The mixture solidifies in few minutes and is kept at room temperature overnight. The reaction product is extracted with chloroform, the chloroform solution washed with water, dried over sodium sulfate and evaporated. The residue crystallizes from a mixture of chloroform and methanol in the form of prismatic plates, m. p. 148–149°, yield 20 g. (78.5%).

Anal. Calcd. for $C_{35}H_{44}O_2S_2$: C, 74.95; H, 7.91. Found: C, 74.81; H, 7.95.

Diethylmercaptol of Dehydroisoandrosterone Acetate (V).—The preparation proceeds in the manner described above for dibenzylmercaptol. The crude product crystallizes from acetone, m. p. 147–149°.

Anal. Calcd. for $C_{25}H_{40}O_2S_2$: C, 68.76; H, 9.23. Found: C, 69.00; H, 9.33.

Acid Hydrolysis of the Dibenzylmercaptol Acetate (III).—One hundred milligrams of the compound (III) is refluxed for one hour with 5 cc. of dioxane, 5 cc. of methanol and 0.4 cc. of concentrated hydrochloric acid. The warm solution is diluted with water and the precipitated needles are filtered off, m. p. 138–140°. The product gives no depression with dehydroisoandrosterone.

Alkaline Hydrolysis of the Dibenzylmercaptol Acetate (III).—One and one-tenth grams of the compound (III) is dissolved in 10 cc. of dioxane and a solution of 0.5 g. of sodium hydroxide in 20 cc. of methanol is added. The dibenzylmercaptol of dehydroisoandrosterone is precipitated by dilution with water and recrystallized from acetone; prismatic needles, m. p. 185–186°.

Anal. Calcd. for $C_{33}H_{42}OS_2$: C, 76.40; H, 8.16. Found: C, 76.48; H, 8.31.

Acetylation of the compound with acetic anhydride in pyridine at room temperature gives the original acetate.

Reaction of the Dibenzylmercaptol Acetate (III) with Mercuric Chloride and Cadmium Carbonate.—Two-hundred-fifty milligrams of the compound (III), 300 mg. of mercuric chloride and 400 mg. of cadmium carbonate are refluxed in 10 cc. of acetone and 1 cc. of water for eight hours. The inorganic salts are filtered off, the crude reaction product purified by adsorption on activated alumina, the benzene fraction yielding crystals of dehydroisoandrosterone acetate of the melting point 165–166°. The resulting dehydroisoandrosterone acetate may be isolated from the crude product by recrystallization from methanol if the reaction is carried out in acetic acid instead of acetone.

Desoxo-dehydroisoandrosterone Acetate (VII).—To a suspension of 40 g. of Raney nickel[5] in 120 cc. of methanol is added a solution of 4 g. of dibenzylmercaptol of dehydroisoandrosterone acetate in 120 cc. of acetone and the mixture is refluxed for two hours. The nickel is filtered off, washed with methanol, the filtrate evaporated and the residue (2 g., m. p. 86–91°) recrystallized from methanol, yielding leaflets of constant melting point, 96–97°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.56; H, 10.03.

Hydrogenolysis of the diethylmercaptol (V) is carried out in the same manner and gives an identical product.

Desoxo-dehydroisoandrosterone (VIII).—Nine-tenths gram of the acetate (VII) is refluxed with 1 g. of potassium hydroxide in 20 cc. of methanol for one hour. The hot solution is diluted with water until the first crystals appear and the mixture is cooled to complete the precipitation; long needles, m. p. 136–137°. Repeated recrystallization from aqueous methanol or from hexane does not change the melting point.

Anal. Calcd. for $C_{18}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.16; H, 11.16; $[\alpha]_D$ −75.8° (in dioxane).

Summary

1. The dibenzylmercaptol and the diethylmercaptol of dehydroisoandrosterone acetate have been prepared; conditions are described under which the selective hydrolysis of either the acetyl or mercaptol group may be carried out.

2. Desoxo-dehydroisoandrosterone and its acetate have been prepared by the hydrogenolysis of the mercaptols of dehydroisoandrosterone acetate with Raney nickel and the advantages of this method over the Wolff–Kishner reduction for this particular case have been shown.

(5) The Raney nickel was prepared according to Mozingo, *et al.*, THIS JOURNAL, **65**, 1477 (1943).

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF MEAD JOHNSON AND COMPANY]

Pyrazine Chemistry. III. Derivatives of 3-Amino-5,6-dimethylpyrazinoic Acid

BY RUDOLPH C. ELLINGSON AND ROBERT L. HENRY

3-Amino-5,6-dimethylpyrazinoic acid[1] can be obtained in excellent yield by the alkaline hydrolysis of 6,7-dimethyllumazine. The decarboxylation of this acid according to a modification of the described method[1] gives 2-amino-5,6-dimethylpyrazine (I) in good yield.

Bromination of I gives 2-amino-3-bromo-5,6-dimethylpyrazine (II). The structure of II was established by amination to the hitherto unknown diamine (III) followed by conversion of the diamine by reaction with glyoxal into the unknown 2,3-dimethylpyrazinopyrazine (IV). The structure of IV was established by its synthesis from diacetyl and the known 2,3-diaminopyrazine.[2] This series of reactions proves that in II the bromine atom is in position 3.

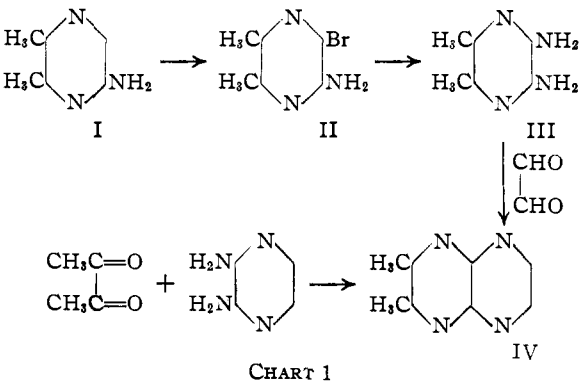

CHART 1

Condensation of III with diacetyl gave tetramethylpyrazinopyrazine. 2,3-Dimethylpyrazinopyrazine and tetramethylpyrazinopyrazine are

(1) Weijlard, Tishler and Erickson, THIS JOURNAL, **67**, 802 (1945).
(2) McDonald and Ellingson, *ibid.*, **69**, 1034 (1947).

members of a little known class of heterocyclic compounds, the basic ring structure of which is pyrazinopyrazine. The only compound found in the literature which might be considered to belong to this class is quinoxalo[2,3-b]quinoxaline.[3]

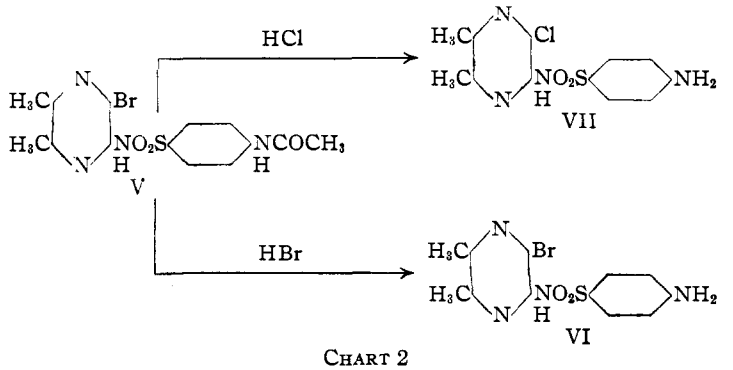

CHART 2

2-Amino-3-bromo-5,6-dimethylpyrazine (II) on reaction with acetylsulfanilyl chloride gave 2-(N^4-acetylsulfanilamido)-3-bromo-5,6-dimethylpyrazine (V). Deacetylation of V with hydrobromic acid gave the expected 2-sulfanilamido-3-bromo-5,6-dimethylpyrazine (VI), but deacetylation with hydrochloric acid gave the unexpected 2-sulfanilamido-3-chloro-5,6-dimethylpyrazine (VII). Even compound II is converted into 2-amino-3-chloro-5,6-dimethylpyrazine (VIII) when treated under similar conditions with a solution of ethanol and hydrochloric acid.

The replacement of carbon-linked halogen atoms in aliphatic and aromatic compounds by ionic halogen is not to our knowledge a frequently occurring phenomenon. Hepp[4] recorded the rapid conversion of chlorotrinitrobenzene into the iodo compound by treatment with a hot alcoholic solution of potassium iodide. Bennett and Vernon[5] reported the conversion of chloro-2,4-dinitrobenzene into the iodo compound by boiling it in a solution of sodium iodide in ethylene glycol. In compounds II, V and VI we have found that the bromine atom is readily replaced by chlorine on being treated with a solution of ethanol and hydrochloric acid.

Reaction between 2-amino-3-chloro-5,6-dimethylpyrazine (VIII) and acetylsulfanilyl chloride gives a mixture of the mono- and di-coupled compounds, the greater portion of which is the mono-coupled compound. Note that in the reaction[2] between 2-amino-3-chloropyrazine and acetylsulfanilyl chloride largely di-coupling occurred.

When III reacts mole for mole with acetylsulfanilyl chloride, the major portion of the product is the di-coupled compound from which 2,3-disulfanilamido-5,6-dimethylpyrazine (IX) may be obtained by deacetylation. Its solubility in dilute aqueous alkali indicates the 2,3-disulfanilamido structure. For an analogous case of 2,3-disulfanilamido substitution refer to paper II[2] of this series. A more soluble fraction which consists of a mixture of III and the mono-coupled compound, 2-(N^4-acetylsulfanilamido)-3-amino-5,6-dimethylpyrazine (X), was obtained by concentration of the mother liquors after removal of the di-coupled compound. X was separated from III by virtue of its greater solubility in aqueous alkali. This method, however, is unsatisfactory for preparing 2-sulfanilamido-3-amino-5,6-dimethylpyrazine (XI). XI is more readily obtained from VI by replacement of the bromine atom with the amino group.

The value of compounds VI, VII, IX and XI as anti-bacterial agents has been investigated by others and will be reported elsewhere. In preliminary studies 2-sulfanilamido-3-chloro-5,6-dimethylpyrazine (VII) proved to be the most interesting.

Experimental

3-Amino-5,6-dimethylpyrazinoic Acid.—This acid was prepared from 6,7-dimethyllumazine as described by Weijlard, *et al.*[1] The conversion of this acid into the methyl ester and amide was done by essentially the same procedure as was used for making 2-amino-3-carbomethoxypyrazine and 3-aminopyrazinamide.[6] The yield of crude ester was 51%. For analysis[7] the product was crystallized from water and came out as light yellow needles; m. p. 170–171° (cor.).

Anal. Calcd. for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 53.06, 52.78; H, 6.28, 6.24; N, 23.80, 23.66.

The yield of crude amide was low, 19.3%. The product was purified by crystallization from 85 parts of a 16% dioxane–water solution (v/v). The yellow, finely granular solid melted at 243–245° (dec.).

Anal. Calcd. for $C_7H_{10}N_4O$: C, 50.59; H, 6.07; N, 33.72. Found: C, 50.51, 50.41; H, 6.33, 6.22; N, 34.75, 34.57.

2-Amino-5,6-dimethylpyrazine (I).—This amine was prepared by Weijlard, *et al.*,[1] by decarboxylation of 3-amino-5,6-dimethylpyrazinoic acid in sulfuric acid. We made I by decarboxylation of the acid in carbitol acetate in much the same manner as the above-mentioned authors prepared aminopyrazine from 3-aminopyrazinoic acid. Pure 2-amino-5,6-dimethylpyrazine (I) exists as slightly yellow, brittle plates; m. p. 151° (cor.).

2-Amino-3-bromo-5,6-dimethylpyrazine (II).—One mole (123 g.) of crude 2-amino-5,6-dimethylpyrazine (I) was dissolved in 400 cc. of warm glacial acetic acid. After complete solution 54 cc. of bromine (5% excess) was added dropwise with stirring over a period of one hour. After five hours 1200 cc. of ethyl ether was added and the orange precipitate was collected. Without drying it was dissolved in 1600 cc. of hot water and the solution was decolorized with Norite. After filtration, the filtrate was made weakly alkaline by the addition of about 325 cc. of a 20% sodium hydroxide solution. The yellow granular solid was collected and air-dried. The yield was 154–163 g. (70.2–80.7%); m. p. 111–114°. For analysis a sample was crystallized three times from a 1 to 3 mixture

(3) Hinsberg and Pollak, *Ber.*, **29**, 785 (1896).

(4) Hepp, *Ann.*, **215**, 344 (1882).

(5) Bennett and Vernon, *J. Chem. Soc.*, 1783 (1938).

(6) Ellingson, Henry and McDonald, THIS JOURNAL, **67**, 1711 (1945).

(7) Dr. Carl Tiedcke, Laboratory of Microchemistry, New York, N. Y., performed the analyses recorded in this paper.

of ethanol and water. This compound crystallized as light yellow cubes; m. p. 114.7° (cor.). The compound sublimes readily in vacuum.

Anal. Calcd. for $C_6H_8BrN_3$: C, 35.66; H, 3.99; Br, 39.55; N, 20.80. Found: C, 35.65, 35.57; H, 3.84, 3.91; Br, 39.58, 39.84; N, 20.39, 20.31.

2,3-Diamino-5,6-dimethylpyrazine (III).—In each of four Carius tubes were placed 8.08 g. (0.04 mole) of crude 2-amino-3-bromo-5,6-dimethylpyrazine (II), 24 cc. of concentrated ammonium hydroxide and a trace of copper powder and the tubes were heated at 128° for twenty-four hours. After cooling, each tube was rinsed out with 75 cc. of water and the suspensions were combined and heated to dissolve all the crystalline solid. The hot solution was decolorized and filtered. After refrigeration the yellow needles were collected; they weighed 17.1 g. (77.4%); m. p. 211–214°. On repeated crystallizations of this diamine from water almost colorless needles were obtained; m. p. 216° (cor.).

Anal. Calcd. for $C_6H_{10}N_4$: C, 52.15; H, 7.29; N, 40.55. Found: C, 52.30, 52.08; H, 7.48, 7.38; N, 41.11, 40.90.

2,3-Dimethylpyrazinopyrazine (IV). A. (From glyoxal and 2,3-diamine-5,6-dimethylpyrazine).—A mixture of 4.14 g. (0.03 mole) of 2,3-diamino-5,6-dimethylpyrazine (III), 10 g. of glyoxal di-sodium bisulfite and 75 cc. of water was boiled under reflux for one hour. After cooling to room temperature, 20 cc. of concentrated ammonium hydroxide was added. On refrigeration long yellow needles separated; they weighed 1.83 g. (38.1%); m. p. 212–216° (dec.). On crystallization from 95% ethanol small, light yellow needles were obtained, m. p. 219° (dec.).

Anal. Calcd. for $C_8H_8N_4$: C, 59.98; H, 5.03; N, 34.98. Found: C, 59.97, 59.90; H, 4.87, 4.89; N, 36.14, 36.02.

B. **(From diacetyl and 2,3-diaminopyrazine).**—In 25 cc. of hot water were dissolved 0.75 g. of 2,3-diaminopyrazine[2] and 1.0 cc. of diacetyl. The solution was boiled under reflux for thirty minutes. On refrigeration yellow crystals separated; they weighed 0.5 g. (45.9%); m. p. 215–217° (dec.). On crystallization from ethanol, light yellow needles were obtained; m. p. 216–218° (dec.). There was no depression of the melting point on mixed melting of this compound with that obtained in A.

Anal. Calcd. for $C_8H_8N_4$: C, 59.98; H, 5.03; N, 34.98. Found: C, 59.23; H, 5.01; N, 36.24.

Tetramethylpyrazinopyrazine.—To a warm solution of 4.0 g. (0.028 mole) of 2,3-diamino-5,6-dimethylpyrazine (III) in 400 cc. of water was added 4.0 cc. of diacetyl. The solution was boiled under reflux for twenty-five minutes. As the clear orange solution cooled, long needles separated; they weighed 1.1 g.; m. p. 261–262°. By concentration of the mother liquors a second crop weighing 1.8 g. and melting at 260° was obtained. The total yield was 2.9 g. (55%). On two crystallizations from water, bright yellow needles were obtained; m. p. 261° (cor.).

Anal. Calcd. for $C_{10}H_{12}N_4$: C, 63.80; H, 6.43; N, 29.77. Found: C, 63.20, 63.51; H, 6.31, 6.19; N, 30.30, 30.16.

2-(N^4-Acetylsulfanilamido)-3-bromo-5,6-dimethylpyrazine (V).—A suspension of 156 g. (0.773 mole) of crude 2-amino-3-bromo-5,6-dimethylpyrazine (II) (dried over phosphorus pentoxide) in 980 cc. of dry pyridine was cooled to about 5° in an ice-bath. With constant stirring of the chilled suspension 190 g. (5.4% excess) of crystalline acetylsulfanilyl chloride was added over a period of forty-five minutes. After holding the reaction mixture at about 5° for five hours, it was allowed to come to room temperature and to stand overnight. The red-brown reaction mixture was poured into water and the pyridine removed by steam distillation in vacuum. After thorough cooling at 0°, the solid was collected and dried. The yield was 210 g. (68.2%) of a tan, light-weight powder; m. p. 204–206° (dec.). After one crystallization from a mixture of dioxane and water the melting point rose to 216° (dec.). For analysis the compound was crystallized from a mixture of ethanol and water; it came out in fluffy clusters of almost colorless small needles; m. p. 218° (dec.).

Anal. Calcd. for $C_{14}H_{15}BrN_4O_3S$: C, 42.11; H, 3.79; Br, 20.02; N, 14.03; S, 8.03. Found: C, 42.16, 42.13; H, 3.64, 3.71; Br, 19.76, 19.91; N, 14.90, 14.97; S, 8.00, 8.02.

2-Sulfanilamido-3-bromo-5,6-dimethylpyrazine (VI).—A mixture of 10 g. (0.025 mole) of 2-(N^4-acetylsulfanilamido)-3-bromo-5,6-dimethylpyrazine (V), 20 cc. of 40% hydrobromic acid and 60 cc. of 95% ethanol was boiled under reflux for thirty minutes. To the solution 200 cc. of water and 25 cc. of concentrated ammonium hydroxide then Darco-G60 were added. After filtration the filtrate was made weakly acid by the addition of hydrobromic acid. After thorough cooling the yellow granular solid was collected and dried. It weighed 7.7 g. (86%); m. p. 183–185°. After two crystallizations from 95% ethanol, the sulfonamide existed as small, light yellow crystals; m. p. 185° (cor.).

Anal. Calcd. for $C_{12}H_{13}BrN_4O_2S$: C, 40.34; H, 3.67; Br, 22.37; N, 15.68; S, 8.97. Found: C, 40.22, 40.13; H, 3.78, 3.79; Br, 22.70, 22.53; N, 16.67, 16.70; S, 8.40, 8.83.

2-Sulfanilamido-3-chloro-5,6-dimethylpyrazine (VII).—**A.** A mixture of 179 g. (0.449 mole) of 2-(N^4-acetylsulfanilamido)-3-bromo-5,6-dimethylpyrazine (V), 1000 cc. of 95% ethanol and 360 cc. of concentrated hydrochloric acid was boiled under reflux for forty-five minutes. Then Norite was added and the solution boiled five minutes longer. After filtration the hot solution was diluted with five liters of water and enough concentrated ammonium hydroxide was added to bring the *p*H to about 4. After thorough cooling the yellow granular solid was collected and dried. It weighed 119 g. (84.8%); m. p. 182–184°. After two crystallizations from 95% ethanol, large yellow crystals were obtained; m. p. 185° (cor.).

Anal. Calcd. for $C_{12}H_{13}ClN_4O_2S$: C, 46.08; H, 4.19; Cl, 11.34; N, 17.91; S, 10.25. Found: C, 45.82; H, 4.50; Cl, 11.70, 11.52; N, 17.90; S, 10.12.

B. To 50 cc. of pyridine at 55–60° a mixture of 6.0 g. (0.038 mole) of crystalline 2-amino-3-chloro-5,6-dimethylpyrazine (VIII) and 9.2 g. (5.0% excess) of acetylsulfanilyl chloride was added over a period of thirty minutes. The reaction mixture was held at that temperature for a total of four and one-half hours; then it was allowed to stand overnight at room temperature. The pyridine was removed by steam distillation in vacuum and after thorough cooling of the solution, the solid was collected and dried. The light yellow, fluffy product weighed 6.35 g. and melted at 195–207° (dec.). It was dissolved in 100 cc. of dioxane; the solution was filtered and the filtrate was diluted with 100 cc. of boiling water. The undissolved solid weighed 0.85 g. and melted at about 240° (dec.). As the filtrate cooled to room temperature a small quantity of solid separated; this was collected and dried; 0.7 g. melting at about 250° (dec.). The filtrate was then chilled in an ice-bath for several hours whereupon an almost colorless precipitate filled the solution. It weighed 4.4 g.; m. p. 208–210° (dec.).

The two portions of high melting material (0.85 g. and 0.7 g.) were combined and crystallized from 440 cc. of a 1 to 1 mixture of dioxane and water. After a second crystallization the small colorless crystals were analyzed; m. p. 269–270° (dec.). The analytical data show that some di-coupling has occurred; this compound is probably 2-di-(N^4-acetylsulfanilyl)-amino-3-chloro-5,6-dimethylpyrazine.

Anal. Calcd. for $C_{22}H_{22}ClN_5O_6S_2$: C, 47.87; H, 4.02; Cl, 6.42; N, 12.69; S, 11.60. Found: C, 47.70; H, 4.16; Cl, 6.20; N, 13.51; S, 11.54.

The 4.4-g. fraction was crystallized from a mixture of 150 cc. of dioxane and 300 cc. of water; 3.4 g. of slightly yellow granules was obtained; m. p. 210–212° (dec.). On another crystallization from a 2 to 1 mixture of water

and ethanol the compound came out as light yellow, glistening plates; the melting point remained unaltered. Analysis shows it to be 2-(N^4-acetylsulfanilamido)-3-chloro-5,6-dimethylpyrazine.

Anal. Calcd. for $C_{14}H_{15}ClN_4O_3S$: C, 47.39; H, 4.26; Cl, 9.99; N, 15.79; S, 9.04. Found: C, 47.18, 47.01; H, 4.22, 4.40; Cl, 10.02, 9.96; N, 16.66, 16.42; S, 8.88, 9.03.

Deacetylation of this compound gave a slightly yellow crystalline substance which melted at 185° and showed no depression on mixed melting with 2-sulfanilamido-3-chloro-5,6-dimethylpyrazine (VII) obtained in A.

2-Amino-3-chloro-5,6-dimethylpyrazine (VIII).—A mixture of 10 g. (0.0495 mole) of crude 2-amino-3-bromo-5,6-dimethylpyrazine (II), 60 cc. of 95% ethanol and 20 cc. of concentrated hydrochloric acid was boiled to effect solution. The solution was then diluted with 250 cc. of water and made weakly alkaline by the addition of ammonium hydroxide. After cooling the colorless granules were collected and dried; they weighed 3.5 g. (45%); m. p. 97–100°. The compound crystallizes from water in long colorless prisms; m. p. 98° (cor.).

Anal. Calcd. for $C_6H_8ClN_3$: C, 45.72; H, 5.12; Cl, 22.50; N, 26.66. Found: C, 45.60, 45.84; H, 5.22, 5.06; Cl, 22.63, 22.40; N, 27.40, 27.15.

2,3-Disulfanilamido-5,6-dimethylpyrazine (IX).—The reaction between 13.8 g. (0.1 mole) of 2,3-diamino-5,6-dimethylpyrazine (III) and 48 g. (0.206 mole) of crystalline acetylsulfanilyl chloride was carried out in pyridine under essentially the same conditions as those used for the preparation of V. The yield of crude 2,3-di-(N^4-acetylsulfanilamido)-5,6-dimethylpyrazine was 40.9 g. (76.8%) of yellow granules; m. p. 253–257° (dec.). Before analysis the compound was crystallized three times from a 2 to 1 mixture of water and ethanol (v/v). Small yellow crystals were obtained; m. p. 264° (dec.).

Anal. Calcd. for $C_{22}H_{24}N_6O_6S_2$: C, 49.61; H, 4.54; N, 15.78; S, 12.04. Found: C, 49.53, 49.40; H, 4.46, 4.35; N, 16.53, 16.32; S, 11.92, 11.90.

The deacetylation was carried out in an alcoholic solution of hydrochloric acid as described for the deacetylation of V. The yield was 90% of a yellow granular product melting at 257° (dec.). 2,3-Disulfanilamido-5,6-dimethylpyrazine (IX) was purified by solution in 31 parts of a 4 to 1 mixture of dioxane and water and, after decolorization and filtration, dilution with an equal volume of hot water; light yellow granular crystals were obtained. IX is insoluble in ethanol and in water and only slightly soluble in dioxane. It dissolves both in weakly acidic or basic aqueous solutions.

Anal. Calcd. for $C_{18}H_{20}N_6O_4S_2$: C, 48.20; H, 4.49; N, 18.74; S, 14.30. Found: C, 48.90, 48.80; H, 4.55, 4.58; N, 18.67, 18.73; S, 14.11, 13.99.

2-Sulfanilamido-3-amino-5,6-dimethylpyrazine (XI).—**A.** In a Carius tube were sealed 5.35 g. (0.015 mole) of 2-sulfanilamido-3-bromo-5,6-dimethylpyrazine (VI), 25 cc. of concentrated ammonium hydroxide and a trace of copper powder. The tube was heated at 105° for eight hours. The contents of the tube were diluted with 40 cc. of water and filtered. The filtrate was chilled and then neutralized by the gradual addition of dilute hydrochloric acid.[8] A yellow solid separated; it weighed 3.6 g. (84.7%); m. p. 204–207°. It was crystallized from a 10 to 1 mixture of ethanol and water. After three crystallizations large, slightly yellow crystals which melted at 207° (cor.) were obtained.

Anal. Calcd. for $C_{12}H_{15}N_5O_2S$: C, 49.13; H, 5.15; N, 23.88; S, 10.93. Found: C, 48.90, 48.71; H, 5.30, 5.27; N, 24.01, 24.04; S, 10.80, 10.98.

(8) If the acid is added too rapidly, and/or the solution has not been thoroughly chilled (0°), the compound may separate as a gray gummy mass which soon solidifies. It can be purified by crystallization from aqueous ethanol.

More drastic reaction conditions such as higher temperatures and/or longer reaction times lowered the yield of the desired compound. Since 2,3-diamino-5,6-dimethylpyrazine was then also isolated, the more drastic conditions cause cleavage of either the starting sulfonamide, VI, or the product, XI.

B. To a mechanically stirred suspension of 6.9 g. (0.05 mole) of 2,3-diamino-5,6-dimethylpyrazine (III) in 100 cc. of dry pyridine cooled to about 2° was added gradually over a period of thirty minutes 12 g. (0.051 mole) of crystalline acetylsulfanilyl chloride. One hour after the addition had been completed a solution of 2 g. of sodium hydroxide in 100 cc. of water was added and the pyridine was removed by steam distillation in vacuum. The aqueous solution, freed from pyridine, was diluted with water to a volume of 1.5 liters and then cooled to room temperature. The light yellow, granular solid was collected and dried. It weighed 4.5 g. and melted at 258–260° (dec.). It is 2,3-di-(N^4-acetylsulfanilamido)-5,6-dimethylpyrazine as there was no depression of the melting point on mixed melting of it with an authentic sample of 2,3-di-(N^4-acetylsulfanilamido)-5,6-dimethylpyrazine.

The filtrate was concentrated in vacuum to a volume of about 500 cc. and then cooled overnight in the refrigerator. The tan, partially crystalline solid (9.8 g.) melted at 205–230° and evidently was a mixture.

The 9.8 g. of mixture was suspended in 100 cc. of a 2.5 per cent. aqueous sodium hydroxide solution; 2.3 g. of solid remained undissolved. It melted at 215–217° and gave no depression of the melting point on mixed melting with an authentic sample of 2,3-diamino-5,6-dimethylpyrazine (III). Evidently it is unreacted diamino-dimethylpyrazine, III.

The clear yellow filtrate was carefully neutralized with dilute hydrochloric acid. On scratching the solution, a yellow solid separated. It weighed 2.7 g.; m. p. 225–231°. Crystallization from 150 cc. of a 2 to 1 ethanol–water solution (v/v) gave 2 g. of slightly pink crystals; m. p. 235–236°. This substance we believed to be 2-(N^4-acetylsulfanilamido)-3-amino-5,6-dimethylpyrazine (X). To confirm this belief we deacetylated the material in aqueous alcoholic hydrochloric acid and obtained 1.15 g. of colorless granules melting at 203–205°. There was no depression of the melting point on mixed melting of this compound with an authentic sample of 2-sulfanilamido-3-amino-5,6-dimethylpyrazine (XI) prepared from 2-sulfanilamido-3-bromo-5,6-dimethylpyrazine (VI). Obviously the way to prepare XI is by reaction of VI with ammonium hydroxide in the presence of copper rather than from III and acetylsulfanilyl chloride.

Summary

1. The preparation of five new simple pyrazine derivatives, namely, methyl-3-amino-5,6-dimethylpyrazinoate, 3-amino-5,6-dimethylpyrazinamide, 2-amino-3-bromo-5,6-dimethylpyrazine, 2-amino-3-chloro-5,6-dimethylpyrazine and 2,3-diamino-5,6-dimethylpyrazine, is described.

2. The chemical structures of 2-amino-3-bromo-5,6-dimethylpyrazine and 2,3-diamino-5,6-dimethylpyrazine have been established.

3. Two new members, 2,3-dimethylpyrazinopyrazine and tetramethylpyrazinopyrazine, of a little known class of heterocyclic compounds have been prepared and characterized.

4. Four new derivatives of sulfapyrazine have been synthesized, namely, 2-sulfanilamido-3-bromo-5,6-dimethylpyrazine, 2-sulfanilamide-3-chloro-5,6-dimethylpyrazine, 2-sulfanilamido-3-amino-5,6-dimethylpyrazine, and 2,3-disulfanilamido-5,6-dimethylpyrazine.

5. The replacement of the bromine atom in 2-amino-3-bromo-5,6-dimethylpyrazine and some of its derivatives with chlorine on treatment with aqueous hydrochloric acid in ethanol was unexpected.

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Strains in Methyl Amines and Hydrocarbons[1]

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H. C. Brown and co-workers have written a series of interesting articles on the anomalous basic strength of the methyl amines.[2] In order to eliminate complicating effects due to hydration, they worked in the gas phase and used trimethylboron as reference acid. They concluded that trimethylamine was weakened, in comparison with ammonia or mono- or dimethylamine, by a type of steric effect to which they referred as B-strain and which resulted from spreading of the methyl groups. We propose to show, by a semi-quantitative calculation, that the magnitude of the B-strain is far too small to account for the observed anomaly and that the anomaly is probably due to ordinary steric effects of the type referred to by Brown as F-strain.

Perhaps a brief description of our understanding of Brown's use of the term F-strain is in order at this time. Under this heading are lumped all types of steric strain resulting from the interference of groups attached to two adjacent atoms, including van der Waals repulsion, increase in the bonded distance, and interference with the preferred rotational configuration about the bond. It is our opinion that strains of this type are primarily responsible for the weakness of trimethylamine.

Let us quote from Dr. Brown's paper his definition of B-strain: "There are theoretical reasons for believing that the three bonds of a trivalent nitrogen atom should be directed in space at angles of 90° to each other. In all cases which have been investigated, however, the angles are considerably greater, probably because they must be increased to accommodate the attached groups. An electron diffraction investigation of trimethylamine led Brockway and Jenkins to the conclusion that the C–N–C angle in this molecule is 108 ± 4°.[3a] In the explanation here proposed, it is assumed that the bond angle in trimethylamine is somewhat greater than the normal tetrahedral angle, probably close to the upper limit set by Brockway and Jenkins. In other words, the three rather bulky methyl groups spread the bonds of the nitrogen atom from their preferred configuration (90°) to a value greater than the tetrahedral angle.

"In the trivalent nitrogen derivative, such spreading of the bond angles is relatively easy since the fourth position in the valence shell is not occupied. However, the addition of a fourth group to the vacant position, be it a proton or a trimethylboron molecule, forces the nitrogen atom toward a tetrahedral configuration and results in a reduction of the expanded angles. The methyl groups are, therefore, crowded toward each other, setting up a strain which reduces the stability of the addition compound.

"The term B-strain is proposed for this effect. (The letter B is used to indicate that the interference which causes the strain is localized at the "back" of the molecule—trimethylamine in the case under discussion—away from the entering group; it is thus contrasted to F-strain which results from interference at the front of the molecule, at the interface between the two components of the addition compound."

Our problem is thus to calculate the energy needed to crowd the methyl groups together to tetrahedral angles. This will be accomplished by calculating the energy needed to bend trimethylamine into the tetrahedral configuration. As long as the C–N–C bond angles remain the same, the actual addition of the acid can introduce only F, not B strain. Also any B strain already in the free base at its expanded angles is not significant since it is the change in B-strain on addition of the acid which would affect the energy or equilibrium in that reaction.[3b]

Total Strain in Amines.—In order to discuss this concept, it is necessary to estimate the amount of the B-strain. Brown estimates that the total strain is about 9000 kcal. per mole in the free energy of the trimethylamine–trimethylboron complex. Although he does not divide this into B-strain and ordinary steric strain (F-strains), he implies that the B strain is of considerable im-

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(2) (a) H. C. Brown, M. D. Taylor and M. Gerstein, THIS JOURNAL, **66**, 431 (1944). (b) H. C. Brown, H. Bartholomay, Jr., and M. D. Taylor, *ibid.*, p. 435. (c) H. C. Brown and M. D. Taylor, *ibid.*, **69**, 1332 (1947).

(3a) L. O. Brockway and Jenkins, *ibid.*, **58**, 2036 (1936). More recently V. Schomaker (private communication) has obtained for the C–N–C angle, 109 ± 2° for trimethylamine, 111 ± 3° for dimethylamine, 112 ± 3 for diethylamine and 113 ± 3° for triethylamine.

(3b) We have discussed this matter at considerable length because Dr. Brown does not agree that our calculation is in accord with his definition quoted above.