amino-6-methoxyquinoline, 16.0 g. (0.087 mole) of 1-ethyl-3-chloropiperidine hydrochloride and 25 cc. of water was heated with stirring at 60–70° for twenty hours. The temperature of the solution was raised to 110° for two hours. The warm solution was added to 75 cc. of warm water, made acidic to congo red with concentrated hydrochloric acid, cooled, filtered and the gold crystals were washed with water. The filtrate was brought to *p*H 4.5 with solid sodium acetate and extracted four times with 100-cc. portions of ether. Then the solution was made strongly basic (*p*H 12) and a black tar separated. This was taken up in about 300 cc. of ether. After drying the ethereal extracts over magnesium sulfate the ether was removed and the residue was distilled at reduced pressure. The main portion, 9.1 g., boiled at 186–190° (0.2 mm.). After recrystallization from absolute ethanol–ether, light yellow hygroscopic needles of 6-methoxy-8-(1-ethyl-2-pyrrolidylmethylamino)-quinoline dihydrochloride melted at 214–216° with some sintering at 212°.

Anal. Calcd. for $C_{17}H_{23}N_3O\cdot 2HCl$: C, 56.98; H, 7.03; Cl, 19.79. Found: C, 56.55, 56.93; H, 6.84, 6.51; Cl, 18.76.

The dipicrate melted at 202.5–203.5° after recrystallization from ethanol.

Anal. Calcd. for $C_{29}H_{29}N_9O_{15}$: C, 46.84; H, 3.93; N, 16.95. Found: C, 46.76; H, 4.13; N, 16.13.

1-Ethyl-3-hydroxypiperidine.—A solution of 26.4 g. (0.206 mole) of 1-ethyl-3-piperidone was reduced in methanol with hydrogen in the presence of Raney nickel at 125° and an initial hydrogen pressure of 2270 pounds. After forty minutes 75% of the theoretical amount of hydrogen had been absorbed. The catalyst was removed by filtration and the methanol distilled at atmospheric pressure. The residue was distilled at water pump pressure using a short helice-packed column to give 1-ethyl-3-hydroxypiperidine which boiled at 99–100° (19 mm.); $n^{19.5}D$ 1.4774. The benzoate hydrochloride was prepared from 1 g. of the distillate in 15 cc. of methylene chloride by adding 1.1 cc. of benzoyl chloride and heating for ten minutes. After removal of the solvent a sample of the residue was recrystallized from methanol–ether to give white needles, m. p. 197–198°.

Anal. Calcd. for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 65.36; H, 11.62; N, 10.66.

The benzoate hydrochloride prepared from a sample of 1-ethyl-3-hydroxypiperidine obtained from ethyl tetrahydrofurfuralamine melted at 195–198°. Mixed melting point of the two benzoates was 196–198°.

Summary

1. Treatment of 1-alkyl-3-chloropiperidines with amines has been shown to give products distinct from the expected 3-aminopiperidines. On the basis of various studies these products have been given the structure of 2-aminomethylpyrrolidines.

2. A new analog of Plasmochin is described.

3. Additional proof of the structure of 3-hydroxypiperidines formed from tetrahydrofurfuralamines has been obtained.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

Syntheses in the Pyrazine Series: The Proof of the Structure and the Reactions of 2,6-Dibromopyrazine

BY KURT H. SCHAAF[1] AND PAUL E. SPOERRI

In their investigations of the preparations and properties of the pyrazyl halides, Erickson and Spoerri[2] prepared a dibromopyrazine (III) by the reaction of hydroxypyrazine (I) with a mixture of phosphorus pentabromide and phosphorus oxybromide. Bromopyrazine (II) was obtained as a second product of the reaction. As the identity of the dibromo derivative was not established, it seemed desirable to determine its structure and to study its chemical behavior.

Since the physical properties of III differ from those reported for 2,5-dibromopyrazine by Ellingson and Henry,[3] it was concluded that III might be either 2,3- or 2,6-dibromopyrazine.

By heating the unknown dibromopyrazine (III) with cuprous cyanide and cupric sulfate, it was converted into the hitherto unknown 2,6-dicyanopyrazine (IV) and 2-bromo-6-cyanopyrazine (V). The dinitrile was then hydrolyzed by means of concentrated sulfuric acid and yielded pyrazine-2,6-diamide (VI).

The hydrolysis of 2,6-dicyanopyrazine (IV) by means of aqueous sodium hydroxide yielded the known pyrazine-2,6-dicarboxylic acid (VII). The identity of this compound was established by a mixed melting point determination with pyrazine-2,6-dicarboxylic acid which was prepared in the following manner.

2-Methylquinoxaline (VIII) was oxidized to pyrazine-2,5,6-tricarboxylic acid (IX) by means of potassium permanganate in alkaline medium. This acid, which had been previously prepared by Stoehr,[4] was decarboxylated and yielded pyrazine-2,5- and 2,6-dicarboxylic acids. The latter derivative showed no depression in the melting point when mixed with the dicarboxylic acid (VII) obtained by the hydrolysis of the new dinitrile (IV).

In order to gain some understanding of the reaction which takes place when hydroxypyrazine (I) is brominated, bromopyrazine (II) was treated with phosphorus pentabromide and phosphorus

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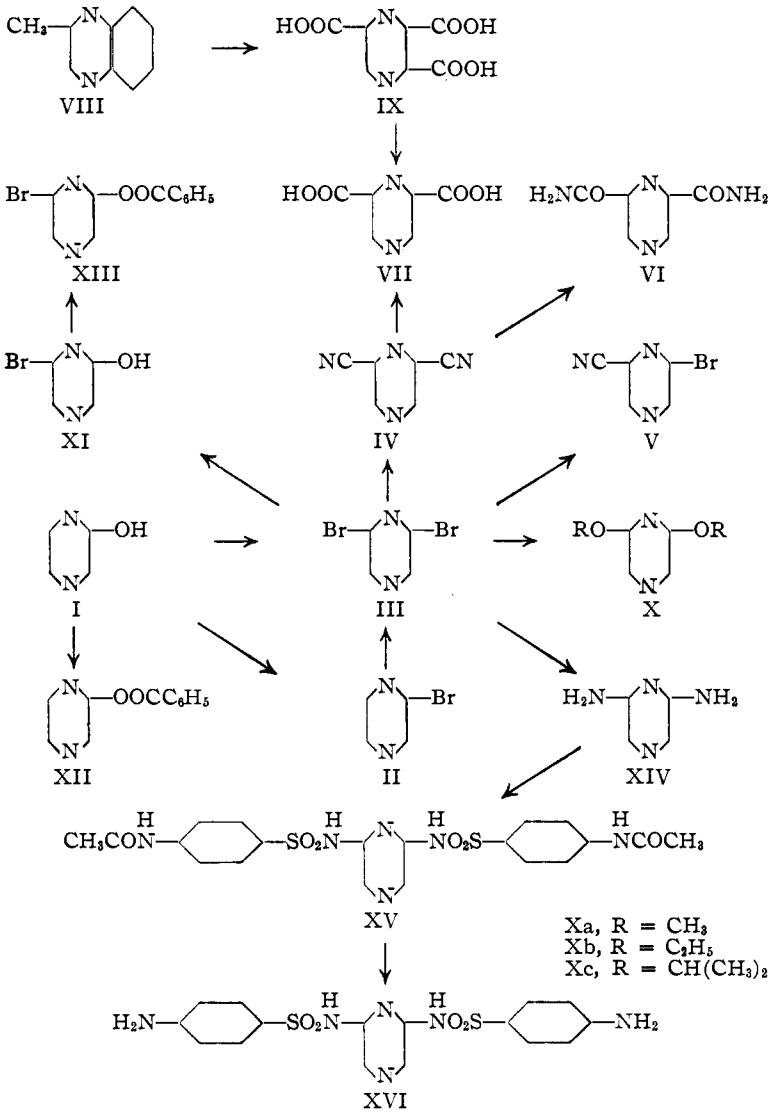
(2) A. E. Erickson, Ph.D. Dissertation, Polytechnic Institute of Brooklyn, 1945; A. E. Erickson and P. E. Spoerri, THIS JOURNAL, **68**, 400 (1946).

(3) R. C. Ellingson and R. L. Henry, paper presented at the 109th Meeting of the American Chemical Society, Atlantic City, New Jersey, April, 1946 and private communication with Dr. R. C. Ellingson.

(4) C. Stoehr, *J. prakt. Chem.*, **55**, 248 (1897).



oxybromide under the same conditions which were employed for hydroxypyrazine by Erickson and Spoerri.[2] In this manner 2,6-dibromopyrazine (III) was obtained.[5]

Three dialkyl ethers (X) were prepared from III, namely, 2,6-dimethoxy-, 2,6-diethoxy- and 2,6-di-(1-methylethoxy)-pyrazines.

When 2,6-dibromopyrazine (III) was refluxed with dilute, aqueous–alcoholic sodium hydroxide, 6-bromo-2-hydroxypyrazine (XI) was obtained. In order to determine the conditions for the benzoylation of this derivative, hydroxypyrazine (I) was first converted into benzoxypyrazine (XII) by means of benzoyl chloride in anhydrous pyridine. Upon applying these conditions to 6-bromo-2-hydroxypyrazine (XI), 2-benzoxy-6-bromopyrazine (XIII) was obtained.

(5) Since the yield approximated that obtained by brominating hydroxypyrazine, it is concluded that bromopyrazine (II) is formed as an intermediate in the bromination of hydroxypyrazine.

2,6-Dibromopyrazine (III) was also converted into 2,6-diaminopyrazine (XIV) by heating the halogen-derivative with 28.5% ammonia water in a Carius tube. This diamine was subsequently condensed with *p*-acetylaminobenzenesulfonyl chloride and yielded 2,6-di-(N^4-acetylsulfanilamido)-pyrazine (XV) which was isolated as the monoacetate. This derivative was hydrolyzed to 2,6-disulfanilamidopyrazine (XVI).

The pharmacological properties of this pyrazine derivative are being investigated.

Experimental[6]

2,6-Dicyanopyrazine (IV) and 2-Bromo-6-cyanopyrazine (V).—In a test-tube (1″ × 6″), which was equipped with a T 24/40 female-jointed main neck and a side neck for connection to an oil pump, the following substances were placed and intimately mixed: 1.190 g. (0.005 mole) of 2,6-dibromopyrazine, 1.340 g. of powdered, anhydrous cuprous cyanide, and 0.070 g. of powdered, anhydrous cupric sulfate. The tube was connected to an inner, T 24/40 male-jointed condenser the bottom of which was two inches above the bottom of the test-tube.

The lower part of the apparatus was placed into a preheated (100°) oil-bath, and the temperature was gradually raised to 143–145° over a period of about twenty-five minutes. The mixture first turned brown and then began to melt at 137°. As the bath-temperature reached 143°, vapors appeared above the melt, and the liquid decomposed within fifteen to thirty seconds to a black, carbonaceous solid.

As soon as the first vapors were noticed, a high vacuum was applied[7] to remove the reaction products which collected on the condenser as a yellowish-white, hard solid. This material was subsequently dissolved in diethyl ether and the solution was saved.

Four more preparations were similarly conducted, and the combined ether solutions, after having been dried over sodium sulfate and evaporated to dryness, yielded 1.90 g. of slightly yellow solid. It was dissolved in boiling hexane, and from the solution, after cooling to room temperature, 0.190 g. of crude 2,6-dicyanopyrazine was isolated; m. p. 160–162°. From the mother liquor a second fraction (0.060 g.) of impure dinitrile (m. p. 146–153°) was isolated after standing at room temperature overnight.

The filtrate was then chilled at 0° overnight and yielded 0.540 g. of crude 2-bromo-6-cyanopyrazine as a white, crystalline solid; m. p. 59.5–64.5°. The mother-liquor of this fraction was evaporated to dryness under reduced pressure and gave 1.00 g. of yellow, liquid residue. It was crystallized from aqueous methanol and yielded 0.780 g. of unreacted 2,6-dibromopyrazine. The net yields of 2,6-dicyanopyrazine and of 2-bromo-6-cyanopyrazine were thus 8.85% and 13.5% of the theoretical, respectively.

(6) All melting points are corrected.

(7) This modification was based on the procedures of: L. C. Craig, THIS JOURNAL, **56**, 231 (1934); H. Gilman and S. M. Spatz, *ibid.*, **63**, 1556 (1941).

For analysis[8] the crude dinitrile (0.190 g.) was crystallized twice from heptane and twice from water. The colorless needles melted at 162–163°.

Anal. Calcd. for $C_6H_2N_4$: C, 55.38; H, 1.55; N, 43.06. Found: C, 54.91; H, 1.57; N, 41.35.

For analysis[8] the crude 2-bromo-6-cyanopyrazine was recrystallized twice each from diethyl ether–pentane, from hexane, and from a 1:1 mixture of ethanol and water. The colorless needles melted at 72–73°.

Anal. Calcd. for $C_5H_2BrN_3$: C, 32.63; H, 1.10. Found: C, 32.75; H, 1.28.

Pyrazine-2,6-diamide (VI).—A mixture of 0.130 g. (0.001 mole) 2,6-dicyanopyrazine and 0.52 ml. of concentrated (98.5%) sulfuric acid in a small test-tube was heated at 70° for two hours with occasional stirring. The dinitrile dissolved gradually yielding a slightly brownish solution. After two hours heating, the solution was heated for another hour at 115–117°. The light-brown solution was then cooled to about 70° and added to 5.2 ml. of cold water with stirring. The grayish-white precipitate was filtered off and dried yielding 0.145 g. of solid, or 87.25% of the theoretical amount. The product did not melt up to 320°. It was crystallized from 29 ml. of water and yielded 0.120 g. of colorless, crystalline solid, which did not melt up to 355°.

For analysis[8] the crystals were recrystallized from water. Pyrazine-2,6-diamide was isolated as microcrystalline, colorless plates which did not melt up to 355°.

Anal. Calcd. for $C_6H_6N_4O_2$: C, 43.37; H, 3.64; N, 33.73. Found: C, 43.38; H, 3.72; N, 33.47.

Hydrolysis of 2,6-Dicyanopyrazine (IV) to Pyrazine-2,6-dicarboxylic Acid (VII).—A cold solution of 0.470 g. of 97% sodium hydroxide in 9.40 ml. of water was added to 0.370 g. (0.00284 mole) of 2,6-dicyanopyrazine. The mixture turned yellow immediately and then dark-brown, accompanied by the liberation of ammonia. The reagents were heated on the steam-bath while a fine stream of nitrogen was passed through the mixture to sweep out the ammonia formed. After two hours of heating, the reaction mixture was gently boiled for ten minutes to remove the residual ammonia. The cooled solution was neutralized with 5% hydrochloric acid and decolorized with Darco G60. The light-yellow filtrate was evaporated to dryness *in vacuo* and yielded 1.005 g. of yellowish-white solid. Upon adding 3.0 ml. of 10% hydrochloric acid, the mixture turned dark-brown and short prisms separated. The isolated, crude product amounted to 0.545 g. of dark-brown, crystalline solid; m. p. 210° (dec.).

The crude dicarboxylic acid was dissolved in 4.0 ml. of hot water, and the solution was decolorized with Darco G60. From the pale-yellow filtrate 0.320 g. of faintly yellow needles were isolated; m. p. 216° (dec.). The yield of pyrazine-2,6-dicarboxylic acid was thus 67% of the theoretical. Two further purifications yielded colorless needles which melted at 218° (dec.).

Oxidation of 2-Methylquinoxaline (VIII) to Pyrazine-2,5,6-tricarboxylic Acid (IX).—2-Methylquinoxaline (7.20 g., 0.05 mole) was dissolved in 720 ml. of hot water containing 3.60 g. of potassium hydroxide. While the solution was heated on the steam-bath (internal temp., 90–95°), a solution of 58.0 g. of potassium permanganate in 1160 ml. of water, preheated to 85–90°, was added dropwise with stirring. The addition required two and one-half hours. The reaction mixture was then stirred with heating for an additional three-quarters hour and filtered with suction to remove the manganese dioxide.

The light-yellow filtrate was concentrated to a volume of 200 ml. in the water-bath (55–60°) *in vacuo*. The alkaline concentrate was acidified to *p*H 5.5 with 50% acetic acid. Carbon dioxide was liberated during the acidification. The solution was then heated to 85°, and 100 ml. of a saturated solution of barium chloride was added with stirring and heating to boiling. The yellowish-white precipitate formed was collected after the mixture had been chilled. The washed precipitate was suspended in 100 ml. of cold water, and 250 ml. of 1.0 *N* sulfuric acid was slowly added with stirring. After the mixture had been stirred for three-quarters hour, the barium sulfate was separated by centrifugation. The supernatant liquid was neutralized to *p*H 7 with 28% ammonia water. A test portion of the solution gave a strong, reddish-purple coloration upon adding a solution of ferrous sulfate.

A solution of 20.0 g. of cupric chloride dihydrate in 40 ml. of water was then added with stirring and yielded a green precipitate. The collected, dried product amounted to 10.09 g. of light-green solid. To the mother liquor was added a solution of 10.0 g. of cupric chloride dihydrate in 20 ml. of water. The small amount of green precipitate, which separated on standing at 2°, amounted to 0.71 g.

The combined cupric salt was suspended in water, and the mixture was treated with hydrogen sulfide for one-half hour. The cupric sulfide was then filtered off and washed with water. The combined filtrate and washings were evaporated to dryness in the water-bath (50–55°) *in vacuo* and yielded 4.67 g. of brownish solid. It was crystallized from water with intermittent treatment with Darco G60 and yielded 2.67 g. of faintly brown, fine needles, or 25.2% of the theoretical yield. The crude acid melted at 159° with strong evolution of gas and decomposition. After two further crystallizations from water, almost colorless, fine needles were obtained which melted at 180° with strong evolution of gas and decomposition.

No further amounts of pyrazine-2,5,6-tricarboxylic acid could be isolated from the mother liquor of the crude acid.

Preparation of 2,6-Dibromopyrazine (III) from Bromopyrazine (II).—Freshly distilled phosphorus tribromide (13.6 g.) was placed into a 100-ml., 2-neck, round-bottom flask equipped with a dropping-funnel and drying-tube. The flask was cooled in ice-water, and 8.0 g. of bromine was added dropwise with gentle shaking. After the reagents had been mixed with a glass rod, 15.9 g. (0.10 mole) of freshly distilled bromopyrazine and 15.0 g. of phosphorus oxybromide were added. The reagents were thoroughly mixed, and the flask was then connected to a reflux condenser protected by a drying-tube. The mixture was heated in an oil-bath to 105° (bath temp.) over a period of fifteen minutes and held at 105–110° for one hour, during which the reaction mixture darkened and became semi-solid.

The cooled reaction mixture was added in small portions to 300 g. of crushed ice to which 50 ml. of water had been added to facilitate stirring. The brownish-black solution was repeatedly extracted with diethyl ether. The extract was dried over sodium sulfate, and the solvent was evaporated yielding 18.67 g. of amber, liquid residue. It was fractionally distilled under reduced pressure and yielded the following fractions: (a) 5.60 g. of bromopyrazine, b. p.: 54–57° (9 mm.); (b) 0.86 g. of intermediate fraction, faintly yellow liquid, b. p. 58–93° (10 mm.); (c) 5.06 g. of crude 2,6-dibromopyrazine, which solidified partly in the receiver, b. p. 94–101.5° (10 mm.); (d) 1.69 g. of colorless liquid, b. p. 62.5–65° (1.5 mm.).

The last two fractions were crystallized, each one from an equal volume of methanol, and yielded the following amounts of 2,6-dibromopyrazine: (c) 1.74 g. of colorless needles, m. p. 51–52°; (d) 0.60 g. of colorless needles, m. p. 51–52°.

The determination of the melting point of this compound mixed with 2,6-dibromopyrazine, which was obtained from hydroxypyrazine, showed no depression. From the combined mother liquors 0.230 g. of crude 2,6-dibromopyrazine (m. p. 49.5–51°) was isolated. Since 5.60 g. of unreacted bromopyrazine was recovered, the net yield of 2,6-dibromopyrazine was 16.7% of the theoretical amount.

2,6-Dimethoxypyrazine (Xa).[9]—To a solution of 0.590 g. of sodium in 11.8 ml. of methanol was added a warm

(8) The microanalyses of the compounds were performed by: Mr. Carl Larson, The Microlab, Staten Island 9, N. Y. Dr. Francine Schwarzkopf, 62-12 79th Street, Elmhurst, N. Y. Mr. Ralph Schachat, Microlaboratory of the Polytechnic Institute of Brooklyn, Brooklyn, N. Y.

(9) This preparation was based on the formation of ethoxypyrazine from chloropyrazine reported by Erickson and Spoerri.[4]

solution of 1.190 g. (0.005 mole) 2,6-dibromopyrazine in 2.4 ml. of methanol, using two additional 1.2-ml. portions of methanol as washings. From the mixture, after having been refluxed under anhydrous conditions for twenty minutes, sodium bromide began to separate.

After the mixture had been refluxed for seventy-two hours, it was chilled and then 35 ml. of water was added, whereupon a small amount of colorless needles separated. The mixture was extracted with eight 15-ml. portions of diethyl ether, and the colorless extract was dried over sodium sulfate. Removal of ether and methanol under reduced pressure left 0.605 g. (86.5% yield) of liquid residue. On chilling to 2°, the liquid crystallized completely but melted again on warming.

The crude 2,6-dimethoxypyrazine was fractionally distilled under reduced pressure and yielded 0.500 g. of distillate which crystallized completely as long, thin needles (b. p. 75° at 10 mm.). No forerun was obtained.

For analysis[8] the crystals were recrystallized three times from a 1:1 mixture of methanol and water and chilled to −15° before filtration. The freshly filtered, colorless needles melted at 47°. After drying in the desiccator over calcium chloride, the crystals melted at 31–31.5°. The higher-melting variety is probably a hydrate of 2,6-dimethoxypyrazine. Both this and the anhydrous compound have rather high vapor pressures under atmospheric conditions.

Anal. Calcd. for $C_6H_8N_2O_2$: C, 51.42; H, 5.75. Found: C, 51.86; H, 6.05.

2,6-Diethoxypyrazine (Xb).[9]—To a solution of 0.920 g. of sodium in 25.0 ml. of ethanol was added a solution of of 2.38 g. (0.1 mole) 2,6-dibromopyrazine in 9.6 ml. of ethanol, using two additional 2.4-ml. portions of ethanol as washings. Sodium bromide precipitated from the mixture within one-half minute after the addition. The mixture was refluxed under anhydrous conditions for one hour, and then most of the ethanol was distilled off *in vacuo* (50 mm.) in the water-bath (35–40°).

The residual mixture of sodium bromide and yellow liquid was taken up in 25 ml. of water and extracted with five 25-ml. portions of diethyl ether. The extract was dried over sodium sulfate, and the ether and residual ethanol were distilled *in vacuo* from a water-bath. The golden-yellow, liquid residue thus obtained amounted to 1.58 g., or 94.0% of the theoretical yield. On chilling the residue to 2°, it crystallized completely but melted again on warming.

The crude 2,6-diethoxypyrazine was fractionally distilled under reduced pressure and yielded the following colorless, liquid fractions: (a) 0.080 g., b. p. 60–68° (5 mm.); (b) 0.360 g., b. p. 68° (5 mm.); (c) 0.580 g., b. p. 68–70° (5 mm.).

For analysis[8] the last two fractions were combined and crystallized twice from aqueous ethanol, with chilling to −15° before filtration. The crystals were dried in the vacuum desiccator over calcium chloride. The colorless needles melted at 27–27.5°.

Anal. Calcd. for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19. Found: C, 57.00; H, 7.56.

2,6-Di-(1-methylethoxy)-pyrazine (Xc).[9]—To a boiling-hot solution of 0.580 g. sodium in 11.6 ml. of 2-propanol was added a hot solution of 1.190 g. (0.005 mole) 2,6-dibromopyrazine in 2.40 ml. of 2-propanol, using two further 1.20-ml. portions of 2-propanol as washings. Sodium bromide precipitated immediately. The mixture was refluxed under anhydrous conditions for one and one-half hours, cooled to room temperature, and dissolved in 25 ml. of water. The solution was extracted with eight 15-ml. portions of diethyl ether, and the extract was dried over sodium sulfate. The diethyl ether was evaporated in the water-bath, and the remaining 2-propanol was distilled off at 50° and 100 mm. pressure.

The pale-yellow, liquid residue was fractionally distilled under reduced pressure. No forerun was obtained. 2,6-Di-(1-methylethoxy)-pyrazine distilled at 105–106° (10 mm.). The colorless, fractionating liquid amounted to 0.620 g. (63.3% yield). It crystallized completely on chilling to 0° but melted again on warming.

Anal.[8] Calcd. for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22. Found: C, 61.50; H, 8.04.

6-Bromo-2-hydroxypyrazine (XI).—To a solution of 0.910 g. 97% sodium hydroxide in 4.60 ml. of water were added 1.190 g. (0.005 mole) of 2,6-dibromopyrazine and 4.60 ml. of 95% ethyl alcohol. The mixture was refluxed for five hours with stirring. When the cooled, yellow solution was acidified to *p*H 5 with 10% hydrochloric acid, a crystalline solid precipitated. It was isolated from the chilled mixture and amounted to 0.600 g. (68.6% yield) of faintly cream-colored, crystalline solid. It darkened in a sealed tube at 201° and melted at 205° (dec.).

The crude 6-bromo-2-hydroxypyrazine was recrystallized from 40% alcohol and yielded 0.445 g. of colorless plates. They darkened in a sealed tube at 205.5° and melted at 208° (dec.). For analysis[8] the crystals were recrystallized twice from 50% alcohol and then darkened in a sealed tube at 205.5° and melted at 209° (dec.).

Anal. Calcd. for $C_4H_3BrN_2O$: N, 16.01. Found: N, 16.08.

Benzoxypyrazine (XII).—To a mixture of 2.40 g. (0.025 mole) of hydroxypyrazine in 9.6 ml. of anhydrous pyridine was added dropwise 3.690 g. of benzoyl chloride. The mixture became moderately warm, and all hydroxypyrazine dissolved. After a few minutes crystals separated from the solution.

The reaction mixture, after having been stored at room temperature for twenty-four hours, was poured into 25 ml. of cold water. An amber oil separated which solidified to a crystalline mass on stirring. The collected solid was washed with ice-water and dried yielding 3.40 g. (68.0% yield) of tan crystals.

The crude product was dissolved in hot hexane. A small amount of insoluble, amber solid was removed by filtration, and from the chilled filtrate faintly yellow crystals (2.98 g. of plates) were isolated; m. p. 72–73°. Recrystallization from hexane yielded 2.65 g. of faintly yellow plates; m. p. 73–74°.

For analysis[8] 0.50 g. of the product was dissolved in hot hexane, and the solution was treated with Darco G60 and filtered. The isolated, colorless plates melted at 73–74°.

Anal. Calcd. for $C_{11}H_8N_2O_2$: C, 65.99; H, 4.03; N, 14.00. Found: C, 66.64; H, 4.49; N, 13.78.

2-Benzoxy-6-bromopyrazine (XIII).—Benzoyl chloride (0.309 g.) was added dropwise with cooling to a solution of 0.112 g. of 6-bromo-2-hydroxypyrazine in 1.12 ml. of anhydrous pyridine. A crystalline solid separated during the addition, and the mixture was allowed to stand at room temperature for forty-eight hours.

The dark-amber reaction mixture was added to 7.0 ml. of ice-cold water. An oily layer separated and crystallized partly on standing at 2°. The mixture was extracted with eight 5-ml. portions of diethyl ether, and the extract was dried over sodium sulfate and treated with Darco G60. The ether was evaporated in the water-bath, and the pyridine removed by distillation under reduced pressure. There was obtained 0.530 g. of light-amber, oily residue. It was dissolved in hot methanol, and water was added to turbidity. The mixture was stored at 2° for fifteen hours with occasional stirring to facilitate the crystallization of the benzoate. The isolated crystals (needles) amounted to 0.175 g. (98.0% yield); m. p. 61–63.5°.

For analysis[8] the crude product was recrystallized three times from aqueous ethanol with intermittent treatment with Darco G60. 2-Benzoxy-6-bromopyrazine was obtained as colorless needles; m. p. 67–68°.

Anal. Calcd. for $C_{11}H_7BrN_2O_2$: N, 10.04. Found: N, 9.92.

2,6-Diaminopyrazine (XIV).—2,6-Dibromopyrazine (1.190 g., 0.005 mole) and 40 ml. of 28.5% aqueous ammonia were heated in a sealed Carius tube at 195–200° for twenty-one hours.[10] The cooled tube was opened, and

(10) The conditions were based on the preparation of aminopyrazine from chloropyrazine by Erickson and Spoerri.[8]

the yellowish-brown reaction mixture was filtered to remove a negligible amount of dark-brown, amorphous solid. The tube and solid were washed twice with 28.5% aqueous ammonia.

The combined filtrate and washings were extracted for eight hours with peroxide-free diethyl ether in a liquid–liquid extractor. A light-yellow extract showing a strong, green fluorescence was thus obtained. The extract was dried over sodium sulfate, and the ether was evaporated from a water-bath. The residue, after having been kept *in vacuo* for one hour to remove any residual solvent, amounted to 0.450 g. (81.8% yield) of yellow liquid. On standing at room temperature, the liquid crystallized completely and yielded fine, yellow needles; m. p. 125–132° (dec.).

For analysis[8] the product was recrystallized from anhydrous ethyl acetate. Pale-yellow needles separated and were isolated after chilling to 2°. Two further recrystallizations from ethyl acetate yielded 2,6-diaminopyrazine as pale-yellow needles; m. p. 136° (dec.).

Anal. Calcd. for $C_4H_6N_4$: C, 43.62; H, 5.49. Found: C, 43.85; H, 5.12.

2,6-Diaminopyrazine was found to be fairly sensitive to oxidation. Aqueous solutions turned dark-brown on standing and formed brownish-black precipitates. Similar but slower decompositions were observed with solutions of the diamine in organic solvents.

2,6-Di-(N⁴-acetylsulfanilamido)-pyrazine Monoacetate (XB).[11]—2,6-Diaminopyrazine (0.440 g., 0.004 mole) was dissolved in 4.40 ml. of anhydrous pyridine in a 50-ml. flask equipped with a stirrer, drying-tube, and nitrogen inlet tube. To the chilled, yellow solution was gradually (10 min.) added with stirring 2.06 g. of *p*-acetaminobenzenesulfonyl chloride, while a slow stream of nitrogen was passed through the apparatus. Finally 1.60 ml. of anhydrous pyridine was used to wash any residual sulfonyl chloride into the flask.

The amber solution was stirred at room temperature for sixteen hours in an atmosphere of nitrogen and then stored for twenty hours at 2°. Finally a solution of 0.36 g. of sodium hydroxide in 6.0 ml. of water was added with cooling. From the mixture a tan solid separated after a few minutes. The pyridine was distilled in the water-bath (50–55°) *in vacuo*. Then 6.0 ml. of water was added, and the vacuum distillation was continued until the volume of the residual mixture amounted to about 6–8 ml. After chilling the mixture to 2°, the solid was isolated and dried yielding 1.90 g. of the crude derivative; m. p. 220–221° (dec.). This represents a yield of 94.2% of the theoretical, based on the formation of 2,6-di-(N⁴-acetylsulfanilamido)-pyrazine.

The crude product was dissolved in 19 ml. of 15% aqueous ammonia, and the dark-amber solution was treated with Darco G60 and filtered. The amber filtrate was acidified to *p*H 6.5 with 15% aqueous acetic acid and yielded a yellow-orange, fine precipitate. It was separated by centrifugation and melted at 255–257° (dec.). This purification process was repeated three times and yielded finally 1.34 g. of yellow-orange solid; m. p. 257° (dec.).

For analysis[8] the derivative was crystallized twice from 50% aqueous acetic acid and yielded light-tan, rectangular plates, the melting-point of which remained unaltered. The analytical results showed that the derivative was obtained as the monoacetate in the purification process.

Anal. Calcd. for $C_{22}H_{24}N_6O_8S_2$: C, 46.80; H, 4.29; N, 14.89. Found: C, 46.27; H, 4.62; N, 15.16.

2,6-Disulfanilamidopyrazine (XVI).—A mixture of 0.970 g. (0.00172 mole) of 2,6-di-(N⁴-acetylsulfanilamido)-pyrazine monoacetate and 9.70 ml. of 6 *N* hydrochloric acid was heated on the steam-bath with stirring.[12] After five minutes heating, the solid had completely dissolved, and the dark, reddish-amber solution was heated with stirring for two minutes and then poured over 15 g. of crushed ice, using 5 ml. of ice-water as washings.

The combined solution was treated at room temperature for one-half hour with 0.20 g. of Darco G60 and filtered. The light-amber filtrate was neutralized to *p*H 6.0 by adding 10% sodium hydroxide solution with cooling in ice. The reddish-orange solid thus obtained was collected and dried; yield, 0.605 g. It was dissolved in 12 ml. of boiling-hot nitrobenzene, and the solution was treated with Darco G60 and filtered. Crystals (needles) separated from the filtrate on cooling. They were isolated from the chilled mixture, washed with ethanol, and dried. The yield of crude 2,6-disulfanilamidopyrazine amounted to 0.310 g. (42.9% yield) of tan-colored needles; m. p. 250.5° (dec.).

For analysis[8] the product was crystallized from 95% alcohol with intermittent treatment with Darco G60 and yielded colorless prisms; m. p. 252° (dec.). Upon recrystallization from ethanol, the prisms melted at 252.5° (dec.).

Anal. Calcd. for $C_{16}H_{16}N_6O_4S_2$: N, 19.99. Found: N, 20.06.

Summary

The structure of 2,6-dibromopyrazine has been established by converting it to the known pyrazine-2,6-dicarboxylic acid.

Bromopyrazine has been converted into 2,6-dibromopyrazine by means of phosphorus pentabromide and phosphorus oxybromide.

2-Methylquinoxaline has been oxidized to pyrazine-2,5,6-tricarboxylic acid.

The following new compounds have been prepared: 2,6-dicyanopyrazine, 2-bromo-6-cyanopyrazine, pyrazine-2,6-diamide, 2,6-dimethoxypyrazine, 2,6-diethoxypyrazine, 2,6-di-(1-methylethoxy)-pyrazine, benzoxypyrazine, 6-bromo-2-hydroxypyrazine, 2-benzoxy-6-bromopyrazine, 2,6-diaminopyrazine, 2,6-di-(N⁴-acetylsulfanilamido)-pyrazine monoacetate and, 2,6-disulfanilamidopyrazine.

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(11) The preparation was carried out according to the conditions employed for the isomeric 2,3-diaminopyrazine by F. G. McDonald and R. C. Ellingson, THIS JOURNAL, **69**, 1034 (1947).

(12) The hydrolysis was conducted according to the preparation of sulfanilamidopyrazine by J. W. Sausville and P. E. Spoerri, THIS JOURNAL, **63**, 3153 (1941).