β-Methyl-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic Acid (V); Brucine Salt.—A solution of 3 g. of the acrylic acid (V) and 4.63 g. of anhydrous brucine in absolute ethanol was warmed on the steam-bath. Following removal of the solvent, 50 cc. of absolute ether was added and the viscous material triturated until a fine powder was formed. A sample of 3 g. of this product, m. p. 115–126° (cor.), was refluxed with 400 cc. of absolute ether and filtered from a small amount of brucine. The solution was kept at 0° for twenty-four hours, whereupon an additional 0.5 g. of brucine was obtained. The solution was filtered, concentrated, seeded, and within forty-eight hours 0.5 g. of the brucine salt, m. p. 132–134° (cor.), was obtained. The salt was analyzed without further crystallization since fresh solvent was found to decompose the salt causing brucine to precipitate. Further low-melting crops could be obtained on concentration of the mother liquors.

Anal. Calcd. for $C_{13}H_{15}ClO_3 \cdot C_{23}H_{26}N_2O_4$: C, 66.60; H, 6.37; N, 4.31. Found: C, 66.76; H, 6.42; N, 4.44.

Rotation. 0.1 g. made up to 5 cc. with absolute ethanol at 22° gave α_D −0.55; *l*, 1; $[\alpha]^{22}D$ −22°. No mutarotation was observed after seventeen hours. Decomposition of all salt fractions with cold aqueous hydrochloric acid gave only inactive acids.

β-Methyl-β-(2,4-dimethyl-6-methoxyphenyl)-N-acrylylglycine (XII); Brucine Salt.—A solution of 0.7 g. of β-methyl-β-(2,4-dimethyl-6-methoxyphenyl)-N-acrylylglycine (XII) and 1 g. of anhydrous brucine in 10 cc. of absolute ethanol was warmed on the steam-bath, then transferred to a breaker and the solvent removed in a vacuum desiccator over calcium chloride at room temperature. On digesting the oily residue with absolute ether, a white powder readily formed, m. p. 152–155° (cor.). The substance was instantaneously soluble in water. On refluxing 1 g. of the crude salt with 600 cc. of absolute ether all went into solution leaving merely a trace of an amorphous solid. Following filtration the solution was concentrated by spontaneous evaporation. After five days the volume had decreased to 200 cc. and 0.45 g. of a white crystalline solid, m. p. 158° (cor.), was obtained (Fraction A). Further concentration to 25 cc. gave 0.2 g. (Fraction B). The residue after complete evaporation was an oily solid.

Anal. Calcd. for $C_{15}H_{19}NO_4 \cdot C_{23}H_{26}N_2O_4$: C, 67.93; H, 6.75; N, 6.25. Found: C, 67.71; H, 6.64; N, 6.36.

Rotation. Fraction A. 0.1 g. made up to 5 cc. with absolute ethanol at 27° gave α_D −0.232; *l*, 1; $[\alpha]^{27}D$ −11.6°. After twelve and a half hours no evidence of mutarotation was observed.

Attempts to liberate the free glycine with cold aqueous hydrochloric acid gave merely oils.

Attempted Resolution of Other Acrylic Acids.—β-Methyl-β-(2,4-dimethyl-6-methoxyphenyl)-acrylic acid (IV) and α,β-dimethyl-β-(2,4-dimethyl-3-nitro-6-methoxyphenyl)-acrylic acid (IX) could not be induced to give crystalline alkaloidal salts by the procedures previously described.

Summary

1. 4,5,7-Trimethylcoumarin, prepared from 3,5-dimethylphenol and ethyl acetoacetate, and its 6-nitro and 6-chloro derivatives were hydrolyzed with alkali and methylated to β-methyl-β-(2,4-dimethyl-6-methoxyphenyl)-acrylic acid, β-methyl-β-(2,4-dimethyl-3-nitro-6-methoxyphenyl)-acrylic acid and β-methyl-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic acid.

2. 3,4,5,7-Tetramethylcoumarin, prepared from 3,5-dimethylphenol and ethyl methylacetoacetate and its 6-nitro and 6-chloro derivatives were hydrolyzed and methylated to α,β-dimethyl-(2,4-dimethyl-6-methoxyphenyl)-acrylic acid, α,β-dimethyl-(2,4-dimethyl-3-nitro-6-methoxyphenyl)-acrylic acid and α,β-dimethyl-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic acid.

3. Several of these acrylic acids formed alkaloidal salts which were oils, others crystalline salts which dissociated readily. Success attended only the resolution of α,β-dimethyl-β-(2,4-dimethyl-6-methoxyphenyl)-acrylic acid. Its half-life was seventy-four minutes in *n*-butanol at 44° and therefore much less than that of α-methyl-β-chloro-β-(2,4-dimethyl-3-chloro-6-methoxyphenyl)-acrylic acid (one hundred and seventy-three minutes). Thus it would appear that in this series of arylacrylic acids, a β-methyl has less effect on the stability than a β-chlorine atom.

4. A discussion of the geometric structure about the double bond of these acrylic acids is given.

URBANA, ILLINOIS RECEIVED JANUARY 29, 1945

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Some New Aminopyrazines and their Sulfanilamide Derivatives

BY JOHN WEIJLARD, MAX TISHLER AND A. E. ERICKSON

It has been established that the introduction of methyl groups into the heterocyclic system of N′ heterocyclic derivatives of sulfanilamides affects chemotherapeutic activity. In some instances the methyl derivatives are superior to the parent drug.[1] The therapeutic importance of 2-sulfanilamidopyrazine (sulfapyrazine)[2] indicates the necessity for the study of the substituted pyrazine-sulfonamides as effective chemotherapeutic agents.

A search of the literature for the requisite alkyl and aryl substituted aminopyrazines revealed that only one such derivative, 2-amino-3,6-dimethylpyrazine (prepared in poor yields by aminating 3,6-dimethylpyrazine with sodamide[3]) seems to be known. Moreover, the recorded methods for preparing aminopyrazine itself are laborious and the yields poor.[4] These processes entail the oxida-

(1) For a recent review of this subject see E. H. Northey, *Ind. Eng. Chem.*, **35**, 829 (1943).

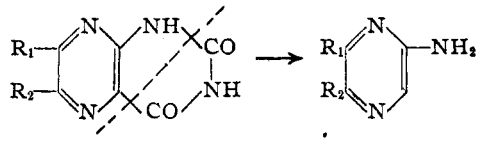
(2) Ellingson, THIS JOURNAL, **63**, 2524 (1941); Raiziss, Clemence and Freifelder, *ibid.*, **63**, 2739 (1941); Sansville and Spoerri, *ibid.*, **63**, 3153 (1941); Hamburger, Reugsegger, Brookens and Eakin, *Am. J. Med. Sci.*, **204**, 186 (1942).

(3) Chichibabin and Shukina, *J. Russ. Phys.-Chem. Soc.*, **62**, 1189 (1930); Joiner and Spoerri, THIS JOURNAL, **63**, 1929 (1941).

(4) Gabriel and Sonn, *Ber.*, **40**, 4859 (1907); Hall and Spoerri, THIS JOURNAL, **62**, 664 (1940).

tion of quinoxaline to pyrazine-2,3-dicarboxylic acid and conversion of the latter to aminopyrazine by a series of steps involving a Hofmann degradation.

We have developed a simple and probably general method for preparing 5- and 6-alkyl or aryl substituted aminopyrazines as well as the parent amine whereby the amines are formed directly on heating the corresponding lumazines[5] with sulfuric acid. Aminopyrazine (I) is obtained from lumazine in 79% yield; however, substituted aminopyrazines are formed in lower yields from the corresponding lumazines. The substituted aminopyrazines prepared by this simple procedure include 2-amino-5,6-dimethylpyrazine (II), 2-amino-5,6-diphenylpyrazine (III), 2-amino-5 (or 6)-phenylpyrazine (IV), and 2-amino-6-methylpyrazine (V).

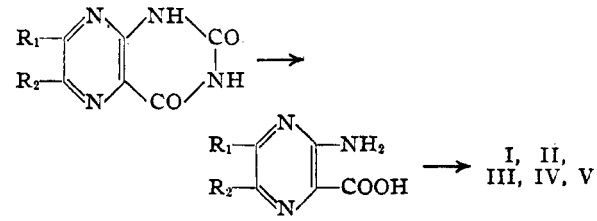


I, R_1, R_2 = H
II, R_1, R_2 = CH_3
III, R_1, R_2 = C_6H_5
IV, R_1 = C_6H_5; R_2 = H
V, R_1 = CH_3; R_2 = H

The concentration of the sulfuric acid is important in cleavage of lumazines. For lumazine itself, 100% sulfuric acid is best, whereas with methyl and phenyl derivatives 80% sulfuric acid gives optimum yields. The reaction is carried out by heating the lumazines with sulfuric acid above 190°. The high yield of aminopyrazine from lumazine by heating with 100% sulfuric acid at 240° for fifteen minutes is striking and bears witness to the resistance of the pyrazine nucleus to substitution reactions.

As methyllumazine, prepared from methyl glyoxal and 4,5-diamino-2,6-dihydroxypyrimidine, is either 6- or 7-methyllumazine or a mixture of the two,[5] the aminomethylpyrazine derived from it must be either 2-amino-5- or -6-methylpyrazine or a mixture. The product obtained by us after recrystallization was essentially a pure compound. A phase-solubility study indicated that the purified amine was at least 97% pure.[6] To establish the structure of the amine, we synthesized 2-amino-5-methylpyrazine from 2-carboxyl-5-methylpyrazine[7] by conversion to the amide and Hofmann degradation of the latter. As the resulting 2-amino-5-methylpyrazine is different from the compound obtained by cleaving monomethyllumazine, the amine in question must be 2-amino-6-methylpyrazine (V).

The lumazines are also cleaved by alkalies. The products are derivatives of 2-aminopyrazine-3-carboxylic acids which are readily decarboxylated to the aminopyrazines. Lumazine is very slowly



attacked by alkali at 100–105°.[8] At this temperature a mixture of lumazine in 20% sodium hydroxide is only slightly hydrolyzed in five hours but is converted in good yields to the amino acid in 72 to 96 hours. The optimum yield of 2-aminopyrazine-3-carboxylic acid is obtained when a solution of lumazine and two to three equivalents of 12% alkali is heated at 170° for two hours. Stronger alkali and longer heating times yield some 2-hydroxypyrazine-3-carboxylic acid, the sole product when lumazine is heated with four equivalents of alkali at 170° for twenty-four hours. Under these conditions 2-aminopyrazine-3-carboxylic acid is also converted to the hydroxy acid. The latter is readily decarboxylated to hydroxypyrazine by heating in an appropriate solvent at about 200°. It is interesting to note that although substituted hydroxypyrazines have been prepared,[9] the parent compound, hydroxypyrazine, has not been described.

In contrast to lumazine, the substituted lumazines under the alkaline cleavage conditions do not form the hydroxy acids. The substituted amino acids, unlike 2-aminopyrazine-3-carboxylic acid, are stable to strong alkali at elevated temperatures. The substituted amino acids are decarboxylated conveniently by heating with 80% sulfuric acid.

The sulfanilamidopyrazines were prepared by the reaction of the aminopyrazines and acetylsulfanilyl chloride in the presence of pyridine followed by acid hydrolysis of the acetyl derivatives thus formed. 2-Sulfanilamido-5,6-diphenylpyrazine is particularly interesting because of its unusual solubility in organic solvents. The chemotherapeutic activities of these compounds are under investigation in the Merck Institute for Therapeutic Research and will be reported later.

Experimental

Lumazines.—The method for preparing the lumazines consists of allowing the appropriate α-dicarbonyl compound

(5) The preparation of lumazines has been investigated by (a) Kuhn and Cook, *Ber.*, **70**, 761 (1937); (b) Ganapati, *J. Indian Chem. Soc.*, **14**, 627 (1937).

(6) We are indebted to Dr. N. R. Trenner of the Research Laboratories of Merck & Co., Inc., for carrying out this study.

(7) Gabriel and Pinkus, *Ber.*, **26**, 2206 (1893); Stoehr, *J. prakt. Chem.*, **47**, 480 (1895).

(8) The possibility of converting lumazine to aminopyrazine by hydrolysis under both acid and alkaline conditions was disclosed to and discussed with Drs. C. E. Bills, R. C. Ellingson and F. G. McDonald of Mead, Johnson & Co., who at a later time revealed to us (private communication) that they had succeeded in developing the alkaline hydrolysis of lumazine at elevated temperatures to produce 2-aminopyrazine-3-carboxylic acid in commercially satisfactory yields.

(9) Japp and Knox, *J. Chem. Soc.*, **87**, 701 (1905); McCombie and Parry, *ibid.*, **95**, 584 (1909); Ingram, *ibid.*, **130**, 692 (1927); Tota and Elderfield, *J. Org. Chem.*, **7**, 313 (1942).

to react with 4,5-diamino-2,6-dihydroxypyrimidine. As our procedures differ from those recorded[5] and result in better yields, our methods are described. 4,5-Diamino-2,6-dihydroxypyrimidine was prepared according to the procedure of Bogert and Davidson.[10]

(a) **Lumazine.**—Twenty grams of glyoxal sodium bisulfite was dissolved in 400 cc. of water, 20 cc. of concd. ammonia was added, followed by 10 g. of 4,5-diamino-2,6-dihydroxypyrimidine. The mixture was heated to 90° for five minutes. The hot solution was treated with charcoal, filtered and chilled. The crude material containing 12% water weighed 11.4 g. (87.0% yield). This product was sufficiently pure for the cleavage experiments, but to obtain an analytically pure sample it was necessary to crystallize twice in water and dry at 100° (1 mm.). This purified lumazine melted at 348–349°.

Anal. Calcd. for $C_6H_4O_2N_4$: C, 43.89; H, 2.48; N, 34.14. Found: C, 43.77; H, 2.54; N, 34.08.

(b) **6,7-Dimethyllumazine.**—A mixture of 21.3 g. (0.15 mole) of 4,5-diamino-2,6-dihydroxypyrimidine and 15.6 g. (0.18 mole) of diacetyl in 800 cc. of water was boiled gently for fifteen minutes and cooled at 2° overnight. The product, after washing with water and alcohol and drying, weighed 19.8 g. (68.7%); m. p. 350–351° dec.

Anal. Calcd. for $C_8H_8O_2N_4$: C, 49.97; H, 4.20; N, 29.16. Found: C, 49.76; H, 4.35; N, 29.19.

(c) **6,7-Diphenyllumazine.**[5b]—A mixture of 14.2 g. (0.1 mole) of 4,5-diamino-2,6-dihydroxypyrimidine, 21.0 g. (0.1 mole) of benzil, 1 liter of water, 1 liter of alcohol and 100 cc. of concentrated ammonia was heated at 85–90° for one-half hour and filtered while hot. After cooling at 2° for forty-eight hours, the product was collected, washed with ice water, and then alcohol. The product weighed 20.2 g. (64.5%) and melted at 315–322°. After dissolving in dilute ammonia and precipitating with acetic acid, the melting point remained unchanged.

Anal. Calcd. for $C_{18}H_{12}O_2N_4$: C, 68.34; H, 3.82; N, 17.72. Found: C, 68.34; H, 3.57; N, 18.02.

(d) **6 or 7-Monomethyllumazine.**—To a solution of 87 g. (1 mole) of isonitrosoacetone in 3 liters of water was added 250 cc. of 50% sulfuric acid, and the mixture was boiled under reflux for fifteen minutes. After adding to the hot solution 106.5 g. (0.75 mole) of 4,5-diamino-2,6-dihydroxypyrimidine, the mixture was boiled under reflux for thirty minutes, filtered, and cooled to 2°. The collected product was washed with water and dried at 85°, yield 104 g. (77.9%).

Monomethyllumazine was also prepared by the recorded procedure[5a] yielding a product identical with that obtained above with respect to physical properties and behavior on cleavage. In each case the product was difficult to recrystallize because of the tendency to form gels. The crude product was used with satisfactory results.

(e) **6- or 7-Phenyllumazine.**[11] To a warm solution of 57 g. of 4,5-diamino-2,6-dihydroxypyrimidine in 750 cc. of water and 150 cc. of concentrated ammonia was added 57 g. of phenylglyoxal. The mixture was refluxed for one hour, cooled, and acidified with acetic acid. The product was separated and washed with alcohol. The yield of pale yellow product was 72.5 g. (71%); m. p. above 300°.

Anal. Calcd. for $C_{12}H_8N_4O_2$: C, 60.01; H, 3.36. Found: C, 60.11; H, 3.54.

2-Aminopyrazine-3-carboxylic Acid.—A solution of hydrated lumazine, corresponding to 20 g. of anhydrous material, in 80 cc. of water containing 11 g. of sodium hydroxide, was heated in a bomb for two hours at 170°. The reaction mixture was acidulated with hydrochloric acid (*p*H 2.5), chilled to 2° and the product collected and washed with ice water; yield 15.85 g., 93.5%; m. p. 198°.

The compound was purified by dissolving 2 g. of the crude acid in 120 cc. of boiling water, adjusting the *p*H to 2.5 with hydrochloric acid, decolorizing, and cooling; yield 1.6 g., m. p. with dec. 201°.[12] The product gives a wine-red color when treated with a solution of ferric chloride.

Anal. Calcd. for $C_5H_5O_2N_3$: C, 43.15; H, 3.61; N, 30.23. Found: C, 43.26; H, 3.61; N, 29.86.

2-Amino-6-methylpyrazine-3-carboxylic Acid.—A mixture of 18.7 g. of monomethyllumazine and a solution of 16 g. of sodium hydroxide in 95 cc. of water was heated at 170–172° for twenty hours. The solution was cooled to 80° and acidified with hydrochloric acid to *p*H 2.5. After cooling to 2°, the product was filtered, washed with ice water and dried at 80°. The average yield of several such runs was 4.7 g. (31.4%) melting at 205°. When the crude acid was purified as outlined above, the product melted with dec. at 211–212°.

Anal. Calcd. for $C_6H_7O_2N_3$: C, 47.05; H, 4.60; N, 27.45. Found: C, 46.67; H, 4.47; N, 27.42.

2-Amino-5,6-diphenylpyrazine-3-carboxylic Acid.—Three grams of crude diphenyllumazine was added to a solution of 6 g. of sodium hydroxide in 30 cc. of water, and the mixture was boiled under reflux for thirty-five hours. An oily mass separated which solidified on cooling. The upper layer was decanted and the lower was washed with ice water and dried *in vacuo*. The product (crude sodium salt) was dissolved in 30 cc. of warm water, and the amino acid was precipitated with barium chloride solution. The barium salt (2.57 g.) was suspended in 50 cc. of water, 10 cc. of 10% hydrochloric acid was added and the mixture was heated to 80°. About 200 cc. of methanol was added to effect solution. The hot solution was filtered, diluted with four volumes of water, and the precipitated fine crystals were collected, washed and dried; yield 1.50 g.; m. p. 188° dec. The material was dissolved in ethyl ether, and the solution was filtered and concentrated to a small volume. The product crystallized out on adding petroleum ether. The product (m. p. 189° with dec.) gives a wine-red ferric chloride test.

Anal. Calcd. for $C_{17}H_{13}O_2N_3$: C, 70.07; H, 4.50; N, 14.44. Found: C, 69.90; H, 4.77; N, 14.25.

2-Amino-5,6-dimethylpyrazine-3-carboxylic Acid.—A mixture of 2.7 g. of crude 6,7-dimethyllumazine and a solution of 2.7 g. of sodium hydroxide in 25 cc. of water was heated at 170–175° for twenty hours. The solution was acidified with hydrochloric acid to *p*H 2.5 and cooled to 2°. The crystals were collected, washed with ice water and dried at 80°; yield 2.15 g. (91.5%); m. p. with dec. 208–209°.

A pure sample was prepared by dissolving 0.40 g. of crude acid in 65 cc. of boiling water containing a little hydrochloric acid, chilling the clear solution, collecting the crystals, etc.; yield 0.30 g.; m. p. 209–210° with dec. A mixture with the above monomethyl compound melted at 192° with dec. The product gave a wine-red ferric chloride test.

Anal. Calcd. for $C_7H_9O_2N_3$: C, 50.29; H, 5.42; N, 25.15. Found: C, 50.25; H, 5.18; N, 25.60.

2-Aminopyrazine.—(a) To 50 cc. of preheated 100% sulfuric acid (prepared from 95% sulfuric acid and oleum) was added 5 g. of hydrated (12% water) crude lumazine and the mixture was held at 240–245° for fifteen minutes. To the cooled reaction mixture was added 200 g. of ice followed by excess 30% sodium hydroxide. The strongly alkaline solution was extracted with ether and the ether extracts evaporated to dryness; yield 2.01 g. of material (79.1%); m. p. 118–120°. A mixed melting point with 2-aminopyrazine made by the Hall and Spoerri method[4] showed no depression.

Anal. Calcd. for $C_4H_5N_3$: C, 50.50; H, 5.30; N, 44.20. Found: C, 50.72; H, 5.24; N, 43.83.

(b) Twenty-five grams of 2-aminopyrazine-3-carboxylic acid was mixed with 75 cc. of carbitol acetate and boiled

(10) Bogert and Davidson, THIS JOURNAL, **55**, 1668 (1933).

(11) The preparation of this compound, the corresponding aminopyrazine and the sulfanilamide derivative of the latter were carried out by Dr. F. Wolf of the Research Laboratories of Merck & Co., Inc.

(12) The melting points in all cases were carried out according to U. S. P. If a faster rate of heating is employed, much higher melting points are obtained; 210° was recorded by Gabriel and Sonn.[4]

under reflux for fifteen minutes. The hot reaction mixture was filtered after adding a little charcoal, diluted with 225 cc. of petroleum ether and chilled to 0°. The crystals were collected and washed with petroleum ether; yield, 14.0 g., 82.0%; m. p. 118–120°.

Anal. Found: C, 50.61; H, 5.32; N, 44.29.

2-Amino-5,6-dimethylpyrazine.—(a) Eight grams of crude dimethyllumazine was mixed with 120 cc. of 80% sulfuric acid, and the mixture was boiled under reflux at 195–200° for seventy-five minutes. The reaction mixture was worked up as described above; 0.96 g. (18.9%) of product was obtained.

This crude product was purified by dissolving 0.25 g. in 5 cc. of hot benzene, adding a few drops of petroleum ether and chilling at 0°. The crystals were collected and washed with petroleum ether; yield 0.15 g., m. p. 140–144°. The product was found to be appreciably volatile *in vacuo* at 65°.

Anal. Calcd. for $C_6H_9N_3$: C, 58.48; H, 7.38; N, 34.14. Found: C, 58.20; H, 7.15; N, 34.55.

(b) A mixture of 2.15 g. of crude 2-amino-5,6-dimethylpyrazine-3-carboxylic acid in 20 cc. of 80% sulfuric acid, was refluxed for ten minutes at about 200°. The reaction mixture was worked up and the product purified as described above under (a); yield 1.48 g.; (93.7%); m. p. 140–144°. A mixed melting point with the product obtained under (a) showed no depression.

Anal. Found: C, 58.26; H, 7.23; N, 33.80.

2-Amino-5,6-diphenylpyrazine.—(a) Crude diphenyllumazine (15 g.) in 225 cc. of 80% sulfuric acid was boiled under reflux for thirty minutes at 195–200°. To the cooled reaction mixture was added 1500 g. of ice followed by 700 cc. of 30% sodium hydroxide solution. The insoluble compound was filtered off, washed several times with 15% sodium hydroxide, then water until free from alkali, and dried *in vacuo;* yield 2.40 g., 21.9%; m. p. 224–226°. After one crystallization from ether, the white compound melted at 227–228°.

Anal. Calcd. for $C_{16}H_{13}N_3$: C, 77.70; H, 5.30; N, 17.00. Found: C, 77.84; H, 5.15; N, 16.67.

(b) One-half gram of crude 2-amino-5,6-diphenylpyrazine-3-carboxylic acid was added to 10 cc. of 80% sulfuric acid and the mixture was refluxed for thirty minutes. The reaction mixture was worked up as under (a); yield 0.125 g. (30.0%); m. p. 225–227°. After one crystallization from ether, the compound melted at 227–228°. A mixed melting point determination with the product obtained under (a) showed no depression.

Anal. Found: C, 77.68; H, 5.40; N, 17.01.

2-Amino-5(or 6)-phenylpyrazine.—A mixture of 60 ml. of 80% sulfuric acid and 4.8 g. of phenyllumazine was heated at 217–222° for fifteen minutes. After cooling and diluting with ice water, the solution was made alkaline with ammonia and extracted with ether. The combined ether extracts were dried over anhydrous sodium sulfate and evaporated to dryness. The residue (0.5 g., 14.5%) was recrystallized from water as lustrous white platelets, m. p. 130–131°.

Anal. Calcd. for $C_{10}H_9N_3$: C, 70.16; H, 5.30. Found: C, 70.18; H, 5.18.

2-Amino-6-methylpyrazine.—(a) Ten grams of crude hydrated (8% water) monomethyllumazine was mixed with 200 cc. of 80% sulfuric acid, and the mixture was boiled under reflux for two hours at 195–200°. To the cooled reaction mixture was added 1200 g. of ice followed by 800 cc. of 30% sodium hydroxide solution and 200 g. of ammonium sulfate. The alkaline solution was extracted with ether and the combined ether extracts were concentrated to dryness; yield 0.34 g. (6.2%) of crude product. After one crystallization in ether–petroleum ether, the yellow compound melted at 124–125°.

Anal. Calcd. for $C_5H_7N_3$: C, 55.00; H, 6.47; N, 38.53. Found: C, 55.06; H, 6.52; N, 38.27.

(b) Crude 2-amino-6-methylpyrazine-3-carboxylic acid (12.5 g.) was added to 37.5 cc. of 80% sulfuric acid. While stirring, the mixture was heated as rapidly as the frothing permitted to 180° and maintained at this temperature for ten minutes. The hot solution was poured onto ice and made alkaline by the addition of 30% caustic solution. The mixture was extracted with ether and the combined ether extracts, after drying over anhydrous sodium sulfate, were concentrated to dryness. The residue, 6.7 g. (76.1%) was essentially pure product (m. p. 124–126°). A sample for analysis was recrystallized from ether–petroleum ether. A sample mixed with (a) melted at 124–125°.

Anal. Found: C, 55.30; H, 6.59; N, 38.91.

2-Amino-5-methylpyrazine.—A mixture of 5.4 g. of 5-methylpyrazine-2-carboxylic acid, 15 cc. of methanol, 1 g. of anhydrous sodium sulfate and 0.4 cc. of concentrated sulfuric acid was boiled under reflux for six hours. The reaction mixture was treated with charcoal and filtered. The alcoholic solution of the ester was chilled in ice, saturated with anhydrous ammonia and then chilled at 2° overnight. Three volumes of cold ether was added whereby the product separated. The yield of crude 2-carboxamido-5-methylpyrazine was 4.85 g. (89.2%); m. p. 210–211°.

To a cold solution of potassium hypochlorite prepared from 13.3 g. of potassium hydroxide, 24 cc. of water, 24 g. of ice and 4.23 g. of chlorine was added 60 g. of ice and 8.1 g. of crude 2-carboxamido-5-methylpyrazine. The mixture was agitated about twenty minutes at 0°, allowed to warm up to room temperature gradually, then heated on the steam-bath forty-five minutes. After cooling, 20 g. of sodium hydroxide was added, and the solution was extracted with ether. The ether extracts were concentrated to dryness. The residue of bright yellow crystals weighed 4.37 g. (67.8%); m. p. 116–118°. A mixture with 2-amino-6-methylpyrazine melted at 62–70°.

Anal. Calcd. for $C_5H_7N_3$: C, 55.00; H, 6.47; N, 38.53. Found: C, 54.94; H, 6.20; N, 38.45.

2-Hydroxypyrazine-3-carboxylic Acid.—(a) Two grams of 2-aminopyrazine-3-carboxylic acid was dissolved in 20 cc. of 20% sodium hydroxide solution and the mixture was heated in a steel bomb at 170° for twenty hours. The reaction mixture was diluted with 50 cc. of water and acidulated with hydrochloric acid to a *p*H of 2.5 to 3. The crystals were collected, washed with ice-water and dried; yield 1.62 g. (81%); m. p. 218–220°.

A sample for analysis was prepared by dissolving the crude acid in a solution of sodium bicarbonate in water, decolorizing, and reprecipitating with acid. The white compound melted at 218–220° and gave a wine-red color when treated with ferric chloride solution.

Anal. Calcd. for $C_5H_4O_3N_2$: C, 42.84; H, 2.88; N, 20.00. Found: C, 42.64; H, 3.21; N, 20.40.

(b) To a solution of 122 g. of sodium hydroxide in 600 cc. of water was added 125 g. of lumazine, and the mixture was heated at 170° for twenty-four hours in a bomb. The reaction mixture was worked up and purified as under (a); yield 96.4 g., 91%; m. p. 218–220°.

Anal. Found: C, 42.90; H, 2.89; N, 20.29.

2-Hydroxypyrazine.—Five grams of crude 2-hydroxypyrazine-3-carboxylic acid, obtained under (b), was mixed with 15 cc. of carbitol acetate and boiled under reflux for ten minutes. After cooling, 50 cc. of petroleum ether was added, the crystals were collected and washed with petroleum ether; yield 3.09 g., 90.1%; m. p. 181–182°.

The crude material was extracted in a Soxhlet extractor with benzene for five hours, and the crystals removed from the benzene solution at room temperature; yield 2.5 g.; m. p. 186–187°. The product was dissolved in hot alcohol, the solution was decolorized, filtered and chilled to 0°. The brilliant yellow needles were collected on a filter and washed with ether; yield about 90%; m. p. 187–188°.

Anal. Calcd. for $C_4H_4ON_2$: C, 50.00; H, 4.17; N, 29.17. Found: C, 50.15; H, 4.44; N, 29.40.

Sulfanilamidopyrazines: Example.—Two grams of 2-amino-5,6-dimethylpyrazine was dissolved in 25 cc. of pyridine. To the cooled solution was added 4.2 g. of acetylsulfanilyl chloride in small portions with stirring at 5 to 10°.

TABLE I

Compound[a]	Over-all yield, %	M. p., °C.[b]	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2-S-5,6-Dimethylpyrazine	80	261.5–262	$C_{12}H_{14}O_2N_4S$	51.76	5.07	20.16	51.62	4.95	20.31
2-N⁴-Acetyl-S-5,6-dimethylpyrazine		233 –234	$C_{14}H_{16}O_3N_4S + {}^1/_2H_2O$	51.03	5.20	17.02	51.26	4.97	17.38
2-S-5,6-Diphenylpyrazine[c]	41	115	$C_{22}H_{18}O_2N_4S + H_2O$	62.83	4.79	13.33	62.94	5.01	13.50
2-N⁴-Acetyl-S-5,6-diphenylpyrazine		194.5–195	$C_{24}H_{20}O_3N_4S$	64.83	4.54	12.61	64.90	4.22	12.56
2-S-6-Methylpyrazine	68	258 –259	$C_{11}H_{12}O_2N_4S$	49.96	4.58	21.21	50.16	4.74	21.36
2-N⁴-Acetyl-S-6-methylpyrazine[d]		239 –239.5	$C_{13}H_{14}O_3N_4S + {}^1/_2H_2O$	49.49	4.79	17.77	49.56	4.75	17.85
2-S-5-Methylpyrazine	70	237.5–238.5	$C_{11}H_{12}O_2N_4S$	49.96	4.58	21.21	50.20	4.57	21.11
2-N⁴-Acetyl-S-5-methylpyrazine[d]		240 –241	$C_{13}H_{14}O_3N_4S$	50.94	4.61	18.30	51.16	4.97	18.60
2-S-5- or 6-phenylpyrazine	80	270 –271	$C_{16}H_{14}O_2N_4S$	58.88	4.32	17.17	58.82	4.73	17.16
2-N⁴-Acetyl-S-5- or 6-phenylpyrazine		237 –240	$C_{18}H_{16}O_3N_4S$	58.68	4.38		57.95	4.66	

[a] S = sulfanilamido. [b] All m. p. corrected. [c] This sulfa drug dissolves in ether, alcohols, benzene and chloroform. [d] Mixed m. p. between 2-N⁴-acetyl-S-6-methylpyrazine and 2-N⁴-acetyl-S-5-methylpyrazine, 210°.

The mixture was held at 40–50° for two hours and allowed to stand overnight at room temperature. The greater part of the pyridine was distilled off *in vacuo*, and the residue was diluted with 100 cc. of water. The crystalline product was filtered off, washed with water and dried; yield 4.22 g., 81.1%.

Four grams of the crude acetyl compound was hydrolyzed by boiling with a mixture of 30 cc. of alcohol and 15 cc. of concentrated hydrochloric acid under reflux for one hour. The mixture was diluted with 100 cc. of water and 50 cc. of concentrated ammonia water was added in order to effect solution. After decolorizing with a suitable charcoal, the solution was acidified with acetic acid, the crystals were collected, washed thoroughly and dried; yield 3.00 g. of 2-sulfanilamido-5,6-dimethylpyrazine, 86.4%.

The other compounds were obtained in a similar manner. In some cases it was necessary to crystallize the compounds from solvents.

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Summary

Improved methods for preparing lumazine and derivatives substituted in the 6,7-positions have been described. A degradation reaction for converting lumazine and substituted lumazines to aminopyrazines is recorded which has been utilized for the rapid and convenient preparation of 2-aminopyrazine and 2-aminopyrazines substituted in 5 and 6 positions. On alkaline hydrolysis the lumazines are converted to the corresponding 2-aminopyrazine-3-carboxylic acids which can be decarboxylated to the 2-aminopyrazines. More vigorous alkaline hydrolysis of lumazine and of 2-aminopyrazine-3-carboxylic acid yields 2-hydroxypyrazine-3-carboxylic acid.

From the new aminopyrazines, the corresponding new sulfanilamide compounds and their acetyl derivatives have been prepared.

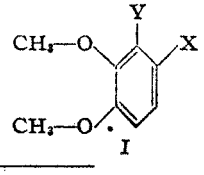
RAHWAY, N. J. RECEIVED FEBRUARY 13, 1945

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Studies in the Veratrole Series

BY RICHARD T. ARNOLD AND NEWMAN BORTNICK[1,2]

Disubstituted veratrole derivatives of type I are not readily available, and in the past these have been obtained by the degradation of certain alkaloids[3] or by tedious indirect synthetic methods. Direct nuclear substitution usually gives rise to the exclusive formation of compounds related to II.[4]



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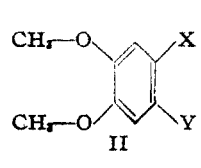

II

Carboxyl groups often undergo replacement during aromatic substitution reactions when they occupy a position ortho or para to an alkoxyl group. On the contrary, ester groups are not eliminated unless they are converted to carboxyl during the course of the reaction. By applica-

(1) Abstracted from the Ph.D. thesis of Newman M. Bortnick which was accepted by the Graduate Faculty in February, 1944.

(2) Sharp and Dohme Fellow, 1942–1944.

(3) Haworth, Perkin and Stevens, *J. Chem. Soc.*, 1764 (1926).

(4) Arnold and Bordwell, THIS JOURNAL, **64**, 2983 (1942).