The Synthesis of Pyrazines, Pyrazino[2,3-*d*]pyridazines and a Dipyridazino[4,5-*b*:4′,5′-*e*]pyrazine

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The chemistry of pyrazino[2,3-*d*]pyridazines has not been extensively studied. The first reported compound was pyrazino[2,3-*d*]pyridazine-5,8-dione prepared by Jones (2) and later reported by Hemmerich and Fallab (3). The second pyrazino[2,3-*d*]pyridazine reported was 5,8-bis(*p*-methoxyphenyl)pyrazino[2,3-*d*]pyridazine (4).

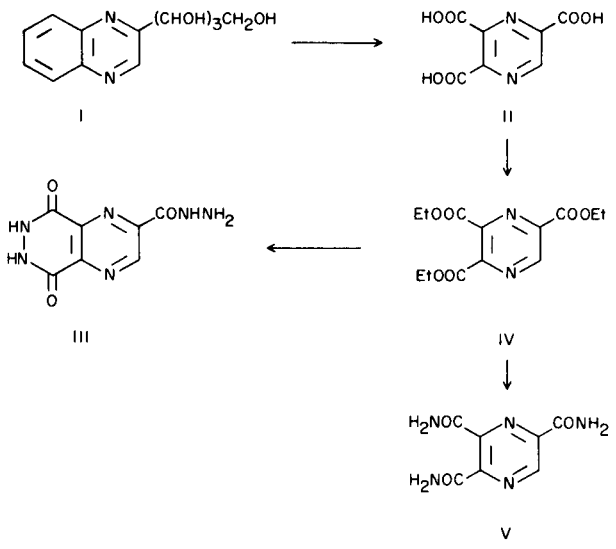
More recently from this laboratory we have reported the synthesis of a number of pyrazino[2,3-*d*]pyridazines including the parent compound (5). In a later report from this laboratory (6) we have extended this work with the synthesis of several additional pyrazino[2,3-*d*]pyridazines including 1,2,3,4-tetrahydropyrazino[2,3-*d*]pyridazin-5-one. Another pyrazino[2,3-*d*]pyridazine has been reported by Spiro, *et al.* (7).

The purpose of the present work was to extend the synthesis to additional pyrazino[2,3-*d*]pyridazines and to prepared an example of the novel dipyridazino[4,5-*b*:4′,5′-*e*]-pyrazine ring system. In order to accomplish this objective several new pyrazines were required as intermediates.

For the synthesis of pyrazino[2,3-*d*]pyridazine-5,8-dione-2-carboxhydrazide (III), 2-(D-arabino)tetrahydroxybutylquinoxaline (I) (8) was subjected to permanganate oxidation. Pyrazine-2,3,5-tricarboxylic acid (II) (9) was obtained in 70-80% yield. Compound II was readily converted into triethyl pyrazine-2,3,5-tricarboxylate (IV) in 68% yield. The triester (IV) when allowed to react with methanolic hydrazine gave pyrazino[2,3-*d*]pyridazine-5,8-dione-2-carboxhydrazide (III) in 74% yield. The action of methanolic ammonia on the triester (IV) readily produced pyrazine-2,3,5-tricarboxamide (V) in 99% yield. These transformations are outlined in Flow Sheet I.

For the synthesis of 2-aminopyrazino[2,3-*d*]pyridazine-5,8-dione (XI), pyrimido[4,5-*b*]quinoxaline-2,4-dione (VI) (10) gave 2-aminoquinoxaline (VII) (10) in 45% yield upon hydrolytic decarboxylation. Acetylation of VII gave 2-acetylaminoquinoxaline (IX) (10). Permanganate oxidation of IX gave 2-aminopyrazine-5,6-dicarboxylic acid (VIII) (11). The acid (VIII) was smoothly esterfied with ethanolic hydrogen chloride to give diethyl 2-aminopyrazine-5,6-dicarboxylate (X) in 56% yield. With methanolic hydrazine the diester (X) gave 2-aminopyrazino[2,3-*d*]pyridazine-5,8-dione (XI) in 40% yield. This sequence of reactions is outlined in Flow Sheet II.

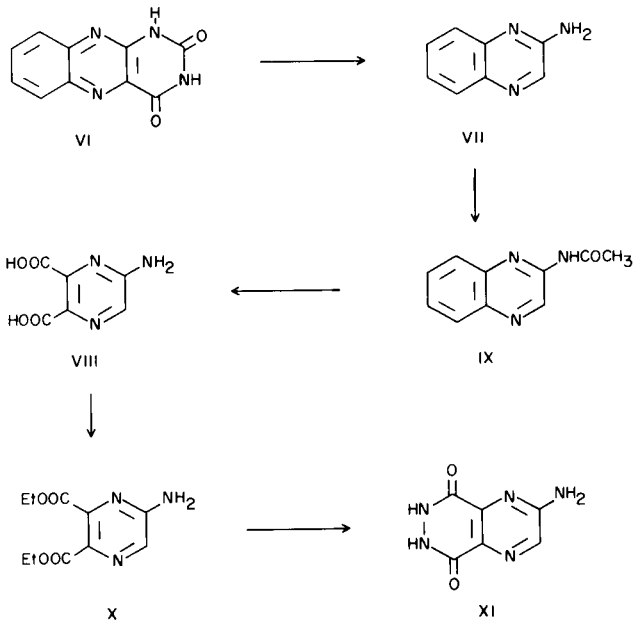
FLOW SHEET I



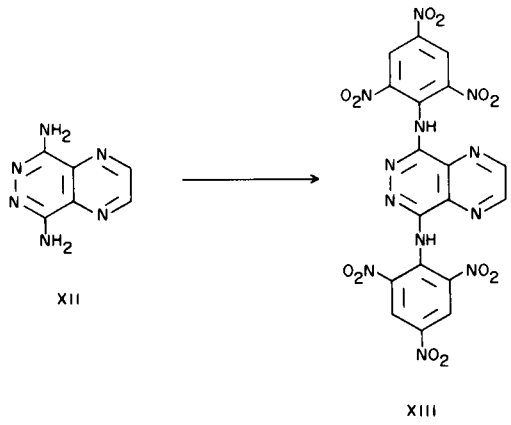
5,8-Diaminopyrazino[2,3-*d*]pyridazine (XII) (5) was treated with picryl fluoride in dimethyl sulfoxide. The product was 5,8-bispicrylaminopyrazino[2,3-*d*]pyridazine (XIII). This transformation is shown in Flow Sheet III.

o-Phenylenediamine (XIV) served as the starting material for the synthesis of dipyridazino[4,5-*b*:4′,5′-*e*]pyrazine-1,4,6,9-tetrone (XIX). Ferric chloride oxidation of XIV gave 2,3-diaminophenazine (XV) (12). Permanganate oxidation of XV gave pyrazine-2,3,5,6-tetracarboxylic acid (XVII) (12). Ethanolic hydrogen chloride converted the acid (XVII) to tetraethyl pyrazine-2,3,5,6-tetracarboxylate (XVI) in 70% yield. The ester (XVI) was treated with methanolic hydrazine. The product was pyrazine-2,3,5,6-tetracarboxyhydrazide (XVIII) in quantitative yield.

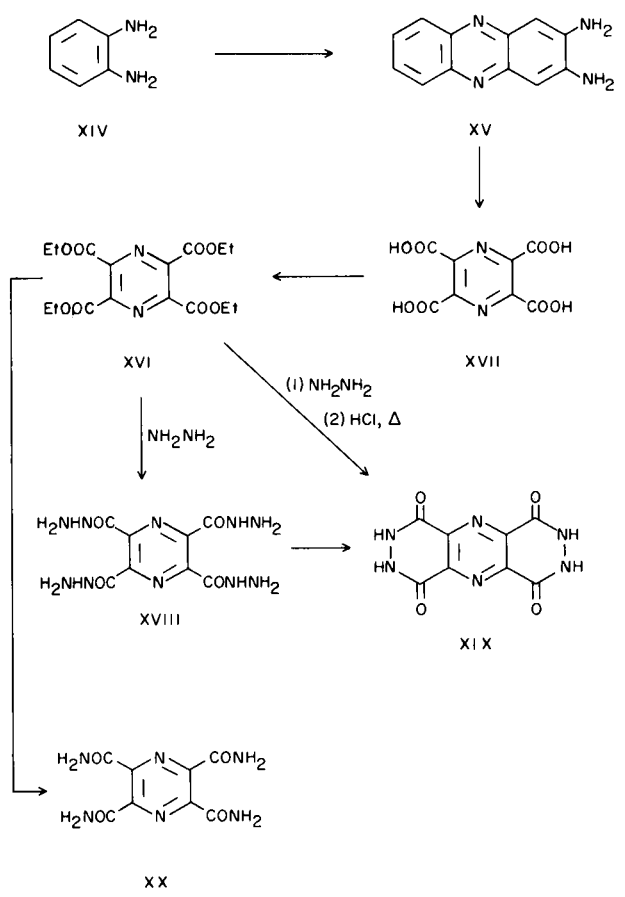
FLOW SHEET II



FLOW SHEET III



FLOW SHEET IV



Dipyridazino[4,5-*b*:4′,5′-*e*]pyrazine-1,4,6,9-tetrone (XIX) was prepared from XVIII by refluxing with 10% hydrochloric acid in 60% yield. Compound XIX was also prepared from XVI by treatment with methanolic hydrazine followed by heating with hydrochloric acid. The yield by the latter method was 60%. The action of methanolic ammonia on the tetraester (XVI) gave pyrazine-2,3,5,6-tetracarboxamide (XX) in 99% yield. This sequence of reactions are outlined in Flow Sheet IV.

EXPERIMENTAL (13)

2-(D-Arabino)tetrahydroxybutylquinoxaline (I) was prepared by the method of Weygand and Bergmann (8), m.p. 192° [lit. (8) 182-183° (crude)] and pyrazine-2,3,5-tricarboxylic acid (II) was prepared by the permanganate oxidation of I following the method described by Mager and Berends (9), m.p. 190° [lit. (9) 190°].

Triethyl Pyrazine-2,3,5-tricarboxylate (IV).

Ten g. (0.05 mole) of pyrazine-2,3,5-tricarboxylic acid (II) (9) dissolved in 200 ml. of absolute ethanol was saturated with dry hydrogen chloride for 0.5 hour with external cooling. The solution was heated under reflux on the steam bath for 14 hours. The solvent was evaporated under reduced pressure and about 100 ml. of water was added to the residue. The aqueous solution was extracted three times with about 125 ml. of ether and the ether extract was washed with 10% sodium bicarbonate solution (~ 50 ml.) then washed with water, dried over anhydrous magnesium sulfate, filtered and evaporated. The pale yellow viscous liquid was distilled, b. p. 135-137°, 0.4 mm, yield 10 g. (68%) of colorless liquid; UV λ max (95% ethanol), 217 (ε, 7,600), 275 mμ (ε, 7,300); infrared cm^{-1}; 2980(s), 2940(m), 1750(m), 1725(s), 1475(m), 1450(m), 1375(m), 1295(m), 1280(m), 1225(m), 1160(w), 1090(s), 1020(m), 940(w), 850(m), 770(m), 750(w);

NMR (deuteriochloroform) singlet δ 9.41 (=C*H*), two quartets δ 4.6, δ 4.55 (3-O-CH_2-) and two triplets δ 1.5, δ 1.6 (3-OCH_2-CH_3).

In subsequent experiments the ester was cyclized satisfactorily into III without distillation.

Anal. Calcd. for $C_{13}H_{16}N_2O_6$: C, 52.70; H, 5.44; N, 9.45. Found: C, 52.67; H, 5.73; N, 9.45.

Pyrazino[2,3-*d*]pyridazine-5,8-dione-2-carboxhydrazide (III).

To a solution containing 5.92 g. (0.02 mole) of triethyl pyrazine-2,3,5-tricarboxylate (IV) in 100 ml. of methanol was added slowly with stirring 2.0 g. (0.06 mole) of 95% hydrazine. The orange solution was heated on the steam bath under reflux for 1 hour. After cooling the yellow product which separated was removed by filtration and washed with ~10 ml. of methanol. The yellow product was dissolved in 100 ml. of water with heating, then acidified to *p*H 3 with concentrated hydrochloric acid. The acidified reaction mixture was heated on the steam bath for 0.5 hour and precipitation of the crude pyrazino[2,3-*d*]pyridazine-5,8-dione-2-carboxhydrazide occurred. The product was removed by filtration, washed with water and dried in air to give 3.22 g. (74%) of product. The product was recrystallized from a large amount of water in 0.4 g. batches. About 0.3 g. of purified product, m.p. ~300° dec., was obtained; infrared cm^{-1}, 3450(s), 3200(broad envelope), 1660(s), 1600(m), 1560(m), 1525(m), 1460(m), 1320(s), 1230(m), 1195(m), 940(w), 720(w), 660(w), 590(w), 530(w), 440(m).

Anal. Calcd. for $C_7H_6N_6O_3$: C, 37.85; H, 2.72; N, 37.85. Found: C, 38.07; H, 2.90; N, 38.01.

Pyrazine-2,3,5-tricarboxamide (V).

Triethyl pyrazine-2,3,5-tricarboxylate (IV) (11.84 g., 0.04 mole) was dissolved in methanol (200 ml.) which had been previously saturated with ammonia for ~45 minutes in the cold. The stoppered mixture was allowed to stand overnight in the refrigerator. The next day the white solid which separated was removed by filtration and washed with ~25 ml. of methanol and dried in air, yield 8.16 g. (99%). The analytical sample was recrystallized from water with a loss of ~25%, m.p. 300-305° dec.; infrared cm^{-1}; 3425(s), 3200(w), 1690(s), 1610(m), 1450(m), 1425(m), 1390(m), 1310(s), 1225(m), 1195(m), 1110(s), 780(m), 720(m), 680(w), 650(w), 625(w), 590(w), 530(w).

Anal. Calcd. for $C_7H_7N_5O_3$: C, 40.19; H, 3.37; N, 33.49. Found: C, 39.83; H, 3.84; N, 33.90.

Pyrimido[4,5-*b*]quinoxaline-2,4-dione (VI) was purchased from Aldrich Chemical Company while 2-aminoquinoxaline (VII) was prepared by the hydrolytic decarboxylation method of Weijlard, *et al.*, m.p. 155° [lit. (10) 155-156°] and 2-acetylaminoquinoxaline (IX) was prepared by the method of Weijlard, *et al.*, m.p. 192° [lit. (10) 192.5-193.5°]; likewise 2-aminopyrazine-5,6-dicarboxylic acid (VIII) was prepared by the oxidative hydrolysis of 2-acetylaminoquinoxaline as described by Felder, *et al.*, m.p. 260° dec., [lit. (11) 262° dec.].

Diethyl 2-Aminopyrazine-5,6-dicarboxylate (X).

2-Aminopyrazine-5,6-dicarboxylic acid (0.59 g., 0.003 mole) dissolved in 75 ml. of absolute ethanol was saturated with dry hydrogen chloride for 0.5 hour with external cooling. The solution was heated under reflux on the steam bath for 8 hours, then allowed to stand overnight at room temperature. The solvent was removed under reduced pressure and water was added to the white solid mass in order to effect solution. The solution was neutralized with sodium bicarbonate to *p*H ~7 with cooling. A white crystalline solid began to separate. The product was removed by filtration, washed with ice water and dried in air, followed by recrystallization from aqueous ethanol, m.p. 125°, yield 0.42 g. (56%); infrared cm^{-1}; 3350(s), 3175(s), 2970(m), 1750(s), 1710(s), 1650(s), 1575(s), 1495(m), 1450(m), 1380(s), 1310(s), 1260(s), 1180(s), 1160(s), 1080(s), 1040(m), 970(m), 920(m), 880(m), 820(m), 810(w), 765(m), 660(w), 640(m), 600(w), 550(w), 480(w), 450(w).

Anal. Calcd. for $C_{10}H_{13}N_3O_4$: C, 50.21; H, 5.47; N, 17.57. Found: C, 50.30; H, 5.95; N, 18.05.

2-Aminopyrazino[2,3-*d*]pyridazine-5,8-dione (XI).

Diethyl 2-aminopyrazine-5,6-dicarboxylate (X) (0.48 g., 0.002 mole) was dissolved in 50 ml. of methanol and 1 g. (0.03 mole) of 95% hydrazine was added. The solution was heated under reflux on the steam bath for 1 hour during which time a yellow product separated. The product was removed by filtration, washed with ~15 ml. of methanol and dissolved in 50 ml. of water. The aqueous solution was acidified to *p*H ~3 with concentrated hydrochloric acid and the solution was heated on the steam bath for 0.5 hour during which time the solid product separated and was removed by filtration and washed with water. The product was recrystallized from water, m.p. > 400° dec., yield 0.15 g. (43%); infrared cm^{-1}, 3400(m), 3200(m), 3025(w), 1650(s), 1525(s), 1410(s), 1350(m), 1300(m), 1220(w), 1100(m), 950(m), 810(m), 740(m), 650(w), 560(w), 440(w).

Anal. Calcd. for $C_6H_5N_5O_2 \cdot \frac{1}{2}H_2O$: C, 38.29; H, 3.21. Found: C, 38.23; H, 3.42.

5,8-Bispicrylaminopyrazino[2,3-*d*]pyridazine (XIII).

5,8-Diaminopyrazino[2,3-*d*]pyridazine (XII) (5) (0.4 g., 0.0025 mole) was dissolved in 15 ml. of dry DMSO to which picryl fluoride (0.8 g., 0.0035 mole) was added in 3 portions. Three drops of triethylamine was added to the above mixture. The mixture dissolved, forming a dark red solution upon heating to 70° for 2 hours.

The cooled reaction mixture was poured on ice (~80 g.) and an additional 50 ml. of water was added. The black precipitate which separated was removed by filtration and chromatographed over neutral alumina (~75 g.) and eluted with chloroform-acetone (1:1). The yellow product which was obtained was recrystallized from acetone, m.p. 277° dec., yield 0.22 g. (25%); infrared cm^{-1}; 3450(s), 3100(m), 2920(w), 1660(sh), 1610(s), 1550(s), 1350(s), 1300(m), 1270(m), 1180(m), 1090(m), 1040(w), 920(w), 720(s), 670(w).

Anal. Calcd. for $C_{18}H_8N_{12}O_{12}$: C, 36.99; H, 1.36; N, 28.76. Found: C, 37.29; H, 1.86; N, 28.49.

2,3-Diaminophenazine (XV) was prepared by the ferric chloride oxidation of *o*-phenylenediamine by the method of Mager and Berends (12), m.p. > 400° (no melting point recorded in the literature) while pyrazine-2,3,5,6-tetracarboxylic acid (XVII) was prepared by the permanganate oxidation of 2,3-diaminophenazine (XV) by the method of Mager and Berends, m.p. 205° [lit. (12) m.p. 205°].

Tetraethyl Pyrazine-2,3,5,6-tetracarboxylate (XVI).

Pyrazine-2,3,5,6-tetracarboxylic acid (XVII) (5.0 g., 0.02 mole) was dissolved in 100 ml. of absolute ethanol and this solution was saturated with dry hydrogen chloride for 0.5 hour with cooling. The solution was heated under reflux on the steam bath for 12 hours. The solvent was removed *in vacuo* and 50 ml. of water was added to the residue. The precipitate which separated was removed by filtration and recrystallized from ethanol, m.p. 102-103°, yield 5.0 g. (70%); infrared cm^{-1}; 3000(s), 2450(m), 2410(m), 1750(s), 1550(sh), 1475(m), 1425(m), 1390(m), 1350

(s) 1325(m), 1300(m), 1260(m), 1140(m), 1030(s), 890(s), 865(s), 850(s), 800(s), 790(m), 745(s), 650(m), 570(m), 470(m).

Anal. Calcd. for $C_{16}H_{20}N_2O_8$: C, 52.17; H, 5.47; N, 7.61. Found: C, 51.84; H, 5.30; N, 7.91.

Pyrazine-2,3,5,6-tetracarboxhydrazide (XVIII).

Tetraethyl pyrazine-2,3,5,6-tetracarboxylate (XVI) (1.1 g., 0.003 mole) was dissolved in 100 ml. of methanol to which 3 g. (0.01 mole) of 95% hydrazine was added. The solution was heated under reflux on the steam bath for 1 hour during which time the brown product separated. The product was separated by filtration and washed with about 20 ml. of methanol and recrystallized from water to give the product, m.p. $> 400^\circ$, yield 1.0 g. (quantitative).

Anal. Calcd. for $C_8H_{12}N_{10}O_4 \cdot H_2O$: C, 29.09; H, 4.27; N, 42.42. Found: C, 29.07; H, 4.04; N, 42.70.

Dipyridazino[4,5-*b*:4′,5′-*e*]pyrazine-1,4,6,9-tetrone (XIX).

Method A. From Tetraethyl Pyrazine-2,3,5,6-tetracarboxylate (XVI).

Tetraethyl pyrazine-2,3,5,6-tetracarboxylate (XVI) (0.37 g., 0.001 mole) was dissolved in 75 ml. of methanol and 1 ml. of 95% hydrazine (0.03 mole) was added. The solution was heated under reflux on a steam bath for 1 hour during which time a brown solid separated. The product was separated by filtration and dissolved in 50 ml. of water followed by acidification with concentrated hydrochloric acid to *p*H~2. The solution was heated on the steam bath with stirring for 0.5 hour during which time a yellow solid separated. The product was removed by filtration, washed with water followed by washing with ~10 ml. of methanol. The residue was recrystallized from water in which it was slowly soluble requiring the use of a Soxhlet apparatus, m.p. $> 400^\circ$ dec., yield 0.17 g. (64%); infrared cm^{-1}; 3450(s), 3000(s), (broad envelope), 1660(s), 1600(sh), 1550(m), 1510(w), 1465(m), 1390(m), 1340(m), 1305(s), 1255(m), 1220(m), 1160(m), 1140(m), 1020(m), 805(m), 730(w), 640(m), 540(w), 490(w), 435(w).

Anal. Calcd. for $C_8H_4N_6O_4 \cdot \frac{1}{2}H_2O$: C, 37.36; H, 1.95; N, 32.69. Found: C, 36.90; H, 1.94; N, 33.18.

Method B. From Pyrazine-2,3,5,6-tetracarboxhydrazide (XVIII).

Pyrazine-2,3,5,6-tetracarboxhydrazide (XVIII) (0.6 g., 0.002 mole) was treated as a suspension with 25 ml. of 10% aqueous hydrochloric acid and heated under reflux for 1 hour. The yellow solid was removed by filtration and was washed with water and then with methanol, m.p. $> 400^\circ$, yield 0.15 g. (59%). The infrared spectrum of this sample was identical with that prepared by Method A.

Pyrazine-2,3,5,6-tetracarboxamide (XX).

Tetraethyl pyrazino-2,3,5,6-tetracarboxylate (XVI) (3.67 g., 0.01 mole) was dissolved in 100 ml. of methanol which had been saturated with anhydrous ammonia in the cold. The stoppered solution was allowed to stand in the refrigerator for ~24 hours during which time a white solid separated. The product was separated by filtration, washed with ~25 ml. of water and dried in air. The product was recrystallized from water, m.p. $> 400^\circ$ dec., yield 2.35 g. (98%); infrared cm^{-1}; 3450(s), 3210(w), 1700(s), 1615(m), 1455(m), 1425(m), 1340(m), 1300 (m), 1210(m), 1150(m), 1100(w), 820(m), 780(m), 650(w), 535(w), 475(w), 440(w).

Anal. Calcd. for $C_8H_8N_6O_4$: C, 38.09; H, 3.19; N, 33.33. Found: C, 38.36; H, 3.44; N, 33.46.

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(13) All melting points were determined on a Thomas-Hoover capillary melting point apparatus are uncorrected. The infrared spectra were determined with a Perkin-Elmer 337 spectrophotometer in potassium bromide discs. The ultraviolet spectra were taken in the solvent indicated with a Bausch and Lomb Spectronic 505 Spectrophotometer. The Nuclear Magnetic Resonance spectra were taken in the solvent indicated with a Varian A60 A Spectrophotometer. The NMR spectra were compared with TMS as an internal standard.

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