The infrared absorption of II in potassium bromide pellets did not indicate the presence of a hydroxyl group. The absence of an enolic structure was also consistent with the n.m.r. analysis.

Lithium Aluminum Hydride Reductions of Pyrazine Carboxylic Esters. Synthesis of Pyrazinealdehyde from Methyl Pyrazinoate

HERMAN RUTNER AND PAUL E. SPOERRI

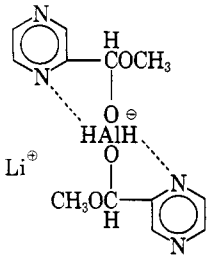
Department of Chemistry, Polytechnic Institute of Brooklyn, Brooklyn 1, New York

Received January 28, 1963

A search of the literature shows that only one pyrazinealdehyde, the 3-amino-2-pyrazinealdehyde,[1] has been described. It was obtained by the acid hydrolysis of the rather inaccessible pteridine. However, the existence of pyrazinealdehyde I, at least as a transitory species, was confirmed by the *in situ* preparations of the 2,4-dinitrophenylhydrazone and the thiosemicarbazone[2,3] *via* the McFadyen–Stevens reaction.

Kakemi, *et. al.*,[4] used the same reaction to prepare nicotinoyl- and isonicotinoylhydrazones of I. Behun and Levine synthesized[5] pyrazinealdehyde dimethyl acetal from sodium methoxide and dichloromethylpyrazine, but preliminary experiments to hydrolize the latter were unsuccessful. We have obtained I in 78% yield (as the 2,4-dinitrophenylhydrazone) by a novel, selective reduction of methyl pyrazinoate with lithium aluminum hydride. The reaction was carried out in tetrahydrofuran at −70° by "inverse" addition of 0.5 mole of lithium aluminum hydride per mole of ester. After standing at −70° for fifteen minutes, the reaction was stopped by adding glacial acetic acid.

A preliminary investigation of the reaction mechanism suggests the formation of a soluble hemiacetal complex. Aldehyde is then liberated upon the addition of acid.



In a series of experiments, increasing amounts of lithium aluminum hydride were used and the corresponding yields of aldehyde were determined. An optimum yield of pyrazinealdehyde was obtained when 0.5 mole of lithium aluminum hydride was allowed to react with one mole of methyl pyrazinoate while excess of the reductant had only a negligible effect. In a number of experiments, pyrazinealdehyde was substituted for methyl pyrazinoate and subjected to the stated lithium aluminum hydride reduction conditions. We were able to recover only small amounts of unchanged aldehyde, the remainder having undergone further reduction.

Pyrazinealdehyde is a light-sensitive, low melting solid (m.p. 31–33°, b.p. at 6 mm., 57–58°). It was characterized by conversion to the octahydroxanthene derivative as well as to the known 2,4-dinitrophenylhydrazone,[2] nicotinoylhydrazone, and isonicotinoylhydrazone.[4] I dissolves in a saturated sodium bisulfite solution with the formation of a soluble addition product. Like pyridine-2-aldehyde, which yields α-pyridyl-α-hydroxymethanesulfonic acid[6] when treated with aqueous sulfurous acid, I forms an analogous reaction product. The aldehyde undergoes a Cannizzaro reaction, yielding pyrazinoic acid and pyrazylmethanol. Since the latter compound is as yet unrecorded in the literature, it was characterized by ultraviolet and infrared spectra and the preparation of its α-naphthylcarbamate derivative.

Benzoin condensation of I affords pyrazoin in 85% yield. The absence of carbonyl absorption in its infrared spectrum as well as its behavior towards Tillmann's reagent[7] suggests an enediolic structure analogous to α-pyridoin.[8] Prior to the described reduction procedure we attempted to obtain pyrazinealdehyde by the reduction of pyrazinoyl chloride with lithium tri-*t*-butoxyaluminohydride.[9] The yield of I, however, never exceeded 20% (as the 2,4-dinitrophenylhydrazone). The major product of this reaction was pyrazylmethyl pyrazinoate, which was isolated in a 55% yield.

It was of interest to ascertain whether the low temperature reduction with lithium aluminum hydride could be extended to esters belonging to other series. Consequently, we initiated a series of experiments in which a number of esters were subjected to standardized reaction conditions. To simplify the experiments, only such esters were selected for which the corresponding aldehydes and their 2,4-dinitrophenylhydrazones were known, and the yields were determined by isolating the 2,4-dinitrophenylhydrazones. We found that while the reaction is not confined to methyl pyrazinoate it appears, however, to be limited to π-electron deficient systems. Aldehyde formation also is favored when the carbomethoxy group is in an electron deficient position. Thus, the three isomeric carbomethoxypyridines gave 75%, 12%, and 50% yields of the corresponding 2-, 3-, and 4-aldehydes. Quinoline-2-aldehyde was formed in 92% yield from methyl quinaldate. Ethyl acetate, methyl benzoate, diethyl phthalate, and benzonitrile failed to give carbonyl positive materials. Methyl *o*-nitrobenzoate produced only 5% of the expected aldehyde (probably because of steric hindrance), while the *p*-nitro ester reacted to the extent of 36% (a yield comparable to that of 4-carbomethoxypyridine).

(1) A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 2066 (1956).
(2) T. I. Fand, dissertation, Polytechnic Institute of Brooklyn, 1954.
(3) S. Kushner, H. Dalalian, J. L. Sanjuro, F. L. Bach, Jr., S. F. Safir, V. K. Smith, Jr., and J. H. Williams, *J. Am. Chem. Soc.*, **74**, 3617 (1952).
(4) K. Kakemi, T. Uno, T. Arita, H. Nakao, I. Shimada, Y. Ikegami, and S. Kitazawa, *Yakugaku Zasshi*, **81**, 1609 (1961); *Chem. Abstr.*, **56**, 10142e (1962).
(5) J. D. Behun and R. Levine, *J. Org. Chem.*, **23**, 406 (1958).
(6) W. Mathes and W. Sauermilch, *Ber.*, **84**, 648 (1951).
(7) Solution of sodium 2,6-dichlorophenol-indophenol.
(8) W. Mathes, W. Sauermilch, and T. Klein, *Ber.*, **84**, 452 (1951).
(9) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **80**, 5377 (1958).

Experimental

All the melting points are corrected. The methyl pyrazinoate was prepared from pyrazinoic acid using the procedure described by Hall and Spoerri.[10] Pyrazinoic acid was obtained by selenium dioxide oxidation[11] of 2-methylpyrazine.[12]

Yield determinations of aldehydes were made *via* the 2,4-dinitrophenylhydrazones according to the method of Iddles, *et al.*[13]

Pyrazinealdehyde I.—Methyl pyrazinoate (25.0 g., 0.181 mole) in 500 ml. of dry tetrahydrofuran was cooled to −70° under nitrogen. While maintaining the temperature at −68° to −73°, 268 ml. of 0.34 *M* lithium aluminum hydride in tetrahydrofuran[14] (0.091 mole) was added with stirring over a period of 30 min. After stirring for an additional 15 min. at −75°, the reaction was stopped by slow addition of 25 ml. of glacial acetic acid. The light brown reaction mixture containing 0.142 mole of I was evaporated *in vacuo*. The residue was dissolved in 170 ml. of 2.5 *N* hydrochloric acid and 100 ml. of chloroform. The aqueous layer was extracted eight times with 50-ml. portions of chloroform. The combined extracts were stirred with 50 ml. of water and 25 g. of sodium bicarbonate until neutral. After filtration, the chloroform layer was dried with anhydrous sodium sulfate and concentrated *in vacuo*. Fractional vacuum distillation with tetraethyleneglycol dimethyl ether (Ansul ether 181) as chaser yielded 9.04 g. (46%) of pyrazinealdehyde, b.p. 57–58° at 6 mm., as a light yellow liquid. Redistillation afforded 5.26 g. of pure I, b.p. 57.0–57.8° at 6 mm., m.p. 31–33°, b.p. (Emich) 174°. The infrared spectrum of I (as a film) revealed a prominent band at 5.90 μ (C=O). I, octahydroxanthene, had m.p. (benzene–hexane) 176–177°.

Anal. Calcd. for $C_{21}H_{24}N_2O_8$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.31; H, 7.08; N, 7.64.

I, 2,4-dinitrophenylhydrazone, had m.p. 239–240° (lit.[2] m.p. 239–240°).

I, nicotinoylhydrazone, had m.p. (ethyl acetate) 195–195.5° (lit.[4] m.p. 195°).

I, isonicotinoylhydrazone, had m.p. (ethyl acetate) 197–198° (lit.[4] m.p. 200°).

α-Pyrazyl-α-hydroxymethanesulfonic Acid (II).—Sulfur dioxide was bubbled into a cooled mixture of 0.35 g. of I in 17 ml. of chloroform and 5 ml. of water. Addition of 100 ml. of acetone and subsequent refrigeration yielded 0.46 g. (75%) of II as light yellow crystals. Recrystallized from water–acetone, II melts at 159–159.5° (partial dec., sealed capillary); neut. equiv., 192.2 (theory, 190.1).

Pyrazoin(1,2-dipyrazyl-1,2-ethenediol) (III).—Potassium cyanide (0.2 g.) was added to 0.27 g. of I in 19 ml. of water. The solution darkens quickly with formation of yellow-brown crystals. The crystal slurry was stirred at room temperature for 1 hr., acidified with 0.2 ml. of glacial acetic acid, and filtered. Yield: 0.23 g. of III (85%), bronze colored crystals, m.p. (ethyl acetate) 218–219° dec.

Anal. Calcd. for $C_{10}H_8N_4O_2$: C, 55.55; H, 3.73; N, 25.92. Found: C, 55.75; H, 3.86; N, 25.78.

Pyrazoin gives a positive Fehling test and decolorizes Tillmann's reagent. The infrared spectrum of III (in potassium bromide) shows no significant absorption bands between 5.5 and 6.2 μ.

Pyrazylmethanol (IV).—Pyrazinealdehyde (2.0 g.) and 3 ml. of 40% aqueous sodium hydroxide were mixed in a test tube cooled in ice–water. The resultant white paste was stirred for 10 min., then diluted with 12 ml. of water. Carbon dioxide was bubbled into the clear solution until the pH was 8–9. Evaporation to dryness *in vacuo*, extraction of the residue with chloroform, and distillation yielded 0.60 g. (59%) of pyrazylmethanol as a colorless, hydroscopic oil; b.p. 59–62° at 0.1 mm., m.p. 35–36°. Infrared spectrum (film): 3.0 μ (–OH), 9.40 μ (–C–OH). Ultraviolet spectrum (in 95% ethanol): maxima at 266 mμ, ϵ 6700; 309 mμ, ϵ 800. For analysis, the α-naphthylcarbamate of IV was prepared; m.p. (benzene–hexane) 110–110.5°.

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.80; H, 4.69; N, 15.04. Found: C, 68.65; H, 4.81; N, 14.99.

The residue from the chloroform extraction was dissolved in water and acidified with hydrochloric acid to liberate the pyrazinoic acid. Yield: 1.02 g. (89%) white crystals, m.p. 224.5° dec., m.m.p. 224.5 dec.

Pyrazylmethyl Pyrazinoate.—This ester was formed in the reduction of pyrazinoyl chloride with lithium tri-*t*-butoxyaluminohydride in tetrahydrofuran by the method of Brown and Subba Rao.[9] With slow addition of the reductant over a 2-hr. period, a yield of 55% of pyrazylmethyl pyrazinoate was obtained as colorless needles, m.p. (benzene–hexane) 115–115.5°.

Anal. Calcd. for $C_{10}H_8N_4O_2$: C, 55.55; H, 3.73; N, 25.92. Found: C, 55.64; H, 3.82; N, 25.83.

Saponification of the ester with 0.1 *N* sodium hydroxide at room temperature for 1 and 2 days gave a saponification equivalent of 211 and 214, respectively (theory 216.2). The distillation residue yielded pyrazinoic acid, m.p. 224.5° dec., undepressed on admixture with authentic pyrazinoic acid.

Lithium Aluminum Hydride Reduction Procedure on Esters Other than Methyl Pyrazinoate.—All reductions were conducted on a 1-mmole scale. The compound dissolved in 4 ml. of tetrahydrofuran was stirred magnetically while cooling to −70° to −75° in a methanol–Dry Ice bath. The lithium aluminum hydride solution (0.43 *M*) was added from a 10-ml. buret (protected from the atmosphere by a nitrogen-filled balloon) over a period of 5–7 min. After an additional 15 min. at −70°, the reaction was stopped by adding 0.25 ml. of glacial acetic acid. On warming to room temperature the reaction mixture was poured into 55 ml. (1.1 mmoles) of saturated 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid and allowed to stand for 48 hr. The 2,4-dinitrophenylhydrazone derivatives were filtered, washed with 5% hydrochloric acid, then water, and dried at 120° for 1 hr. before weighing. As a control, the yield of pyrazinealdehyde 2,4-dinitrophenylhydrazone from methyl pyrazinoate was reproducible within 0.5% in four reductions performed on three different days.

(10) S. A. Hall and P. E. Spoerri, *J. Am. Chem. Soc.* **62**, 664 (1940).

(11) H. Gainer, *J. Org. Chem.*, **24**, 691 (1959).

(12) The 2-methylpyrazine used in this study was generously supplied by Wyandotte Chemicals Corp.

(13) H. A. Iddles, A. W. Low, B. D. Rosen, and R. T. Hart, *Anal. Chem.*, **11**, 102 (1939).

(14) The concentration of LAH was determined by gravimetric analysis of the aluminum with oxine.

Participation of a Neighboring Amide Group in the Decomposition of Esters and Amides of Substituted Phthalamic Acids[1]

J. A. SHAFER AND H. MORAWETZ

Department of Chemistry, Polytechnic Institute of Brooklyn, Brooklyn 1, New York

Received February 15, 1963

The labilization of amide groups by a second neighboring amide function has been described recently for succinamide[2] and for phthalamide.[3] A similar labilization of benzyl esters has been reported also.[4] Because of the predominance of amide groups in proteins, the possibility arises that these groups may also, in some cases, be involved in the mode of action of hydrolytic enzymes. This possibility seemed to justify a further study of activation by neighboring amide groups.

The attack of neighboring amide on amide or ester groups to form an imide intermediate proceeds at a rate inversely proportional to hydrogen ion concentration, suggesting the following mechanism.

(1) Financial support of this research by the National Institute of Health is gratefully acknowledged.

(2) B. Vigneron, P. Crooy, F. Kezdy, and A. Bruylants, *Bull. soc. chim. Belges*, **69**, 616 (1960).

(3) P. Crooy, doctoral dissertation, Catholic University, Louvain, 1961.

(4) S. A. Bernhard, A. Berger, J. H. Carter, E. Katchalski, M. Sela, and Y. Shalitin, *J. Am. Chem. Soc.*, **84**, 2421 (1962).