complex having the formula (tetren·H_2·3HCl)$CuCl_4$ should have been formed with equal ease.

Consequently the structures given in column 3 of Table II are tentatively assigned.

Further investigation of the properties of these crystalline compounds by both X-ray and microscopic methods is under way.

Acknowledgment.—The generous assistance of Mr. Merril E. Jefferson, Physicist at the Southern Regional Research Laboratory, New Orleans, in the microscopic investigation is gratefully acknowledged.

Summary

This paper reports the repetition of the preparation of (1) ethylenediammonium tetrachlorocuproate, and the preparation of (2) diethylenetriammonium pentachlorocuproate, and (3) triethylenetetrammonium hexachlorocuproate.

These compounds appear to be completely dissociated in aqueous solution.

Tentative structures have been assigned in which coördination numbers for the copper of four, five and six, respectively, are assumed.

NEW ORLEANS, LA. RECEIVED APRIL 23, 1945

[CONTRIBUTION FROM THE RESEARCH LABORATORY, MEAD JOHNSON AND CO.]

Pyrazine Chemistry. I. Derivatives of 3-Aminopyrazinoic Acid

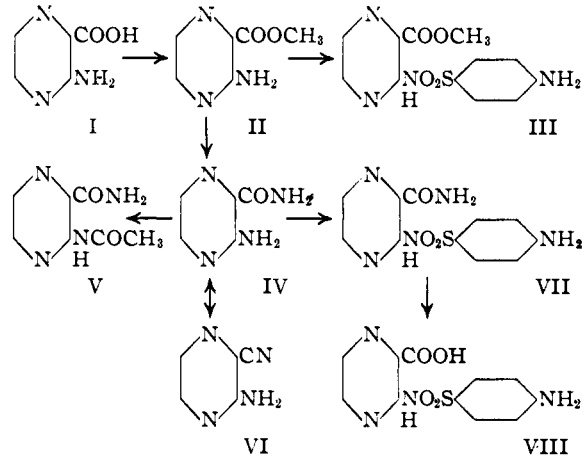
BY RUDOLPH C. ELLINGSON, ROBERT L. HENRY AND FRANCIS G. MCDONALD

The chemical literature describes relatively few derivatives of the simple heterocyclic ring, pyrazine. This may be due to the unsatisfactory methods available for making pyrazine compounds. The observation that lumazines can be hydrolyzed by alkali[1,2] provides a satisfactory method for preparing aminopyrazine-carboxylic acids. The availability of aminopyrazine-carboxylic acids from the alkaline hydrolysis of lumazines makes possible the synthesis of several aminopyrazine derivatives with substituents other than alkyl and aryl groups. These substituents are halogen atoms, amino, cyano, hydroxy, carbamyl and carboxy groups.

In addition to making and studying simple pyrazine derivatives, our object has been to use them in the synthesis of substituted sulfapyrazines. The substituted sulfapyrazines that have been reported have only alkyl[1,3] and aryl[1] groups in the pyrazine ring.

We have included in this paper only those derivatives which are readily obtained from 3-aminopyrazinoic acid.[1,4] Some of these new aminopyrazine derivatives have been converted to the corresponding sulfonamides. The chart shows the routes by which these compounds were made.

Attempts to prepare 3-sulfanilamidopyrazinoic acid (VIII) by condensation of 3-aminopyrazinoic acid (I) with acetylsulfanilyl chloride followed by deacetylation were unsuccessful. The reaction gave tars and a small quantity of a brick-red powder which we were unable to purify. This result was unexpected because the pyridine analog, 2-aminonicotinic acid,[5] has been reported to condense satisfactorily.



In the condensation of 3-aminopyrazinamide (IV) with acetylsulfanilyl chloride we have assumed that the acetylsulfanilyl radical becomes attached to the amino nitrogen and not to the amido nitrogen. Since sulfonamide VII, thus obtained, can be hydrolyzed to compound VIII and this in turn decarboxylated to 2-sulfanilamidopyrazine,[6] this assumption would seem to be correct.

Attempts to degrade 3-aminopyrazinamide (IV) to 2,3-diaminopyrazine by the Hofmann reaction were unsuccessful. When the same reaction was tried on the acetyl derivative (V), two unexpected compounds were obtained. One melts with decomposition in a sealed tube at about 335–338°. The other does not melt up to 350° although it begins to darken at 260°. These two compounds will be given further consideration in a later paper.

To obtain 3-aminopyrazinenitrile (VI) compound IV was dehydrated in pyridine by means of phosphorus pentoxide. To prove that com-

(1) Weijlard, Tishler and Erickson, THIS JOURNAL, **67**, 802 (1945).

(2) In 1942 Weijlard, *et al.*, privately informed us that they had produced pyrazine derivatives by the hydrolysis of lumazine with concentrated sulfuric acid. It occurred to us, and apparently also to Weijlard, *et al.*, that similar cleavages might be effected by alkali.

(3) Joiner and Spoerri, THIS JOURNAL, **63**, 1929 (1941).

(4) Gabriel and Sonn, *Ber.*, **40**, 4859 (1907).

(5) May and Baker Co., (J. A. Ewins and M. A. Philips), British patent 516,288.

(6) (a) Ellingson, THIS JOURNAL, **63**, 2524 (1941); (b) Raiziss, Clemence and Freifelder, *ibid.*, **63**, 2739 (1941); (c) Sausville and Spoerri, *ibid.*, **63**, 3153 (1941).

pound VI is 3-aminopyrazinenitrile, it was subjected to acid hydrolysis. The hydrolysis product was shown to be 3-aminopyrazinamide (IV) which fact indicates that VI has the structure assigned to it. We tried to couple VI with acetylsulfanilyl chloride but under the conditions of our experiments reaction did not take place. As much as 87% of the unchanged nitrile (VI) has been recovered from the reaction mixture. Failure of VI to couple was unexpected. This may probably be attributed to the existence of VI, to a large degree, as one of its tautomeric forms in which there no longer is an amino group available for coupling.

The three new sulfapyrazine derivatives (III, VII and VIII) are being evaluated in order to learn what effect the carbomethoxy, carbamyl, and carboxy groups in the 3 position of 2-sulfanilamidopyrazine have on the antibacterial efficacy of the molecules. According to preliminary tests against pneumococci *in vitro* the presence of the carboxy and carbomethoxy groups greatly reduced or destroyed the antibacterial efficacy whereas the carbamyl group had little or no influence.

Experimental

2-Amino-3-carbomethoxypyrazine (II).—A suspension of 111.2 g. (0.80 mole) of crude 3-aminopyrazinoic acid (I), prepared from lumazine,[1] in 560 cc. of methanol was cooled in an ice-bath and 160 cc. of concd. sulfuric acid[7] was gradually added with stirring. The mixture was stirred for forty-eight hours at room temperature. The dark brown solution was poured into 1400 cc. of water and solid sodium bicarbonate (320–340 g.) was added to alkalinity. The brown crystalline solid was collected and dried; yield 88 g. or 71.8%. The crude product was purified by crystallization from 900 cc. of water, using Darco for decolorizing. The yellow crystalline ester is soluble in ethanol, methanol and water; slightly soluble in ethyl acetate and dioxane; and insoluble in benzene.

For analysis[8] the compound was crystallized again from water; m. p. 172° (cor.).

Anal. Calcd. for $C_6H_7N_3O_2$: C, 47.05; H, 4.60; N, 27.44. Found: C, 46.94; H, 4.59; N, 27.19.

3-Aminopyrazinamide (IV).—A suspension of 111.2 g. (0.80 mole) of 3-aminopyrazinoic acid (I) was treated in the same manner as given above for the preparation of the ester. But in this instance the dark brown solution was poured into 1400 cc. of concd. ammonium hydroxide. After the mixture had been stirred at room temperature for several hours, the gray-green solid was collected, washed with water and dried. The yield was 85–93 g. or 77–84%. The crude product was crystallized from 6 liters of water, using Darco for decolorizing, and gave 52–58 g. of long, slightly yellow needles; m. p. 239.3° (cor.).

Anal. Calcd. for $C_5H_6N_4O$: C, 43.47; H, 4.38; N, 40.56. Found: C, 43.60; H, 4.58; N, 40.53.

3-Acetamidopyrazinamide (V).—To a mixture of 60 cc. of glacial acetic acid and 16 cc. of acetic anhydride was added 20.7 g. of 3-aminopyrazinamide (IV). The mixture was warmed on the steam-bath for ten hours. On cooling, the clear, dark brown solution deposited a tan solid. To the reaction mixture 200 cc. of anhydrous ethyl ether was added, the solid was well suspended, and then collected by filtration. The yield was 21.9 g. of a tan powder; 81%, m. p. 209–211°. By crystallization of the crude product from 700 cc. of dioxane, with Norite as the decolorizer, 13.1 g. of colorless crystals was obtained; m. p. 218.7° (cor.).

Anal. Calcd. for $C_7H_8N_4O_2$: C, 46.66; H, 4.48; N, 31.10. Found: C, 46.54; H, 4.32; N, 31.64.

3-Aminopyrazinenitrile (VI).—To 150 cc. of dry pyridine were added 13.8 g. (0.1 mole) of 3-aminopyrazinamide (IV) and 24 g. of phosphorus pentoxide. The mixture was stirred and heated under reflux for three hours. An additional 8 g. of phosphorus pentoxide was added and the heating continued for another three hours. The hot pyridine was decanted from the brown, gummy mass. To the brown mass 150 cc. of pyridine was added and the mixture was boiled for one hour. The pyridine layer was again decanted and combined with the first fraction. Finally the pyridine was removed by steam distillation. The aqueous solution, upon being cooled, deposited a yellow solid; yield 6.2 g. or 51.6%. From water the compound crystallized in long, yellow needles, m. p. 191.9° (cor.).

Anal. Calcd. for $C_5H_4N_4$: C, 49.99; H, 3.35; N, 46.65. Found: C, 50.03; H, 3.27; N, 46.75.

Hydrolysis of 3-Aminopyrazinenitrile (VI).—A solution of 2 g. of 3-aminopyrazinenitrile (VI) in 10 cc. of 50% sulfuric acid was boiled for five minutes. On dilution with water and neutralization with ammonium hydroxide, a brown solid separated. This was purified by two crystallizations from water; yield 0.5 g. of long, yellow needles; m. p. 238–239°. When mixed with 3-aminopyrazinamide (IV) there was no depression of the melting point.

2-Sulfanilamido-3-carbomethoxypyrazine (III).—To a solution of 15.3 g. (0.1 mole) of 2-amino-3-carbomethoxypyrazine (II) in 150 cc. of dry pyridine at 70° was added, over a period of thirty minutes, 48 g. (0.2 mole) of acetylsulfanilyl chloride. The mixture was held at 70° for three and one-half hours after which it was diluted with 1 liter of water and the pyridine was removed by steam distillation. During the distillation a quantity of brown tar collected on the walls of the distilling flask. As the aqueous solution cooled, a yellow granular solid separated; this was collected and dried; yield 3.4 g.; m. p. 194–196°. A second crop of 2.7 g. was obtained by concentrating and cooling the filtrate. Total yield was 6.1 g. or 17.4% of 2-(N^4-acetylsulfanilamido)-3-carbomethoxypyrazine. This crude product was purified by two crystallizations from 30 parts of 33% methanol (*v/v*). Small, light yellow, granular crystals were formed; m. p. 198° (cor.).

Anal. Calcd. for $C_{14}H_{14}N_4O_5S$: C, 47.99; H, 4.03; N, 15.99; S, 9.15. Found: C, 48.07; H, 4.23; N, 16.30; S, 9.55.

Deacetylation was accomplished by heating, under reflux for thirty minutes, a mixture of 2.4 g. of 2-(N^4-acetylsulfanilamido)-3-carbomethoxypyrazine, 20 cc. of methanol and 5 cc. of concd. hydrochloric acid. The solution was diluted with 60 cc. of water, made basic by the addition of 6 cc. of concd. ammonium hydroxide, treated with Norite and filtered. The light yellow filtrate was neutralized by the addition of dilute hydrochloric acid. After cooling the solution, the solid was collected and dried; yield 1.25 g. of yellow granules or 59%; m. p. 189–192°. The compound was purified by two crystallizations from 35 parts of 44% methanol (*v/v*); large, light yellow needles; m. p. 193.5–194° (cor.).

Anal. Calcd. for $C_{12}H_{12}N_4O_4S$: C, 46.74; H, 3.92; N, 18.17; S, 10.40. Found: C, 46.49; H, 3.91; N, 18.78; S, 10.41.

3-Sulfanilamidopyrazinamide (VII).—To a suspension of 27.8 g. (0.20 mole) of 3-aminopyrazinamide (IV) in 300 cc. of dry pyridine at 70° was added, over a period of thirty minutes, 96 g. (0.41 mole) of acetylsulfanilyl chloride.[9]

(7) Hydrogen chloride is not a satisfactory catalyst for this esterification since it forms a hydrochloride of the pyrazine acid which is insoluble in methanol. However, HCl is an excellent catalyst for the esterification of pyrazine acids which have no amino groups in the ring. See Hall and Spoerri, THIS JOURNAL, **62**, 664 (1940).

(8) Dr. Carl Tiedcke, Laboratory of Microchemistry, New York, N. Y., performed all analyses reported in this paper.

(9) When one mole of acetylsulfanilyl chloride per mole of 3-aminopyrazinamide was used, one-half of the amide was recovered unchanged.

After keeping the reaction mixture at 70° for three additional hours, the product was isolated as described for the preparation of compound III; yield 46.5 g. of gray-brown solid or 69.4%. The compound was purified by crystallization from a mixture of 500 cc. of dioxane and 200 cc. of water; yield 31 g. of small, bright yellow needles; m. p. 261° (dec.).

Anal. Calcd. for $C_{13}H_{13}N_5O_4S$: C, 46.56; H, 3.91; N, 20.89; S, 9.56. Found: C, 46.78; H, 3.93; N, 20.74; S, 9.41.

Deacetylation was accomplished in a mixture of ethanol and hydrochloric acid by essentially the same procedure given for the deacetylation of 2-(N^4-acetylsulfanilamido)-3-carbomethoxypyrazine. The yield from 28.7 g. of 3-(N^4-acetylsulfanilamido)-pyrazinamide was 20.0 g. or 79.6%. The compound was purified by crystallization from ethanol. Large, straw-yellow crystals which exhibit a blue-yellow fluorescence in solution were produced; m. p. 203° (cor.).

Anal. Calcd. for $C_{11}H_{11}N_5O_3S$: C, 45.04; H, 3.78; N, 23.88; S, 10.93. Found: C, 44.77; H, 3.88; N, 23.84; S, 10.78.

3-Sulfanilamidopyrazinoic Acid (VIII).—Two grams of 3-sulfanilamidopyrazinamide (VII) was dissolved in 14 cc. of *N* sodium hydroxide and warmed on the steam-bath for three and one-half hours. After dilution of the clear brown solution with 50 cc. of water, the *p*H was adjusted to about 2 by the addition of hydrochloric acid. The yellow solid was collected and dried; yield 1.9 g. or 95%. The compound was purified by crystallization from 50 parts of water; large, straw-yellow plates; m. p. 178–180° (dec.).

Anal. Calcd. for $C_{11}H_{10}N_4O_4S$: C, 44.89; H, 3.42; N, 19.04; S, 10.89. Found: C, 44.74; H, 3.50; N, 19.95; S, 11.02.

3-Sulfanilamidopyrazinoic acid (VIII) was decarboxylated to 2-sulfanilamidopyrazine in an 89% yield by boiling a solution of the acid in 10 parts of Carbitol acetate. The product melted at 257–259° with decomposition and showed no depression on mixed melting with an authentic sample of 2-sulfanilamidopyrazine.

Acknowledgment.—We appreciate the assistance and encouragement Dr. Charles E. Bills has given us in this work.

Summary

1. The synthesis of four new pyrazine derivatives, 2-amino-3-carbomethoxypyrazine, 3-aminopyrazinamide, 3-acetamidopyrazinamide and 3-aminopyrazinenitrile, is described.

2. The synthesis of three new pyrazine sulfonamides, 2-sulfanilamido-3-carbomethoxypyrazine, 3-sulfanilamidopyrazinamide and 3-sulfanilamidopyrazinoic acid, is described.

3. Two of the aminopyrazines, 3-aminopyrazinoic acid and 3-aminopyrazinenitrile, contrary to expectation, do not condense with acetylsulfanilyl chloride.

4. 2,3-Diaminopyrazine is not obtained when 3-aminopyrazinamide is subjected to the Hofmann degradation.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BANTING INSTITUTE, UNIVERSITY OF TORONTO]

Carbohydrate C-Nitroalcohols: 6-Nitro-6-desoxy-D-sorbitol. A Convenient Source of L-Gulose

BY JOHN C. SOWDEN AND HERMANN O. L. FISCHER

In a previous publication[1] from this Laboratory, we described the preparation of 1-nitro-1-desoxy-D-mannitol. This substance, a carbohydrate C-nitroalcohol, was obtained by treating an acetylated sugar cyanohydrin, in methanol solution, with alkali in the presence of nitromethane. Under these conditions, deacetylation and degradation of the cyanohydrin occurs and the newly-formed aldose sugar reacted with the nitroparaffin to yield the carbohydrate C-nitroalcohol.

The condensation of nitromethane with certain substituted aldose sugars containing the hemiacetal ring structure, to produce carbohydrate C-nitroalcohols, has now been accomplished. Thus, the direct condensation of nitromethane with 2,4-benzylidene L-xylopyranose is described in the present communication.

When the substituted xylose I, prepared from 2,4-benzylidene sorbitol, by cleavage with lead tetraacetate, according to the directions of v. Vargha[2] was treated in methanol solution, at room temperature, with sodium methoxide in the presence of nitromethane, a smooth condensation reaction occurred, yielding 2,4-benzylidene 6-nitro-6-desoxy-D-sorbitol II. The substituted nitrodesoxysorbitol apparently was obtained as a pure individual substance and the corresponding isomer possessing the L-iditol configuration, whose concurrent formation may be expected, was not isolated. Hydrolysis of the benzylidene residue of II with dilute sulfuric acid yielded the crystalline 6-nitro-6-desoxy-D-sorbitol III.

The configuration of III was proved by converting it to L-gulose. When a solution of the sodium salt of 6-nitro-6-desoxy-D-sorbitol was added dropwise to an excess of moderately concentrated sulfuric acid, it was possible to isolate L-gulose IV, as its crystalline benzylphenylhydrazone, from the resulting solution in a yield of about 50%. This elimination of the aliphatic nitro group to produce an aldehyde was discovered by Nef[3] for the simple primary nitroparaffins and was first applied for the production of an aldose sugar by the authors.[1]

L-Gulose was prepared originally by Emil Fischer and O. Piloty[4] by the following series of

(1) Sowden and Fischer, THIS JOURNAL, **66**, 1312 (1944).

(2) v. Vargha, *Ber.*, **68**, 18, 1377 (1935).

(3) Nef, *Ann.*, **280**, 263 (1894).

(4) E. Fischer and Piloty, *Ber.*, **24**, 521 (1891).