydrochloric acid to *p*H 1. The yellow-brown solid was collected, washed with water and air-dried, giving 24.7 g. (95%) of crude product. Repeated recrystallization from absolute ethanol gave a yellow powder, m.p. 230-232°. The qualitative test for sulfur was positive.

U. V. λ max (95% C_2H_5OH): 206 (ε, 34,500); 279 (ε, 27,500); 292 sh (ε, 24,000); 349 mμ (ε, 15,500).

Infrared cm^{-1}; 3200 (w), 1580 (m), 1300 (w), 1240 (s), 1040 (w), 1000 (m), 782 (w), 685 (m).

Anal. Calcd. for $C_{11}H_8N_4S_2$: C, 50.75; H, 3.10; N, 21.52. Found: C, 50.94; H, 3.37; N, 21.59.

Method 2.

Compound VII was also prepared by the novel nucleophilic displacement of halogen by phosphorus pentasulfide in boiling pyridine solution.

Phosphorus pentasulfide (6.6 g.) was cautiously added to a solution of 4,7-dichloro-2-phenylimidazo[4,5-d]pyridazine (XII) (1.33 g., 0.005 mole) in 50 ml. of pure dry pyridine. The mixture was refluxed 30 minutes, cooled and water (8-10 ml.) added gradually followed by heating on the steam bath for about 1 hour. The hot mixture was filtered, cooled, and acidified to *p*H 1 with concentrated hydrochloric acid. The dark yellow precipitate was collected, washed with water, and air-dried yielding 1.25 g. (96%) of crude product. Crystallization from ethanol gave a yellow powder, m.p. 230-232°. A mixed melting point determination with the sample as prepared above showed no depression.

4,7-Bis-(methylthio)-2-phenylimidazo[4,5-d]pyridazine (VI).

Semipure 2-phenylimidazo[4,5-d]pyridazine-4,7-dithiol (VII) (20.8 g., 0.08 mole) was dissolved in 350 ml. of 1 N potassium hydroxide solution. Methyl iodide (25.0 g., 0.176 mole) was added all at once and the dark brown opaque two-phase system was stirred vigorously at room temperature for 2 hours. The dark solution was filtered and the filtrate acidified to *p*H 6 with glacial acetic acid. A large quantity of a pink-grey precipitate was collected and washed with water. Upon warming on the steam bath, water of hydration separated and was decanted off leaving a dark brown hardened gum. The crude yield was 19.7 g. (85%). Repeated crystallization from methanol gave cream-colored needles, m.p. 195-197°.

U. V. λ max (95% C_2H_5OH); 205 (ε, 24,900); 266 (ε, 27,100); 296 (ε, 22,500); (sh) 307 mμ (ε, 19,800).

Infrared cm^{-1}; 1540 (m), 1330 (w), 1290 (m), 1240 (s), 1070 (w), 990 (w), 780 (m), 713 (m), 690 (m).

Anal. Calcd. for $C_{13}H_{12}N_4S_2$: C, 54.14; H, 4.20; N, 19.43. Found: C, 54.10; H, 4.14; N, 19.05.

4(7)-Methylthio-2-phenylimidazo[4,5-d]pyridazine-7(4)-thiol (XI, R = CH_3).

2-Phenylimidazo[4,5-d]pyridazine-4,7-dithiol (VII) (2.6 g., 0.01 mole) was dissolved in 50 ml. of 1 N potassium hydroxide solution. Methyl iodide (1.42 g., 0.01 mole) was added and the dark mixture stirred at room temperature for 1 hour. After filtration and acidification to *p*H 6 with glacial acetic acid, a purple-grey solid precipitated. The solid was collected, washed with water and air-dried, yielding 2.3 g. (89%) of crude product. Upon recrystallization from absolute ethanol, a pale yellow flocculent solid was obtained, m.p. 303-305°.

U. V. λ max (95% C_2H_5OH): 206 (ε, 25,600); 273 (sh) (ε, 22,700) 284 (ε, 24,700); 325 (sh) (ε, 11,000); 344 mμ (ε, 12,900).

Infrared cm^{-1}; 1570 (w), 1520 (w), 1250 (s), 1060 (w), 1000 (m), 787 (w), 712 (m), 684 (m).

Anal. Calcd. for $C_{12}H_{10}N_4S_2$: C, 52.53; H, 3.64; N, 20.71. Found: C, 53.11; H, 3.67; N, 20.67.

4,7-Bis-(ethylthio)-2-phenylimidazo[4,5-d]pyridazine (X, R = C_2H_5).

2-Phenylimidazo[4,5-d]pyridazine-4,7-dithiol (VII) (13.0 g., 0.05 mole) was dissolved in 250 ml. of 1 N potassium hydroxide solution and alkylated with ethyl iodide (0.1 mole) following the procedure for the preparation of VI. There was obtained 10.08 g. (70%) of crude product. Recrystallization from absolute methanol gave cream-colored granular crystals, m.p. 182-184°.

U. V. λ max (95% C_2H_5OH): 207 (ε, 31,000); 268 (ε, 28,500); 298 (ε, 24,200); 309 mμ (ε, 22,500).

Infrared cm^{-1}; 2970 (m), 2925 (m), 1550 (s), 1520 (m), 1470 (s), 1420 (m), 1340 (m), 1308 (m), 1245 (s), 1070 (w), 1050 (w), 990 (m), 940 (m), 780 (m), 710 (s), 690 (s), 620 (m).

Anal. Calcd. for $C_{15}H_{16}N_4S_2$: C, 56.93; H, 5.10; N, 17.71. Found: C, 57.38; H, 5.26; N, 18.01.

4(7)-Ethylthio-2-phenylimidazo[4,5-d]pyridazine-7(4)-thiol (XI, R = C_2H_5).

2-Phenylimidazo[4,5-d]pyridazine-4,7-dithiol (VII) (2.6 g., 0.01 mole) was dissolved in 50 ml. of 1 N potassium hydroxide solution and alkylated with ethyl iodide (1.56 g., 0.01 mole) in the same manner as XI (R = CH_3). The crude, apparently hydrated product amounted to 2.0 g. (69%). Repeated crystallization from absolute methanol gave a light yellow powder, m.p. 306-307°.

U. V. λ max (95% C_2H_5OH): 206 (ε, 29,000); 274 (sh) (ε, 26,000); 284 (ε, 27,700); 324 (ε, 13,000); 342 mμ (ε, 14,000).

Infrared cm^{-1}; 3200 (w), 1570 (w), 1490 (w), 1230 (m), 1080 (w), 1000 (w), 788 (w), 757 (w), 708 (m).

Anal. Calcd. for $C_{13}H_{12}N_4S_2$: C, 54.14; H, 4.20; N, 19.43. Found: C, 53.67; H, 4.39; N, 19.51.

4,7-Bisbenzylthio-2-phenylimidazo[4,5-d]pyridazine (X, R = $C_6H_5CH_2$).

2-Phenylimidazo[4,5-d]pyridazine-4,7-dithiol (VII) (2.6 g., 0.01 mole) was partially dissolved in 60 ml. of concentrated ammonium hydroxide solution. Benzyl chloride (2.78 g., 0.022 mole) was dissolved in 5 ml. of dioxane. The second solution was added dropwise to the first solution with stirring. During this period, the temperature was gradually allowed to increase to 35°. Stirring was continued for 2.5 hours at room temperature and the supernatant liquid decanted from the accumulated brown gum. This was recrystallized from 95% ethanol yielding 1.0 g. (22%) of a cream-colored granular solid. Further recrystallization from ethanol-water gave a pure white powder, m.p. 163-165°.

U. V. λ max (95% C_2H_5OH): 207 (ε, 48,600); 268 (ε, 31,800); 289 (sh) (ε, 22,500); 299 (ε, 27,500); (sh) 309 mμ (ε, 25,800).

Infrared cm^{-1}; 1550 (w), 1315 (m), 1230 (m), 1070 (w), 940 (w), 770 (w), 710 (w), 700 (m), 685 (w).

Anal. Calcd. for $C_{25}H_{20}N_4S_2$: C, 68.14; H, 4.58; N, 12.72. Found: C, 67.77; H, 4.87; N, 12.22.

4(7)-*p*-Chlorobenzylthio-2-phenylimidazo[4,5-d]pyridazine-7(4)-thiol (XI, R = *p*-$ClC_6H_4CH_2$).

A solution of *p*-chlorobenzyl chloride (2.42 g., 0.015 mole) was dissolved in 12.5 ml. of dioxane and this solution was added dropwise to a stirred solution of 2-phenylimidazo[4,5-d]pyridazine-4,7-dithiol (VII) (3.9 g., 0.015 mole) in ammonium hydroxide (150 ml.). The temperature was gradually allowed to increase to 35-40°. The reaction mixture was stirred for 3 hours at room temperature during which time a brown granular solid separated. The product was filtered, washed with water and air-dried, yielding 4.8 g. (76%). Repeated recrystallization from 95% ethanol gave the pure dihydrate, m.p. 235-238°.

U. V. λ max (95% C_2H_5OH): 205 (ε, 24,100); 222 (sh) (ε, 23,200); 283 (ε, 23,500); 323 (sh) (ε, 16,100); 346 mμ (ε, 17,900).

Infrared cm^{-1}; 1570 (m), 1240 (s), 1080 (m), 1020 (w), 1000 (m), 835 (m), 780 (w), 670 (m).

Anal. Calcd. for $C_{18}H_{17}N_4S_2ClO_2$: C, 51.36; H, 4.08; N, 13.31. Found: C, 50.98; H, 3.66; N, 13.35.

4,7-Diamino-2-phenylimidazo[4,5-d]pyridazine (II).

Dry, pure 4,7-bis-(methylthio-2-phenylimidazo[4,5-d]pyridazine (VI) (4 g., 0.014 mole) was placed in a chilled 500 ml. stainless steel autoclave with 250 ml. of absolute ethanol saturated with ammonia. The autoclave was sealed and rocked for 20 hours at an internal temperature of 220°. A clear yellow-brown solution with an intense odor of methylmercaptan was obtained. The solution was evaporated to dryness on the steam bath whereupon a cream-colored solid weighing 2.4 g. (71%) was obtained. After several recrystallizations from water, fine white needles of the mono-hydrated product were obtained. The hydrate melted at 183-200° and the anhydrous form melted at 283-285°.

U. V. λ max (95% C_2H_5OH): 210 (ε, 23,800); 256 (ε, 23,800); 287 mμ (ε, 21,100).

Infrared cm^{-1}; 3400 (w), 1600 (m), 1540 (w), 1290 (w), 1030 (w), 725 (w), 708 (w), 690 (m).

Anal. Calcd. for $C_{11}H_{12}N_6O$: C, 54.08; H, 4.95; N, 34.17. Found: C, 54.23; H, 5.12; N, 33.95.

4,7-Bis-(methylamino)-2-phenylimidazo[4,5-d]pyridazine (XIII).

Two-hundred milliliters of cold absolute ethanol were saturated with dry methylamine (24.5 g.). 4,7-Bismethylthio-2-phenylimidazo[4,5-d]-pyridazine (VI) (5.77 g., 0.02 mole) and the ethanolic solution of methylamine were placed in a 500 ml. stainless steel autoclave which was rocked at 190-200° for 8.5 hours. The volume of the light brown solution obtained from the cooled autoclave was evaporated to about 50 ml. A white powder was collected by chilling. This was washed

with a small amount of cold ethanol, and air-dried, yielding 5.53 g. (quantitative). The product was recrystallized from either ethanol or water yielding fine white needles, m.p. 310-313°. The qualitative sulfur test was negative.

U. V. λ max (95% C_2H_5OH): 211 (ε, 38,000); 262 (ε, 30,300); 288 (sh) (ε, 22,800); 293 mμ (ε, 23,200).

Infrared cm^{-1}; 3275 (s), 2630 (s), 1650 (s), 1550 (s), 1450 (m), 1390 (s), 1340 (m), 1250 (s), 1160 (s), 1115 (m), 1070 (m), 1030 (m), 790 (m), 695 (s), 680 (m).

Anal. Calcd. for $C_{13}H_{14}N_6$: C, 61.40; H, 5.55; N, 33.05. Found: C, 61.00; H, 5.85; N, 32.97.

Mono-hydrochloride of 4,7-dihydrazino-2-phenylimidazo[4,5-d]pyridazine (V).

4,6-Bis-(methylthio)-2-phenylimidazo[4,5-d]pyridazine (VI) (4.63 g., 0.016 mole) was dissolved in 30 ml. of 96% hydrazine and the solution heated on the steam bath for 3 hours. Gradual addition of water to the chilled solution precipitated a white solid which was collected, washed with cold water and air-dried. The 4,7-bishydrazino-2-phenylimidazo[4,5-d]pyridazine obtained (3.6 g., 0.014 mole) was dissolved in absolute ethanol. Dry hydrogen chloride gas was gently bubbled through the chilled solution for 6 hours during which time a white solid gradually precipitated. The solid was collected, washed with cold ethanol, and air-dried. Four grams (quantitative yield) of product was obtained. Recrystallization from ethanol-water gave a pure white powder, m.p. 260-261°.

U. V. λ max (95% C_2H_5OH): 208 (ε, 23,400); 264 (ε, 23,500); (sh) 292 mμ (ε, 21,000).

Infrared cm^{-1}; 3430 (w), 2650 (s), 1680 (m), 1550 (s), 1450 (m), 1290 (m), 1190 (m), 1100 (w), 950 (m), 790 (m), 710 (s).

Anal. Calcd. for $C_{11}H_{13}N_8Cl$: C, 45.13; H, 4.48; N, 38.28. Found: C, 45.37; H, 4.84; N, 38.54.

4,7-Bis-(3-phenyl-1,2-diaza-2-propen-1-yl)-2-phenylimidazo[4,5-d]-pyridazine (IX).

Benzaldehyde (0.8 ml.) was added to a solution of 4,7-bishydrazino-2-phenylimidazo[4,5-d]pyridazine (0.64 g., 0.0025 mole) in 3 ml. of ethanol. Water was added to cloudiness and the solution cooled. The precipitated yellow solid was collected, washed with water, and air-dried, yielding 0.44 g. (25%). Crystallization from absolute ethanol gave the pure yellow product which melted at 318-321°.

U. V. λ max (95% C_2H_5OH): 204 (ε, 21,600); 229 (ε, 20,100); 253 (sh) (ε, 17,600); 296 (sh) (ε, 19,300); 334 mμ (ε, 23,200).

Infrared cm^{-1}; 1620 (m), 1530 (m), 1230 (m), 1130 (s), 750 (m), 720 (m), 690 (s).

Anal. Calcd. for $C_{25}H_{20}N_8$: C, 69.42; H, 4.66; N, 25.91. Found: C, 69.21; H, 4.61; N, 25.76.

4,7-Dichloro-2-phenylimidazo[4,5-d]pyridazine (XII).

4,7-Dihydroxy-2-phenylimidazo[4,5-d]pyridazine (VIII) (22.8 g., 0.1 mole) was refluxed with phosphorus oxychloride (265 ml.) for 9 hours during which time the white solid gradually dissolved. Three-fourth of the excess phosphorus oxychloride was removed under reduced pressure and the brown syrup-like residue was poured cautiously with stirring into 1 liter of crushed ice taking particular care to maintain a temperature near 0°. The coral-colored solid which separated was filtered quickly from the acid solution, washed thoroughly with cold water, and air-dried, giving 19.8 g. (75%) of crude product. Repeated crystallization from absolute ethanol yielded fine light yellow needles, m.p. 282-284°. A Beilstein test was positive.

U. V. λ max (95% C_2H_5OH): 212 (ε, 32,500); 240 (ε, 27,500); 310 mμ (ε, 22,500).

Infrared cm^{-1}; 3200 (m), 1630 (w), 1530 (m), 1320 (m), 1280 (w), 1240 (s), 980 (s), 940 (m), 710 (m), 685 (w).

Anal. Calcd. for $C_{11}H_6N_4Cl_2$: C, 49.83; H, 2.28; N, 21.14. Found: C, 49.82; H, 2.38; N, 20.99.

4(7)-Chloro-7(4)-hydroxy-2-phenylimidazo[4,5-d]pyridazine (XV).

4,7-Dichloro-2-phenylimidazo[4,5-d]pyridazine (XII) (26.5 g., 0.1 mole) was refluxed with glacial acetic acid (200 ml.) until the solid had dissolved (1 hour). Cooling of the solution yielded fine white needles which were collected with suction, washed with water and air-dried. A Beilstein test was positive. The product was recrystallized from glacial acetic acid, m.p. 358-360°.

U. V. λ max (95% C_2H_5OH): 207 (ε, 23,200); 249 (ε, 22,200); 282 mμ (ε, 20,800).

Infrared cm^{-1}; 1670 (s), 1530 (m), 1270 (w), 1160 (m), 1010 (w), 950 (m), 780 (w), 715 (s), 690 (s).

Anal. Calcd. for $C_{11}H_7N_4OCl$: C, 53.56; H, 2.86; N, 22.72. Found: C, 53.28; H, 3.34; N, 22.88.

4-Hydroxy-2-phenylimidazo[4,5-d]pyridazine (XIV).

4(7)-Chloro-7(4)-hydroxy-2-phenylimidazo[4,5-d]pyridazine (XV) (14.47 g., 0.059 mole) was dissolved in 95% ethanol (700 ml.) containing sodium hydroxide (0.059+ mole). The catalyst (30% palladium on charcoal suspended in a small amount of water) was added to the basic ethanolic solution. Hydrogen gas was introduced into the stirred solution for 6 hours. Seventy-four percent of the theoretical amount of hydrogen was absorbed. The catalyst was removed, and the filtrate neutralized with acetic acid and evaporated to dryness under reduced pressure on the steam bath. The residue was crystallized from glacial acetic acid yielding a pure white powder (9.59 g., 77%), which melted at 347-349°. A Beilstein test was negative.

U. V. λ max (95% C_2H_5OH): 210 (ε, 22,700); 246 (ε, 21,100); 283 mμ (ε, 20,000).

Infrared cm^{-1}; 3110 (s), 1670 (s), 1550 (m), 1500 (w), 1460 (m), 1370 (m), 1285 (m), 1140 (m), 1070 (w), 960 (m), 900 (s), 790 (m), 710 (s), 690 (m).

Anal. Calcd. for $C_{11}H_8N_4O$: C, 62.26; H, 3.80; N, 26.40. Found: C, 62.27; H, 3.79; N, 26.41.

2-Phenylimidazo[4,5-d]pyridazine (XVI).

4,7-Dichloro-2-phenylimidazo[4,5-d]pyridazine (XII) (4 g., 0.015 mole) was added to a solution of sodium hydroxide (1.21 g., 0.03 mole) in 95% ethanol (300 ml.). The catalyst (5% palladium on charcoal) was quickly added and hydrogen introduced for a period of 24 hours. The gas was absorbed rapidly for 1 hour and then the absorption slowed considerably. The catalyst was removed, the filtrate made slightly acidic with acetic acid and evaporated to dryness on the steam bath under reduced pressure. Crystallization of the residue from 95% ethanol gave a light yellow powder, m.p. 330-332°. The yield after the first crystallization was 2.18 g. (74%).

U. V. λ max (95% C_2H_5OH): 208 (ε, 37,300); 231 (sh) (ε, 23,400); 236 (ε, 24,400); 245 (sh) (ε, 16,500); 287 mμ (ε, 22,500).

Infrared cm^{-1}; 3050 (m), 2700 (s), 1830 (w), 1550 (m), 1480 (s), 1400 (w), 1300 (s), 1230 (s), 1100 (w), 980 (s), 890 (w), 710 (s), 590 (m).

Anal. Calcd. for $C_{11}H_8N_4$: C, 67.34; H, 4.11; N, 28.56. Found: C, 67.61; H, 4.14; N, 28.30.

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REFERENCES

(1) Abstracted from the Master of Science thesis of Miriam Malm, The University of New Mexico, June, 1964.

(2) To whom reprint requests should be addressed.

(3) A. P. Crosley, Jr., L. M. Ronquillo, W. H. Stricklund, and F. Alexander, *Ann. Internal Med.*, 56, 241 (1962).

(4) R. Jones, *J. Am. Chem. Soc.*, 78, 159 (1956); T. S. Gardner, F. A. Smith, E. Wenis, and J. Lee, *J. Org. Chem.*, 21, 530 (1956); I. Hagedorn and S. Tönjes, *Pharmazie*, 12, 567 (1957); R. N. Castle and W. S. Seese, *J. Org. Chem.*, 23, 1534 (1958); J. A. Carbon, *J. Am. Chem. Soc.*, 80, 6083 (1958); T. Itai and S. Suzuki, *Chem. & Pharm. Bull.* (Tokyo), 8, 999 (1960); J. I. Fernando Alonzo and R. Domingo Sebastián, *Anales real soc. espan. fís y quím* (Madrid), 56 B, 759 (1960); B. Pullman and A. Pullman, *Biochem. Biophys. Res. Commun.*, 2, 239 (1960); P. H. Laursen and B. E. Christensen, *J. Org. Chem.*, 27, 2500 (1962); D. L. Aldous and R. N. Castle, *Arzneim.-Forsch.*, 13, 878 (1963).

(5) R. G. Fargher and F. L. Pyman, *J. Chem. Soc.*, 115, 217 (1919).

(6) R. N. Castle and K. Kaji, *Tetrahedron Letters*, 393 (1962); T. Kuraishi and R. N. Castle, *J. Heterocyclic Chem.*, 1, 42 (1964).

(7) R. N. Castle, R. R. Shoup, K. Adachi, and D. L. Aldous, *ibid.*, 1, 98 (1964).

(8) The authors are indebted to the Smith Kline and French Laboratories for the screening data reported.

(9) The infrared spectra of compounds II, IV, VI, VII, VIII, IX, X (R = $C_6H_5CH_2$) XI (R = CH_3, C_2H_5, and *p*-$ClC_6H_5CH_2$), XII, XV were determined in Nujol on an Infracord spectrophotometer 137. Compounds V, X (R = C_2H_5), XIII, XIV and XVI were determined in potassium bromide discs on an Infracord 337. The ultraviolet spectra were determined on a Bausch & Lomb 505 spectrophotometer.

(10) Y. Tamamushi, *J. Pharm. Soc. Japan*, 53, 580 (1933).

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