Notes

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Synthesis of Pyrazinoic Acid

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Considerable interest is attached to the synthesis of pyrazinoic acid since this compound is used in the preparation of the tuberculostat pyrazinamide.[1] The acid was formerly obtained in low yield by the oxidation of methylpyrazine with potassium permanganate[2] or by the monodecarboxylation of pyrazine-2,3-dicarboxylic acid.[3] The synthesis of the latter compound requires several steps. We wish to report two new simple syntheses of pyrazinoic acid which now make this acid a readily available material.

One method, consisting of the oxidation of methyl pyrazine with selenious acid in pyridine, gave the desired acid in 64% yield. There are several examples of the oxidation of activated methyl groups in a nitrogen heterocyclic compound to the corresponding carboxylic acid with selenium dioxide.[4,5]

The second synthesis is the oxidation of ethylpyrazine in water with potassium permanganate which gave a 48% yield of pyrazinoic acid. Ethylpyrazine was synthesized by a series of steps[6] similar to those used by Kitchen and Hanson[7] in the synthesis of methylpyrazine. Ethylenediamine was reacted with 1,2-butylene oxide to give *N*-(2-hydroxybutyl)ethylenediamine which was then cyclized to 2-ethylpiperazine by heating the substituted diamine at 105° for 2 hours in aqueous solution in the presence of Raney nickel.[8] Dehydrogenation of 2-ethylpiperazine to ethylpyrazine in 57% yield (and 19% recovery of starting material) was effected over copper chromite catalyst at 360° in aqueous rather than in a benzene solution.[7]

(1) E. P. Jordan, *Modern Drug Encyclopedia and Therapeutic Index*, 7th ed., Drug Publications Inc., New York, N. Y., 1958, p. 952.

(2) C. Stoehr, *J. prakt. Chem.*, (2) **51**, 468 (1895).

(3) W. L. McEwen, U. S. Patent **2,675,384** [*Chem. Abstr.*, **49**, 4730 (1955)].

(4) C. W. Larson, Ph.D. dissertation, Polytechnic Institute of Brooklyn, May 1949.

(5) D. Jerchel, J. Heider, and H. Wagner, *Ann.*, **613**, 153 (1958).

(6) These preparations were by Dr. Moses Cenker, Wyandotte Chemicals Corp.

(7) L. J. Kitchen and E. S. Hanson, *J. Am. Chem. Soc.*, **73**, 1838 (1951).

(8) W. K. Langdon, Canadian Patent **557,792**, May 20, 1958.

EXPERIMENTAL[9]

Ethylpyrazine, b.p. 152–153°/760 mm., had n_D^{25} 1.4969. *Anal.* Calcd. for $C_6H_8N_2$: C, 66.64; H, 7.46; N, 25.91. Found: C, 66.87; H, 7.56; N, 26.20.

Pyrazinoic acid. A. To 5 l. of pyridine was added a solution of 1.25 kg. (11.3 moles) of selenium dioxide in 500 ml. of water. Four hundred and forty grams (4.7 moles) of methylpyrazine was added and the mixture was refluxed with stirring for 10 hr. while selenium precipitated. The mixture was filtered and the filtrate evaporated *in vacuo*. The residue was dissolved in 3 l. of 2.5*N* sodium hydroxide. Decolorizing carbon, 50 g., was added and the mixture was stirred overnight. Acidification of the filtrate with one liter of 7.5*N* hydrochloric acid precipitated pyrazinoic acid which was filtered and washed well with water. The dissolution of the pyrazinoic acid in aqueous alkali, treatment with decolorizing carbon, and subsequent acidification was repeated and gave finally 372 g., (64%) of a light tan product, m.p. 219° dec. (m.p. 229–230° dec.)[2] and neut. equiv. 121.4 (calcd. 124.1). The infrared spectrum was identical with that of a sample prepared from methylpyrazine according to Stoehr.[2] The methyl ester, prepared by the Fischer method, melted at 59.5–60.5° (m.p. 61–62°).[10] For purposes of economy in large runs, 92% of the selenium was recovered (as selenium dioxide) from the precipitated selenium and the mother liquors containing selenious acid.[11]

B. A solution of 54 g. (0.5 mole) of ethylpyrazine in 750 ml. of water was treated portionwise with 315 g. (2.0 moles) of solid potassium permanganate in 12 hr. while the mixture was kept at room temperature with slight cooling. After an additional 8 hr. of stirring, the precipitated manganese dioxide was removed by filtration and the filtrate was acidified with 60 ml. of concentrated hydrochloric acid. The precipitated pyrazinoic acid was filtered and washed well with water. The yield was 29.7 g. (48%) of pure white crystals, m.p. 218.5–219° dec., with neut. equiv. 123.8 (calcd. 124.1). There was no depression in the melting point when samples of pyrazinoic acid from both methods A and B were mixed. The methyl ester, m.p. 59.5–60.5° was prepared as noted in method A.

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(9) All melting points are uncorrected.

(10) T. I. Fand and P. E. Spoerri, *J. Am. Chem. Soc.*, **74**, 1345 (1952).

(11) N. Rabjohn, *Org. Reactions*, **5**, 344 (1949).

Microbiological Transformation of Steroids. VII. 15β-Hydroxylation

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Although hydroxylations of steroids by fungi have been demonstrated for a variety of positions