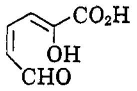
The Formation of α-Hydroxy-*trans*, *cis*-muconic Acid Semialdehyde in the Reduction of 2-Pyrone-6-carboxylic Acid[1]

Sir:

Acid treatment of the intermediates in the enzymatic conversion of 3-hydroxyanthranilic acid to quinolinic acid resulted in a nitrogen-free product, $C_6H_6O_4$, incapable of forming quinolinic acid.[2–4] Recently, Dagley, Evans, and Ribbons reported the degradation of catechol by two strains of Gram-negative bacteria with formation of an isomer of α-hydroxymuconic acid semialdehyde having similar properties to the material isolated from 3-hydroxyanthranilic acid.[5] The suggestion was advanced by these investigators that these materials isolated from catechol and 3-hydroxyanthranilic acid, might be similar. This view has been adopted by subsequent investigators.[6]

We now wish to report that the identities of these materials have been established and must now be formulated as IIIb (α-hydroxy-*trans,cis*-muconic acid semialdehyde[7]) and that a new and general method for the chemical conversion of 2-pyrones (Ia–d) to pyridines (IVa–d) has been developed. Lithium aluminum hydride in cold (−10° to −15°) anhydrous tetrahydrofuran rapidly reduces 2-pyrone-6-carboxylic acid (Ib). Treatment of the reduction complex with cold dilute sulfuric acid gives an almost quantitative yield of a product, $C_6H_6O_4$, m.p. 210–214° dec., which is formulated as IIIb.[8] The infrared spectrum (CH_2Cl_2) of the methyl ester is confirmatory of all the groupings shown in IIIb (free acid) (the shift in OH absorption is attributable to influence of conjugated enolized chelation[9]); while the ultraviolet spectrum [λ_{max} (ϵ), CH_2Cl_2:230 mμ (9333), 280 (27,120), 315 (7000)] of the free acid is entirely consistent with IIIb. The presence of an α-hydroxy-α,β-unsaturated acid ester (6.06 μ) is made obvious since the infrared indicated a conjugated chelated ring (no keto tautomer, 5.78 μ nor hemiacetal observed)[9] spectrum of the free acid in alkaline solution (*p*H 10.5) absorbs at 375 mμ (21,000), and in acid (*p*H 2.5) this absorption and yellow color are abolished and another peak appears, 315 mμ (8500).



IIIb

$-\overset{\vert}{C}=C-OH$	3.41 μ
$-(CH=CH)_2-CHO$	5.95 μ
$-C=\overset{OH}{\overset{\vert}{C}}-\overset{O}{\overset{\Vert}{C}}-$	6.06 μ
$-C=CH-$	6.12 μ
$-C=C-$(*cis*)	12.41 μ

In addition we have shown that when IIIb is treated with acetic anhydride and pyridine a solid acetate can be isolated (m.p. 196–198°) with an ultraviolet absorption (CH_2Cl_2) of 213 mμ (9400), 260 (18,600) which is consistent with the literature [*cf. cis, trans*-mucondialdehyde[10a] (C_2H_5OH): 270 (16,220), *cis,trans*-muconic acid[10b] (*p*H 7): 260 (19,500); *trans*-α,β unsaturated acids[10c]: 213 (10,000)], while the infrared spectrum possesses a strong band at 8.40 μ (—O—CO—). Esterification (with diazomethane) of the vinyl acetate afforded the methyl ester, m.p. 186–188°, having a strong absorption at 5.81 μ (α,β-unsaturated ester, C=O) and 5.61 μ (vinyl acetate, —C=O).[11]

Support for the *cis,trans* configuration is obtained through inspection of the N.M.R. spectrum, with τ-values for the olefinic protons at 2.6 and 3.1, β and γ protons, respectively.[12] The expected proton resonance at −5.4 for a enol hydrogen was also obtained.[12] The *trans* and *cis* relationships of the α,β- and γ,δ-double bonds, respectively, are further demonstrated by the ready conversion of IIIb in glacial acetic acid and ammonium acetate into α-picolinic acid (42%). It is noteworthy that IIIb rapidly forms a mono-2,4-dinitrophenylhydrazone, orange microcrystals, m.p. 183–185° dec., which is slowly converted into a bis-2,4-dinitrophenylhydrazone, brick red needles, m.p. 192–193° dec. The ultraviolet spectrum of the former [409 mμ (43,000), (C_2H_5OH); 475 mμ (30,200,) (0.7 *N* NaOH)] parallels that of αβ,γδ-unsaturated

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[1] This paper is Pyridine Synthesis. III. For the previous paper in this series see J. H. Boyer and L. R. Morgan, Jr., *J. Am. Chem. Soc.*, **83,** 919 (1961).

[2] A. Miyake, A. H. Bokman, and B. S. Schweigert, *J. Biol. Chem.*, **211,** 391 (1954).

[3] C. L. Long, H. N. Hill, I. M. Weinstock, and L. M. Henderson, *J. Biol. Chem.*, **211,** 405 (1954).

[4] A. H. Mehler, *Proc. Fourth Internat. Cong. Biochem. Colloquia*, **13,** 164 (1958).

[5] S. Dagley, W. C. Evans, and D. W. Ribbons, *Nature*, **188,** 560 (1960).

[6] L. M. Henderson and R. A. Mitchell, private communication.

[7] The terms *cis* and *trans* are given in positional order, *i.e.*, the first cited refers to the lower numbered double bond.

$$CHO\underset{cis}{CH{:}CH}\underset{trans}{CH{:}C}(OH)CO_2H$$

[8] Satisfactory analytical data have been obtained for all compounds and/or their derivatives reported in this communication.

[9] R. W. Rasmussen and R. Brattain, *J. Am. Chem. Soc.*, **71,** 1073 (1949).

[10] (a) M. Nakajima, I. Tomida, A. Hashizume, and S. Takei, *Ber.* **89,** 2224 (1956). (10) (b) W. R. Sistrom and R. Y. Stanier, *J. Biol. Chem.*, **210,** 821 (1954). (10) (c) H. E. Ungnade and I. Ortega, *J. Am. Chem. Soc.*, **73,** 1564 (1951).

[11] L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Methuen, London, 1959, *p. 178.*

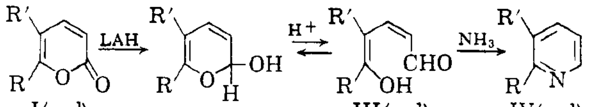
[12] *Cf.* L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, Pergamon Press, London, 1959, p. 71, 124.

aldehydes while the latter's spectrum (355 mμ (20,420), 379 mμ (26,100), (C_2H_5OH); 453 mμ (32,000), 440 mμ (1510), (0.7 *N* NaOH)] parallels what would be expected from a combination of the 2,4-dinitrophenylhydrazones of pyruvic acid and crotonaldehyde.[13]

In an extension of this reaction, 2-pyrone (Ia), coumalic acid (Ic), and 2-pyrone-5,6-dicarboxylic acid (Id) were transformed, respectively, into pyridine (IVa), nicotinic acid (IVc), and quinolinic acid (IVd) in yields up to 35%.[14]

The tentative reaction scheme formulized with IIIb lends itself to the following working hypothesis. Initial reaction between 2-pyrones (Ia–d) and lithium aluminum hydride leads to a hemiacetal (IIa–d) capable of tautomerization to an enol aldehyde (IIIa–d) and condensation with ammonia resulting in a pyridine (IVa–d).

The identities of the compounds obtained from the enzymatic degradations of 3-hydroxyanthranilic acid[2,3] and catechol[5] and the reduction product of 2-pyrone-6-carboxylic acid are established as IIIb by comparison of their infrared, ultraviolet, and NMR spectra.[15] Dr. S. Dagley of the University of Leeds, England, has graciously conducted enzymatic studies on IIIb and found that cell-free extracts of Gram-negative bacteria grown on phenol as a carbon source rapidly attack IIIb with the formation of pyruvic acid and lactic acid.



I(a–d) II(a–d) III(a–d) IV(a–d)

a. R = R′ = H
b. R = CO_2H, R′ = H
c. R = H, R′ = CO_2H
d. R = R′ = CO_2H

Recently Kojima, Itada, and Hayaishi reported that a new metapyrocatechase isolated from cell-free extracts of a strain of *Pseudomonas* catalyzed the transformation of catechol to an isomer of α-hydroxymuconic semialdehyde.[16] As yet this material has not been compared to IIIb.

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[13] For appropriate models, *cf.* G. D. Johnson, *J. Am. Chem. Soc.*, **75,** 2721 (1953); L. A. Jones, J. C. Holmes, and R. B. Seligman, *Anal. Chem.*, **28,** 191 (1956); T. W. Goodwin and G. R. Williams, *Biochem. J.*, **51,** 709 (1952); E. A. Braude and E. R. H. Jones, *J. Chem. Soc.*, 498 (1954).

[14] Due to unstability at room temperature and *in vacuo* the reduction products (IIIa–d) were characterized as their bis-2,4-dinitrophenylhydrazones.

[15] The author is greatly indebted to Drs. S. Dagley, L. M. Henderson, and R. A. Mitchell for critical discussion and samples of their respective materials.

[16] Y. Kojima, N. Itada, and O. Hayaishi, *J. Biol. Chem.*, **236,** 2223 (1961).