Department of Chemistry, University of New Mexico

The Synthesis of Pyrazino[2,3-*d*]pyridazine and Some of its Derivatives

Natu R. Patel and Raymond N. Castle

Pyrazino[2,3-*d*]pyridazine (I) was synthesized by two different routes. 5,8-Dihydroxypyrazino[2,3-*d*]pyridazine (IV) was converted to 5,8-dichloropyrazino[2,3-*d*]pyridazine (V) and 5,8-dibromopyrazino[2,3-*d*]pyridazine (Va). When V was treated with various benzyl mercaptans and alkoxides the corresponding disubstituted derivatives were obtained. Compound V when allowed to react with aromatic amines gave 5,8-bisaminopyrazino[2,3-*d*]pyridazines, however, with aliphatic amines only mono substituted products were obtained substituted in the 8-position. The reaction of pyrazine-2,3-dinitrile with hydrazine gave 5,8-diaminopyrazino[2,3-*d*]pyridazine (X).

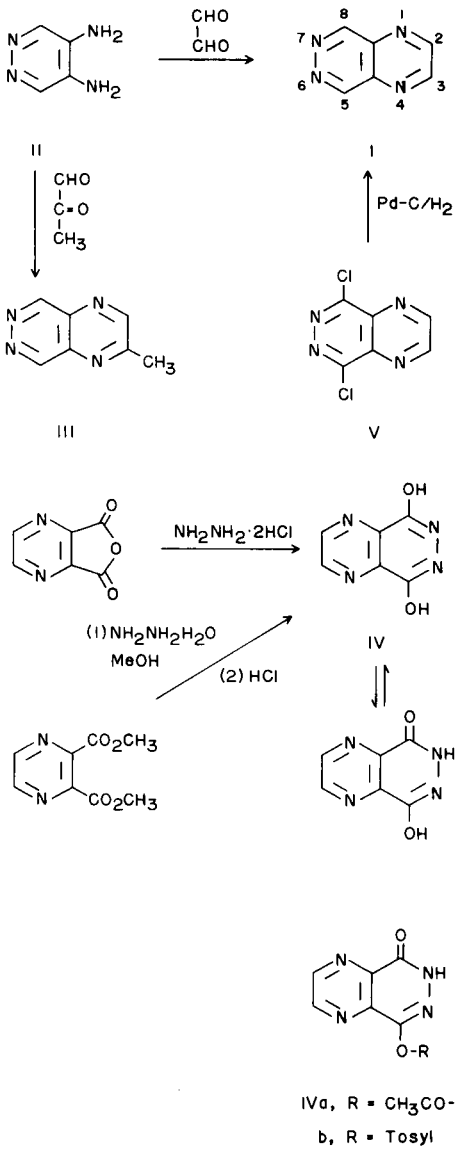
In the pyrazino[2,3-*d*]pyridazine (I) ring system only two compounds have previously been reported in the literature namely 5,8-dihydroxypyrazino-[2,3-*d*]pyridazine (IV) (1,2) and 5,8-bis(*p*-methoxyphenyl)pyrazino[2,3-*d*]pyridazine (3). This ring is of interest because of the close structural similarity to the pteridine ring system. The title compound (I) was synthesized by two different methods. These were (a) condensation of 4,5-diaminopyridazine (II) (4) with glyoxal in methanol (5) and (b) by dehalogenation of 5,8-dichloropyrazino[2,3-*d*]pyridazine (V) with palladium on charcoal. 2-Methylpyrazino-[2,3-*d*]pyridazine (III) was similarly prepared by allowing II to react with pyruvaldehyde.

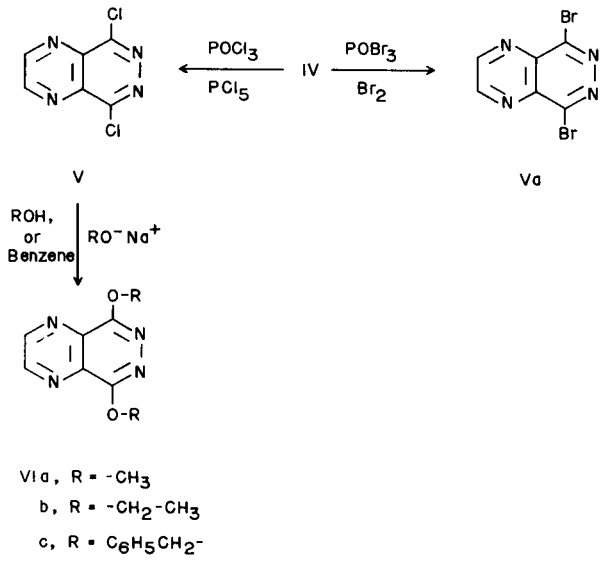
Compound IV was prepared by a slight modification of Hammerich's procedure (2) by using hydrazine dihydrochloride and water (6) instead of hydrazine hydrate and acetic acid. Similarly Jones' procedure (1) was also modified since in our hands erratic results were obtained. We have allowed dimethylpyrazine-2,3-dicarboxylate to react with hydrazine hydrate in methanol under reflux for a longer period of time and the insoluble hydrazonium salt was dissolved in water and IV was precipitated by acid (7).

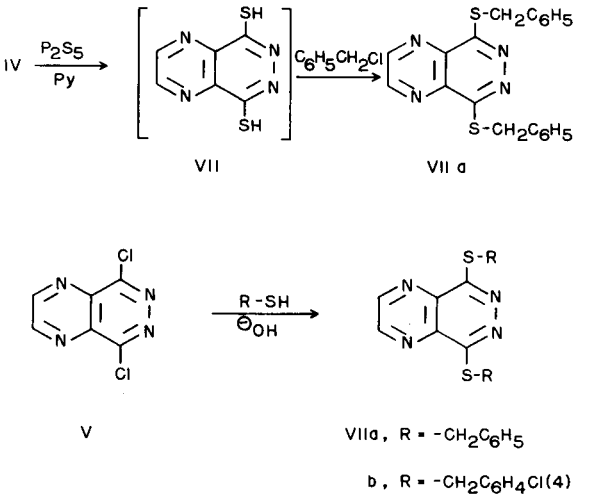
Compound IV failed to give the diacetate as was the case with 5,8-dihydroxypyridino[2,3-*d*]pyridazine observed by Gheorghiu (8), but it gave the monoacetate (IVa). Similarly, a monotosylate (IVb) was obtained when IV was treated with *p*-toluenesulfonyl chloride in pyridine. The spectroscopic data suggest that IVa and IVb exist in the keto forms.

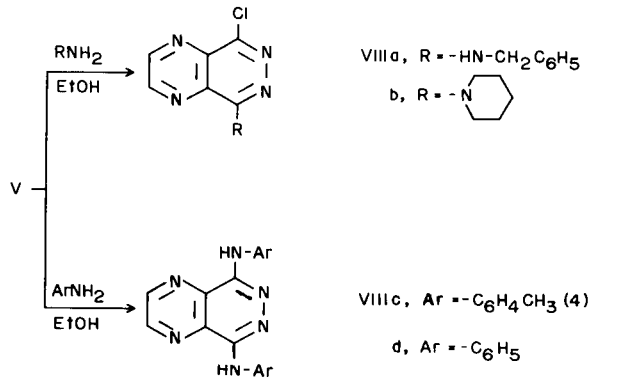
5,8-Dichloropyrazino[2,3-*d*]pyridazine was obtained when IV was allowed to react with a mixture of phosphorus oxychloride and phosphorus pentachloride (9). Similarly the 5,8-dibromopyrazino[2,3-*d*]-pyridazine was the product when IV was treated with phosphorus oxybromide and bromine (10).

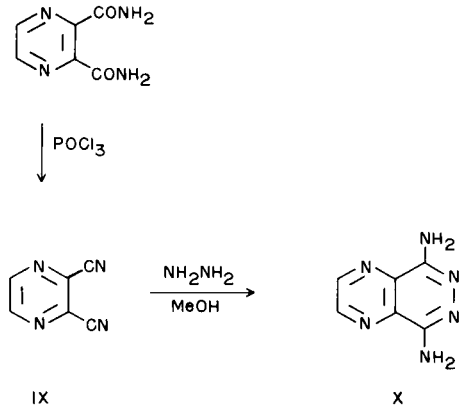
When V was treated with sodium alkoxides the corresponding 5,8-dialkoxypyrazino[2,3-*d*]pyridazines (VIa-c) were obtained in good yields (11). Attempts to prepare 5,8-dimercaptopyrazino[2,3-*d*]pyridazine



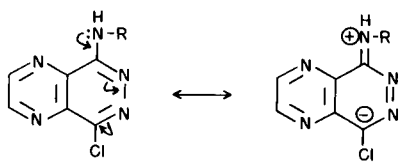








(VII) in pure form from the reaction of IV and phosphorus pentasulfide in pyridine (12) or by allowing V to react with thiourea followed by alkaline hydrolysis (11) were not successful. Yields of Compound VII were poor and the product was crude, however, it was possible to prepare 5,8-bis(benzylthio)pyrazino[2,3-*d*]pyridazine (VIIa) by the reaction of VII with benzyl chloride. Therefore in order to prepare compounds VIIa-c, Compound V was treated with benzyl mercaptan and substituted benzyl mercaptans in alkaline solution at room temperature (13). Compound VIIa obtained by the two methods was identical in all respects. The reaction of V with various amines gave interesting results. When V was allowed to react with weak bases, such as *p*-toluidine and aniline in ethanol, 5,8-disubstituted products VIIIc and VIIId were isolated. However, when V was treated with stronger bases such as piperidine and benzylamine in ethanol, monosubstituted products, VIIIa and VIIIb were obtained even though an excess of amine was used. Similar results have been observed with 3,6-dichloropyridazine (14) and 5,8-dichloropyrido[2,3-*d*]pyridazines (11). This can be explained on the basis of higher electron donating capacity of aliphatic amines compared with aromatic amines at C_5 after mono-substitution has taken place. The carbon atom at position 5 becomes more electronegative and hence the second nucleophilic attack at position 8 is prevented. The 5,8-diaminopyrazino[2,3-*d*]pyridazine



(X) was obtained by the condensation of pyrazine-2,3-dinitrile (IX) with hydrazine in methanol. The synthesis of IX has been reported previously (15) by the condensation of hydrocyanic acid tetramer with glyoxal. We have prepared IX by dehydration

of the readily available pyrazine-2,3-dicarboxamide in 84% yield. The infrared absorption band of the nitrile group at ~2250 cm^{-1} is weak in the dinitrile (IX). This has been observed previously (16) when electron-withdrawing groups are present adjacent to the carbon atom carrying the nitrile group.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Infrared, ultraviolet and NMR spectra were recorded on Perkin-Elmer 337, Bausch and Lomb Spectronic 505 and Varian A60 A spectrophotometers, respectively. Aluminum oxide, (Woelm, Neutral activity, Grade I) and silica gel (E. Merck, 0.05-0.20 mm.) were used for chromatographic purposes. The NMR spectra were compared with TMS as an internal standard except when deterium oxide was the solvent, then TMS was used as an external standard.

Pyrazino[2,3-*d*]pyridazine (I).

Method A.

4,5-Diaminopyridazine was obtained from its hydrochloride after neutralization of the methanolic solution with ammonia gas. The diamine (II) (0.296 g., 0.00269 mole) was dissolved in 15 ml. of methanol. A 40% aqueous solution of glyoxal (0.43 ml., 0.00296 mole) was added and the mixture refluxed for 5 hours. The reaction mixture was allowed to cool, and the methanol was removed using a rotatory evaporator. The residue was treated with 5 ml. of dry benzene and the mixture again evaporated to dryness to give a white residue. The residue was then extracted with 4 x 10 ml. of hot chloroform and unreacted diamine removed by filtration. Evaporation of the chloroform filtrate gave 0.1 g. (22%) of pyrazino[2,3-*d*]pyridazine (I). This material was purified by passing it through a column of alumina using ethyl acetate as eluent, and then recrystallization of the product from ethyl acetate (Norite) to give colorless flakes, m.p. 157.5-158.5°; U. V. λ max (95% ethanol), 219 (ε, 13,300), 284 (ε, 1,330), 295 mμ (ε, 980); infrared cm^{-1}, 3055(m), 2965(w), 1570(w), 1445(w), 1425(s), 1325(m), 1300(w), 1290(m), 1175(m), 1100(w), 1022(s), 968(s), 935(m), 854(w), 793(w), 637(w), 630(w), 548(w), 532(w), (KBr); N.M.R. spectrum ($CDCl_3$), 9.88 δ (C_5-H and C_8-H singlet), 9.23 δ (C_2-H and C_3-H singlet).

Anal. Calcd. for $C_6H_4N_4$: C, 54.54; H, 3.05; N, 42.40. Found: C, 54.57; H, 3.13; N, 42.33.

Method B.

To a solution of 5,8-dichloropyrazino[2,3-*d*]pyridazine (V) (0.201 g., 0.001 mole) in 30 ml. of methanol was added 0.4 ml. of concentrated ammonium hydroxide and 0.8 g. of 10% palladium on charcoal. The mixture was hydrogenated in a Parr apparatus at atmospheric pressure for 12 hours. The solution was filtered and evaporated to dryness. The residue was extracted with ethyl acetate and the solution was concentrated to a low volume. The product which separated was recrystallized from the same solvent to give colorless flakes, 0.040 g. (33%). The infrared and NMR spectra of this compound were identical with the spectra of the product obtained using Method A and a mixture melting point determination with the product from Method A showed no depression.

2-Methylpyrazino[2,3-*d*]pyridazine (III).

4,5-Diaminopyridazine (0.75 g., 0.0068 mole) was dissolved in 25 ml. of absolute ethanol, 1.1 ml. of a 45% aqueous solution (0.0068 mole) of pyruvaldehyde was added, and the mixture refluxed for one hour, during which time the color became reddish-brown. The reaction mixture was treated with Norite, filtered and evaporated to dryness. The residue was purified by passing through a silica gel column using ethyl acetate as eluent. The product was then recrystallized from ethyl acetate to give 0.45 g. (45%) of light pink needles, m.p. 172.5-174°; U. V. λ max (95% ethanol), 221 (ε, 16,200), 287 (ε, 1,530), 298 mμ (ε, 1,250); infrared cm^{-1}, 3030(w), 2975(w), 1580(m), 1555(w), 1430(m), 1365(w), 1340(m), 1320(w), 1272(w), 1215(w), 1170(w), 1045(w), 975(m), 932(m), 900(w), 805(w), 715(w), 640(m), 550(w), 540(w), 480(w), (KBr); N.M.R. spectrum ($CDCl_3$), 9.76 δ (C_5-H and C_8-H, singlet), 9.12 δ (C_2-H, singlet), 2.95 δ ($-CH_3$, singlet).

Anal. Calcd. for $C_7H_6N_4$: C, 57.51; H, 4.14; N, 38.34. Found: C, 57.15; H, 4.21; N, 38.45.

5,8-Dihydroxypyrazino[2,3-*d*]pyridazine (IV).

Method A.

A mixture containing 6.8 g. of 95% hydrazine and 40 ml. of water was cooled in an ice bath and 40 ml. of concentrated hydrochloric acid was added. To this continuously stirred solution, under reflux, was added 30 g. (0.2 mole) of pyrazine-2,3-dicarboxylic acid anhydride. The mixture was allowed to reflux for 3 hours, cooled and filtered. This residue was washed with water and dried to give 19.5 g. (60%) of brownish-yellow powder. Upon recrystallization of the product from water (Norite), golden yellow needles were obtained, m.p. > 240° dec., (Lit. (280° dec., (1) and 315° dec., (2)); U. V. λ max (95% ethanol), 206 (ε, 13,200), 265 mμ (ε, 10,150); infrared cm^{-1}, 3300(s), 3200(m), 3050(m), 2825(m), 2610(m), 2550(m), 1685(s), 1665(s), 1610(s), 1515(m), 1500(w), 1495(m), 1465(m), 1430(w), 1400(m), 1390(m), 1310(m), 1225(m), 1205(s), 1122(m), 1105(s), 1093(s), 1038(w), 1032(w), 907(w), 857(m), 783(s), 748(m), 705(w), 642(m), 635(w), 568(w), 483(m), 428(m), (KBr); N.M.R. spectrum (D_2O, base), 8.85 δ (C_2-H and C_3-H singlet).

Anal. Calcd. for $C_6H_4N_4O_2$: C, 43.90; H, 2.46; N, 34.14. Found: C, 43.77; H, 2.58; N, 34.52.

Method B.

To a solution of 3.92 g. (0.02 mole) of dimethyl pyrazine-2,3-dicarboxylate in 50 ml. of methanol was added with stirring 3 g. (0.06 mole) of hydrazine hydrate. The mixture was refluxed with stirring for one hour, cooled, the dark yellow hydrazine salt was separated by filtration and the solid was washed with methanol. This substance was suspended in 100 ml. of water, heated to 85° with stirring and acidified with concentrated hydrochloric acid to *p*H ~3. After stirring for 20 minutes at 85-90°, the mixture was cooled and the product was separated by filtration. The product was washed with water and dried to give 2.9 g. (88%) of IV. The product was recrystallized from water to give golden yellow needles, m.p. > 240° dec. The infrared spectrum of this compound was identical with the spectrum of the product obtained using Method A.

5-Acetyl-8(7*H*)-pyrazino[2,3-*d*]pyridazinone (IVa).

To 5 ml. of acetic anhydride was added 1 g. (0.06 mole) of IV in a round-bottomed flask, fitted with a condenser and drying tube. The reaction mixture was stirred magnetically and refluxed in an oil bath for 90 minutes, allowed to cool to room temperature, and then evaporated to dryness using a rotatory evaporator. The off-white residue was dried overnight in a vacuum oven at 70° to give a quantitative yield (1.25 g.) of white, powdery compound (IVa). This material was recrystallized from ethanol (Norite) to give white flakes, m.p. 221-223°; U. V. λ max (95% ethanol), 204 (ε, 8,350), 253 (ε, 6,250), 317 mμ (ε, 1,500); infrared cm^{-1}, 3160(m), 3080(m), 2845(w), 1775(s), 1715(s), 1650(m), 1600(w), 1555(w), 1550(w), 1445(m), 1415(w), 1380(m), 1320(m), 1212(s), 1193(s), 1130(m), 1088(s), 1029(m), 1010(w), 910(w), 891(m), 852(m), 833(m), 790(m), 640(w), 587(m), 508(m), 483(m), 430(m), (KBr).

Anal. Calcd. for $C_8H_6N_4O_3$: C, 46.61; H, 2.93; N, 27.18. Found: C, 46.68; H, 3.05; N, 27.17.

5-Tosyl-8(7*H*)-pyrazino[2,3-*d*]pyridazinone (IVb).

A solution of 0.164 g. (0.001 mole) of IV in 25 ml. of dry pyridine was obtained by warming the mixture. The solution was cooled, stirred magnetically and 0.38 g. (0.002 mole) of *p*-toluenesufonyl chloride was added. The mixture was stirred for 12 hours at room temperature under anhydrous conditions. The clear solution was added to 100 g. of crushed ice. After a few minutes, a white precipitate was obtained, filtered, dried and recrystallized from ethanol (Norite) to give 0.2 g. (63%) of white crystals, m.p. 235-236°; U. V. λ max (95% ethanol), 204 (ε, 16,000), 228 (ε, 12,000), 251 (ε, 8,420), 319 mμ (ε, 1,500); infrared cm^{-1}, 3175(m), 3050(m), 2980(w), 2850(w), 1705(s), 1600(m), 1550(w), 1495(w), 1450(m), 1380(m), 1360(s), 1318(m), 1248(w), 1198(s), 1188(s), 1128(w), 1078(s), 1030(w), 870(m), 818(s), 735(m), 717(m), 675(m), 640(s), 628(w), 580(w), 548(m), 525(w), 477(w), 427(m), (KBr).

Anal. Calcd. for $C_{13}H_{10}N_4O_4S$: C, 49.04; H, 3.16; N, 17.60; S, 10.08. Found: C, 49.15; H, 3.37; N, 17.38; S, 10.35.

5,8-Dichloropyrazino[2,3-*d*]pyridazine (V).

A mixture of 5,8-dihydroxypyrazino[2,3-*d*]pyridazine (IV) (8.5 g., 0.518 mole), 24 g. of phosphorus pentachloride and 135 ml. of phosphorus oxychloride was refluxed for 8 hours. The solvent was removed under reduced pressure, the residue treated with ice and made alkaline with sodium carbonate. The aqueous alkaline solution was extracted with 4 x 100 ml. of chloroform and the combined chloroform extracts were dried over anhydrous magnesium sulfate. The mag-

nesium sulfate was removed by filtration, and the chloroform was evaporated to dryness, to give 1.62 g. of crude 5,8-dichloropyrazino-[2,3-*d*]pyridazine (V). This was purified by passing it through a column containing 10 g. of alumina using benzene as the eluent to give 1.3 g. of pure white compound (V). The aqueous alkaline phase, after having been subjected to the chloroform extraction described above, was allowed to stand for 2 to 3 days at room temperature to give a yellow-brown precipitate which was removed from the aqueous phase by filtration and dried at ~90°. The residue was subjected to high vacuum sublimation at 125-135° to give an additional 1.83 g. of pure white compound (V). The total yield of V was 3.13 g. (33.5%). An analytical sample was prepared by recrystallization from ligroin (90-120° B.P.) to give a white cotton-like substance, m.p. 181-182°; U. V. λ max (95% ethanol), 203 (ε, 6,830), 236 (ε, 12,600), 290 mμ (ε, 2,450); infrared cm^{-1}, 3050(w), 1550(m), 1415(m), 1410(w), 1375(m), 1320(s), 1305(m), 1282(w), 1240(w), 1220(m), 1060(m), 1017(s), 1000(m), 965(w), 890(w), 844(w), 668(m), 628(m), 620(m), 543(w), 527(w), 420(m), (KBr); N.M.R. spectrum ($CDCl_3$), 9.42 δ (C_2-H and C_3-H singlet).

Anal. Calcd. for $C_6H_2Cl_2N_4$: C, 35.84; H, 1.00; N, 27.87. Found: C, 35.93; H, 1.19; N, 27.61.

5,8-Dibromopyrazino[2,3-*d*]pyridazine (Va).

In a glass mortar, 6.3 g. (0.384 mole) of IV and 33 g. of phosphorus oxybromide were mixed thoroughly and transferred to a round-bottomed flask, fitted with a condenser and calcium chloride drying tube. To this was added 9.45 g. of bromine and the mixture was heated 3 hours in an oil bath at 95-105°. The excess bromine and phosphorus oxybromide were removed from the reaction mixture by evaporation under reduced pressure, first by employing a water aspirator and then a mechanical pump. The residue was cooled in an ice bath and ice water was added. The aqueous solution was made alkaline with sodium carbonate and extracted with 5 x 70 ml. of chloroform. The combined chloroform extracts were dried over anhydrous magnesium sulfate, the magnesium sulfate was removed by filtration, and the chloroform filtrate was evaporated to dryness to give a brown-yellow residue. The residue was purified by passing it through a column containing 10 g. of alumina using benzene as eluent to give 1.2 g. (10.8%) of white 5,8-dibromopyrazino[2,3-*d*]-pyridazine (Va). Compound Va was recrystallized from ligroin (90-120° B.P.), m.p. 195° as long thin crystals; U. V. λ max (95% ethanol), 205 (ε, 10,100), 247 (ε, 14,100), 291 mμ (ε, 5,660); infrared cm^{-1}, 3050(w), 1560(w), 1550(m), 1530(w), 1410(m), 1370(m), 1325(m), 1312(s), 1304(m), 1265(w), 1243(w), 1213(m), 1053(m), 998(s), 924(w), 891(m), 652(w), 588(m), 542(w), 483(m), 418(m), (KBr); N.M.R. spectrum ($CDCl_3$), 9.31 δ (C_2-H and C_3-H singlet).

Anal. Calcd. for $C_6H_2Br_2N_4$: C, 24.85; H, 0.70; N, 19.32. Found: C, 25.30 and 25.37; H, 1.03; N, 19.11.

5,8-Dimethoxypyrazino[2,3-*d*]pyridazine (VIa).

To a solution of sodium methoxide, prepared from 0.2 g. of sodium in 10 ml. of anhydrous methanol was added 0.201 g. (0.001 mole) of 5,8-dichloropyrazino[2,3-*d*]pyridazine (V). The solution was heated under reflux on a steam bath for one hour, cooled and filtered to remove insoluble material. The residue was washed with water and dried to give 0.17 g. (89%) of compound (VIa). The compound was purified by elution through an alumina column using ethyl acetate as eluent. The product was recrystallized from methanol to give white crystals, m.p. 278-280°; U. V. λ max (95% ethanol), 205 (ε, 8,230), 255 mμ (ε, 19,090); infrared cm^{-1}, 3040(w), 2980(w), 2935(w), 1520(m), 1500(w), 1475(s), 1470(m), 1395(s), 1350(m), 1330(m), 1250(w), 1238(m), 1210(m), 1185(s), 1160(w), 1120(m), 1110(s), 1088(m), 980(m), 957(m), 903(w), 858(w), 762(m), 708(w), 681(m), 485(w), 430(s), (KBr); N.M.R. spectrum ($CDCl_3$), 9.18 δ (C_2-H and C_3-H singlet), 4.34 δ (O-CH_3, singlet).

Anal. Calcd. for $C_8H_8N_4O_2$: C, 50.00; H, 4.20; N, 29.15. Found: C, 49.99; H, 3.99; N, 29.14.

5,8-Diethoxypyrazino[2,3-*d*]pyridazine (VIb).

A procedure identical to that used for the preparation of compound VIa was employed, except that anhydrous ethanol was used in place of methanol. The reaction mixture was processed in the same manner as for compound VIa to give 0.167 g. (76%) of white crystalline compound (VIb). The compound was sublimed at 5 x 10^{-3} mm. of mercury and at 150° in order to prepare the analytical sample, white powder, m.p. 232-234°; U. V. λ max (95% ethanol), 205.5 (ε, 8,760), 256.5 mμ (ε, 19,920); infrared cm^{-1}, 3030(w), 2990(m), 2920(w), 2900(w), 1515(m), 1500(m), 1480(m), 1470(m), 1450(s), 1430(s), 1380(s), 1370(m), 1340(s), 1248(m), 1240(m), 1205(m), 1163(m), 1125(s), 1110(s), 1087(w), 1030(m), 1018(m), 1010(m), 918(m), 908(m), 883(m), 860(m), 823(w), 789(s), 723(w), 687(m), 520(m), 447(s), (KBr); N.M.R. spectrum ($CDCl_3$), 9.18 δ (C_2-H and C_3-H, singlet), 4.78 δ (O-CH_2-, quartet), 1.60 δ (-C-CH_3 triplet).

Anal. Calcd. for $C_{10}H_{12}N_4O_2$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.80; H, 5.52; N, 25.11.

5,8-Bis(benzyloxy)pyrazino[2,3-*d*]pyridazine (VIc).

A solution of sodium benzyloxide was prepared by refluxing on a steam bath a mixture of 15 ml. of dry benzene, 0.45 ml. of benzyl alcohol and 0.1 g. of sodium metal. To this was added 0.201 g. (0.001 mole) of 5,8-dichloropyrazino[2,3-*d*]pyridazine (V), and the mixture was refluxed for one hour. The solution was cooled, filtered and the product was washed with water and dried to give 0.22 g. (64%) of white compound (VIc). The compound was recrystallized from methanol (Norite) to give white crystals, m.p. 239-241°; U.V. λ max (95% ethanol), 208 (ε, 28,710), 256 mμ (ε, 17,970); infrared cm^{-1}, 3090(w), 3065(w), 3025(m), 2945(w), 2880(w), 1585(w), 1570(m), 1550(m), 1500(m), 1475(m), 1465(s), 1450(s), 1380(m), 1360(s), 1340(m), 1248(w), 1239(m), 1205(w), 1127(m), 1110(s), 1100(s), 1082(w), 1038(w), 963(m), 950(m), 919(w), 910(m), 848(m), 790(w), 750(s), 721(m), 695(s), 682(m), 633(m), 587(w), 563(m), 518(m), 500(w), 430(s), (KBr); N.M.R. spectrum ($CDCl_3$), 9.18 δ (C_2-H and C_3-H, singlet), 7.3-7.7 δ (phenyl protons, multiplets), 5.8 δ (benzylic -CH_2-, singlet).

Anal. Calcd. for $C_{20}H_{16}N_4O_2$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.72; H, 4.84; N, 16.20.

5,8-Bis(benzylthio)pyrazino[2,3-*d*]pyridazine (VIIa).

Method A.

To a suspension of 5,8-dihydroxypyrazino[2,3-*d*]pyridazine (IV) (5.0 g., 0.304 mole) in 250 ml. of dry pyridine was added 14.0 g. of phosphorus pentasulfide. The mixture was refluxed for 3 hours and excess pyridine was removed under reduced pressure. Ice water was added to the residue and the aqueous mixture was heated on a steam bath for 3 hours. The mixture was cooled and a 10% aqueous solution of sodium hydroxide was added until most of the black residue dissolved. The solution was filtered, and the filtrate made acidic (*p*H 1-2) with concentrated hydrochloric acid, whereby a gray precipitate was obtained. The gray precipitate was separated by filtration, dissolved in aqueous 10% sodium hydroxide and the solution was filtered. The gray material reprecipitated from the filtrate by addition of concentrated hydrochloric acid to give 5.2 g. of compound (VII). Compound VII (3.6 g., 0.0184 mole) was dissolved in 60 ml. of 1*N* aqueous potassium hydroxide and the solution was filtered. The filtrate was stirred magnetically at room temperature and to this solution was added dropwise a solution of 3.0 g. (0.037 mole) of benzyl chloride in 50 ml. of ethanol. The reaction mixture was refluxed for 90 minutes, cooled to room temperature and filtered to give 3 g. of a black residue. This substance was dried and then purified by elution through an alumina column using benzene as eluent to give 0.2 g. (2%) of VIIa, yellow crystals, m.p. 261-262° from benzene; U. V. λ max (95% ethanol), 206 (ε, 22,400), 255.5 (ε, 12,870), 304 mμ (ε, 1,650); infrared cm^{-1}, 3080(w), 3060(w), 3025(w), 1565(w), 1505(w), 1495(m), 1450(m), 1415(m), 1400(w), 1355(w), 1320(s), 1291(m), 1280(w), 1235(w), 1215(w), 1183(w), 1068(w), 1054(m), 1029(s), 1020(m), 968(w), 910(w), 893(w), 850(w), 812(w), 773(w), 708(m), 690(s), 669(m), 612(w), 580(w), 542(w), 480(m), 418(m), (KBr).

Anal. Calcd. for $C_{20}H_{16}N_4S_2$: C, 63.80; H, 4.28; N, 14.88. Found: C, 63.97; H, 4.53; N, 15.16.

Method B.

A mixture of 6 ml. of 5% aqueous sodium hydroxide, 5 ml. of 28% ammonium hydroxide, 15 ml. of ethanol and 0.7 ml. (0.006 mole) of benzylmercaptan was stirred magnetically at room temperature. To this solution was added dropwise 0.5 g. (0.00249 mole) of the 5,8-dichloropyrazino[2,3-*d*]pyridazine (V) dissolved in 50 ml. of hot ethanol. The reaction mixture was stirred at room temperature for 24 hours. The yellow precipitate which formed was removed by filtration and dried to give 0.9 g. (95%) of VIIa, yellow flakes from benzene. The infrared spectrum of this compound was identical with the spectrum of the product obtained using Method A and a mixed melting point with the product from Method A showed no depression. N.M.R. spectrum ($CDCl_3$), 9.03 δ (C_2-H and C_3-H, singlet), 7.2-7.62 δ (phenyl protons, multiplet), 4.7 δ (benzylic-CH_2-, singlet).

5,8-Bis(*p*-chlorobenzylthio)pyrazino[2,3-*d*]pyridazine (VIIb).

The procedure employed in the preparation of compound VIIa, Method B, was used except that *p*-chlorobenzylmercaptan was used in place of benzylmercaptan to give an 87% yield of VIIb, yellow flakes, m.p. 207-208° from benzene; U.V. λ max (95% ethanol), 203.5 (ε, 38,260), 221.5 (ε, 32,150), 255 (ε, 22,350), 301 mμ (ε, 4,880); infrared cm^{-1},

3035(w), 1600(w), 1560(w), 1495(s), 1435(w), 1420(m), 1410(m), 1360(w), 1323(s), 1294(m), 1283(w), 1238(w), 1226(w), 1218(w), 1196(w), 1101(m), 1056(m), 1028(m), 1023(s), 968(w), 895(w), 835(m), 808(w), 735(w), 670(w), 612(m), 550(w), 503(m), 416(m), (KBr); N.M.R. spectrum ($CDCl_3$), 9.06 δ (C_2-H and C_3-H, singlet), 7.48 δ (C_3'-H and C_5'-H doublet, J = 9 cps), 7.27 δ (C_2'-H and C_6'-H, doublet, J = 9 cps), 4.65 δ (benzylic-CH_2-, singlet).

Anal. Calcd. for $C_{20}H_{14}Cl_2N_4S_2$: C, 53.93; H, 3.17; N, 12.58. Found: C, 54.32; H, 3.36; N, 12.63.

5,8-Bis(3,4-dichlorobenzylthio)pyrazino[2,3-*d*]pyridazine (VIIc).

The procedure employed in the preparation of compound VIIa, Method B, was used except that 3,4-dichlorobenzylmercaptan was used in place of benzylmercaptan to give an 87% yield of VIIIc, yellow flakes, m.p. 199-200° from benzene; U.V. λ max (95% ethanol), 205 (ε, 74,780), 228(sh) (ε, 35,080), 255 (ε, 20,680), 301 mμ (ε, 5,000); infrared cm^{-1}, 3050(w), 1600(w), 1570(w), 1560(w), 1510(w), 1475(s), 1430(w), 1420(m), 1400(m), 1395(w), 1325(s), 1295(w), 1285(w), 1239(m), 1219(w), 1135(m), 1057(m), 1040(m), 1030(m), 1022(m), 970(w), 900(m), 878(m), 825(m), 748(m), 690(m), 670(w), 615(m), 565(w), 603(w), 460(w), 443(w), 418(m), (KBr); N.M.R. spectrum ($CDCl_3$), 9.08 δ (C_2-H and C_3-H, singlet), 7.63 δ (C_5'-H, singlet), 7.38 δ (C_2'-H and C_6'-H, singlet), 4.63 δ (benzylic-CH_2-, singlet).

Anal. Calcd. for $C_{20}H_{12}Cl_4N_4S_2$: C, 46.71; H, 2.35; N, 10.89. Found: C, 46.84; H, 2.36; N, 11.06.

5,8-Bis(phenylthio)pyrazino[2,3-*d*]pyridazine (VIId).

A mixture of sodium hydroxide (0.08 g., 0.002 mole), thiophenol (0.33 g., 0.003 mole) and 10 ml. of ethanol was stirred at room temperature, and to it was added dropwise a solution of 0.201 g. (0.001 mole) of 5,8-dichloropyrazino[2,3-*d*]pyridazine (V) in 15 ml. of ethanol. The reaction mixture was stirred at room temperature for 18 hours, refluxed for 2 hours, and cooled to room temperature. A yellow, insoluble product, VIId was isolated in quantitative yield by filtration. This compound was purified by elution through a column of alumina using benzene as eluent followed by recrystallization of the product from benzene to give yellow plates, m.p. 260-261°; U.V. λ max (95% ethanol), 206 (ε, 59,300), 220(sh) (ε, 47,500), 243 (ε, 26,800), 260(sh) (ε, 22,600), 300 mμ (ε, 8,350); infrared cm^{-1}, 3060(m), 1575(w), 1560(m), 1515(w), 1480(m), 1445(m), 1420(m), 1410(m), 1365(w), 1320(s), 1296(m), 1280(w), 1220(w), 1185(w), 1088(w), 1069(w), 1055(m), 1019(s), 1003(m), 951(w), 904(w), 848(w), 748(s), 706(m), 688(s), 669(m), 620(w), 604(m), 560(m), 487(w), 470(w), 416(m), (KBr); N.M.R. spectrum ($CDCl_3$), 9.23 δ (C_2-H and C_3-H, singlet), 5.6-6.28 δ (phenyl protons, multiplet).

Anal. Calcd. for $C_{18}H_{12}N_4S_2$: C, 62.04; H, 3.47; N, 16.08. Found: C, 62.01; H, 3.50; N, 15.71.

5-Chloro-8-benzylaminopyrazino[2,3-*d*]pyridazine (VIIIa).

A mixture of 5,8-dichloropyrazino[2,3-*d*]pyridazine (V) (0.201 g., 0.001 mole), benzylamine (0.328 g., 0.004 mole) and 10 ml. of ethanol was refluxed for 4 hours, allowed to cool to room temperature, and made alkaline with ammonium hydroxide. An insoluble material was removed from the reaction mixture by filtration. The product was washed with water and dried to give 0.25 g. (91%) of crude, orange-red compound (VIIIa). This compound was purified by elution through a column of alumina using benzene:ethyl acetate (1:1) as eluent followed by recrystallization of the product from ethanol to give bright orange flakes, m.p. 197-198°; U.V. λ max (95% ethanol), 210.5 (ε, 13,650), 224.5(sh) (ε, 12,550), 264 mμ (ε, 5,420); infrared cm^{-1}, 3410(s), 3030(m), 2925(w), 2875(w), 1580(s), 1550(m), 1520(s), 1460(m), 1450(m), 1425(m), 1410(s), 1390(s), 1365(s), 1310(m), 1235(m), 1210(w), 1155(w), 1130(w), 1097(m), 1080(w), 1045(w), 1028(w), 1018(m), 995(s), 920(w), 898(w), 832(m), 822(w), 767(m), 748(m), 700(s), 667(m), 575(m), 540(m), 507(m), 490(w), 445(m), 435(m), (KBr); N.M.R. spectrum ($CDCl_3$), 9.16 δ (C_3-H, doublet, J = 2 cps), 8.95 δ (C_2-H, doublet, J = 2 cps), 7.2-7.44 δ (phenyl protons, multiplet), 6.75 δ (-N-H, broad peak), 4.91 δ (benzylic-CH_2- doublet, J = 5.8 cps, gives a singlet at 4.91 on addition of a drop of D_2O).

Anal. Calcd. for $C_{13}H_{10}ClN_5$: C, 57.46; H, 3.71; N, 25.77. Found: C, 57.57; H, 3.88; N, 25.50.

5-Chloro-8-piperidinopyrazino[2,3-*d*]pyridazine (VIIIb).

The procedure employed in the preparation of compound VIIIa was used except that piperidine was used in place of benzylamine and the molar ratio of compound V to piperidine was 1:2. The product (VIIIb) was obtained in 74% yield. It was purified by elution through an alumina column using benzene as eluent, followed by recrystallization of the product from ethanol to give yellow crystals, m.p. 184-185°; U. V. λ max (95% ethanol), 211 (ε, 15,430), 220(sh) (ε, 14,820), 248 (ε, 11,410), 270(sh) mμ (ε, 7,440); infrared cm^{-1}, 2940(m), 2850(m), 1625(w), 1555(m), 1500(s), 1460(w), 1450(m), 1440(m), 1415(m), 1405(m), 1350(w), 1340(m), 1320(m), 1293(s), 1265(w), 1255(m), 1237(w), 1130(w), 1122(m), 1085(m), 1035(w), 1020(m), 993(w), 898(w), 890(m), 849(m), 822(m), 693(w), 680(w), 650(m), 550(w), 480(w), 455(w), 437(m), (KBr); N.M.R. spectrum ($CDCl_3$), 9.15 δ (C_3-H, doublet, J = 1.6 cps), 9.06 δ (C_2-H, doublet, J = 1.6 cps), 3.94-4.66 δ (C_2'-H and C_6'-H, broad peak), 1.78 δ (C_3'-H, C_4'-H, C_4'-H and C_5'-H, singlet).

Anal. Calcd. for $C_{11}H_{12}ClN_5$: C, 52.90; H, 4.85; N, 28.05. Found: C, 52.70; H, 5.15; N, 28.23.

5,8-Di-*p*-toluidinopyrazino[2,3-*d*]pyridazine (VIIIc).

The procedure employed in the preparation of compound VIIIa was used except that *p*-toluidine was used in place of benzylamine and the molar ratio of compound V to *p*-toluidine was 1:2. The product (VIIIc) which was obtained in 88% yield, was purified by elution through an alumina column using benzene:ethyl acetate (1:1) as eluent, followed by recrystallization from ethanol to give red needles, m.p. 271-272°; U. V. λ max (95% ethanol), 203 (ε, 23,160), 223 (ε, 7,750), 280 mμ (ε, 22,050); infrared cm^{-1}, 3380(s), 3010(w), 2910(w), 2850(w), 1610(m), 1595(s), 1555(m), 1535(s), 1515(s), 1530(s), 1495(m), 1310(m), 1295(w), 1245(w), 1233(m), 1212(w), 1180(w), 1120(w), 1107(w), 1093(m), 1035(w), 1012(w), 930(w), 902(w), 895(w), 850(w), 806(s), 772(w), 740(w), 700(w), 665(w), 650(w), 635(w), 565(m), 520(w), 508(m), 493(s), 432(m), (KBr); N.M.R. spectrum ($CDCl_3$), 8.95 δ (C_2-H and C_3-H, singlet), 7.15 δ (-N-H, broad peak), 7.6 δ (C_3'-H and C_5'-H, doublet, J = 8.5 cps), 7.12 δ (C_2'-H and C_6'-H, doublet, J = 8.5 cps).

Anal. Calcd. for $C_{20}H_{18}N_6$: C, 70.13; H, 5.30; N, 24.55. Found: C, 70.21; H, 5.44; N, 24.46.

5,8-Dianilinopyrazino[2,3-*d*]pyridazine (VIIId).

The procedure employed in the preparation of compound VIIIa was used except that aniline was used in place of benzylamine and the molar ratio of compound V to aniline was 1:2. The product (VIIId) was obtained in 87% yield and was purified by eluting it through a column of alumina using benzene as eluent, followed by recrystallization of the product from ethanol to give bright red needles, m.p. 242-243°; U.V. λ max (95% ethanol), 206 (ε, 29,550), 227(sh) (ε, 17,050), 281 (ε, 35,030), 291(sh) mμ (ε, 31,700); infrared cm^{-1}, 3380(s), 3040(w), 3020(w), 1600(s), 1550(s), 1520(s), 1495(s), 1445(s), 1430(s), 1400(m), 1370(w), 1335(w), 1312(m), 1240(s), 1212(w), 1167(w), 1093(w), 1093(m), 1018(w), 995(w), 888(w), 865(w), 842(w), 812(m), 757(s), 747(s), 690(s), 575(m), 550(m), 541(m), 505(m), 435(m), (KBr).

Anal. Calcd. for $C_{18}H_{14}N_6$: C, 68.77; H, 4.49; N, 26.74. Found: C, 68.90; H, 4.64; N, 26.64.

Pyrazine-2,3-dinitrile (IX).

Pyrazine-2,3-dicarboxamide (1.66 g., 0.01 mole) was suspended in 15 ml. of phosphorus oxychloride, the mixture stirred at room temperature for 5 hours and then refluxed for 80 minutes. The excess of phosphorus oxychloride was removed under reduced pressure and the residue was dried over sodium hydroxide in an evacuated desicator. The residue was suspended in 40 ml. of saturated sodium carbonate solution at 5° and the aqueous alkaline solution was extracted with 5 x 50 ml. of ether. The combined ether extracts were washed with 15 ml. of a saturated aqueous sodium chloride solution. The ethereal solution was dried over anhydrous sodium sulfate. The sodium sulfate was removed by filtration and the ether evaporated to give 1.1 g. (84%) of pyrazine-2,3-dinitrile (IX), snow-white needles, m.p. 131-132° from water (Lit. 132°, (15)); U.V. λ max (95% ethanol), 207(sh) (ε, 4,650), 229 (ε, 9,630), 240(sh) (ε, 6,540), 274.5 (ε, 5,550), 280.5(sh) mμ (ε, 5,140); infrared cm^{-1}, 3100(w), 3070(w), 2230(w), 1975(w), 1800(w), 1550(m), 1520(w), 1415(w), 1395(s), 1360(w), 1180(m), 1142(w), 1121(s), 1053(s), 874(s), 862(m), 693(w), 612(m), 572(w), 470(w), (KBr); N.M.R. spectrum ($CDCl_3$), 8.53 δ (C_5-H and C_6-H, singlet).

Anal. Calcd. for $C_8H_2N_4$: C, 55.37; H, 1.55; N, 43.07. Found: C, 55.48; H, 1.63; N, 43.29.

5,8-Diaminopyrazino[2,3-*d*]pyridazine (X).

A solution of pyrazine-2,3-dinitrile (IX) (0.31 g., 0.00238 mole) and 10 ml. of absolute methanol was stirred magnetically at room temperature, and to it was added dropwise 0.6 ml. of hydrazine (95%). The reaction mixture was stirred overnight at room temperature, and 0.3 g. (77%) of brown product (X) was isolated by filtration. Recrystallization of the product from water (Norite) gave yellow micro needles, m.p. 233-234° dec.; U. V. λ max (95% ethanol), 220 (ε, 14,300), 273 mμ (ε, 11,200); infrared cm^{-1}, 3440(s), 3260(s), 3225(s),

3125(s), 1610(s), 1545(w), 1465(s), 1365(m), 1270(w), 1203(w), 1150(m), 1087(m), 1052(s), 1000(w), 880(m), 865(m), 803(w), 702(m), 692(m), 670(m), 600(w), 559(w), 493(m), 438(s), (KBr).

Anal. Calcd. for $C_6H_6N_6$: C, 44.44; H, 3.73; N, 51.84. Found: C, 44.32; H, 3.96; N, 51.91.

Acknowledgment.

This investigation was supported by a PHS Grant No. CA-04327-07 from the National Cancer Institute, Public Health Service. The authors are grateful to Mrs. Ruby Ju and Mr. S. Martin for the infrared and ultraviolet spectra and analytical data reported. We wish to thank Miss D. Dotavio for the preparation of some of the starting materials.

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Received October 25, 1966 Albuquerque, New Mexico 87106