[CONTRIBUTION FROM THE MALLINCKRODT LABORATORIES OF HARVARD UNIVERSITY]

The Reduction of Ketoacids with a Derivative of 1,4-Dihydropyridine

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RECEIVED MAY 26, 1958

2,5-Dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine reduces pyruvic acid to lactic acid, and reduces benzoylformic acid to mandelic acid. The latter reduction was shown to proceed with direct hydrogen transfer from the dihydropyridine to the keto acid. These reactions are compared with the enzymatic reductions of ketones with reduced diphosphopyridine nucleotide.

Numerous ketones can be reduced enzymatically by reduced diphosphopyridine nucleotide (DPNH), and these reductions have been shown to occur by way of a direct transfer of hydrogen from the coenzyme to the ketone.[2] Various attempts have been made to construct model systems[3-5] which will simulate, non-enzymatically, the reactions between DPNH and ketones. N-Benzyl-1,4-dihydronicotinamide[6] will reduce malachite green with direct hydrogen transfer, and both this "model" compound and DPNH will reduce thiobenzophenone and substituted thiobenzophenones to the corresponding mercaptans. However, N-alkyl derivatives of 1,4-dihydronicotinamide have not yet been used successfully to carry out a non-enzymatic reduction of a ketone. On the other hand, a Hantzsch compound, 2,5-dimethyl-3,5-dicarboethoxy-1,4-dihydropyridine, reduces pyruvic acid to lactic acid.[3] It is shown here that the Hantzsch compound reduces benzoylformic acid in deuterioethanol to ordinary mandelic acid; the reaction is therefore a direct transfer of hydrogen from the dihydropyridine to the α-carbon atom of the acid.

Experimental

Materials.—Commercial pyruvic acid was distilled in vacuum, and boiled at 70–71° (20 mm.). Benzoylformic acid was recrystallized from carbon tetrachloride,[7] and melted at 65–67°. 2,5-Dimethyl-3,5-dicarboethyoxy-1,4-dihydropyridine was prepared according to Meyer and Tropsch.[8] Dimethoxyethane was dried over sodium and fractionated at atmospheric pressure. Deuterioethanol was prepared by mixing 7 parts of ethanol with 10 of D_2O and fractionating. The 95% ethanol prepared in this way was again exchanged with D_2O, and the process repeated a third time.

Reductions.—The Hantzsch compound and benzoylformic were dissolved in diethoxyethane or in ethanol in an ampoule which was flushed with nitrogen and then sealed. It was heated at 85° for 13 hours, cooled and opened; the contents were concentrated in vacuum to a viscous oil. This oil was extracted with about 5 cc. of water. The water extract was brought to *p*H 8 with sodium hydroxide solution, whereupon a precipitate of 2,5-dimethyl-3,5-dicarboethoxypyridine separated from the solution, and was removed by filtration. The filtrate was extracted with chloroform, to remove traces of pyridine derivative, concentrated in vacuum, and chromatographed.

The chromatography was conducted on silicic acid by a modification of the procedure of Marvel and Rands.[9] Mallinckrodt silicic acid (7 g.) was triturated with 4.5 cc. of 0.05 N H_2SO_4. The resulting dry powder was suspended in 50 cc. of chloroform and poured into a chromatographic column 1 cm. in diameter. The concentrated solution containing the mandelic acid was mixed with 1 g. of the acidified silicic acid, and the mixture slurried in 10 cc. of chloroform, and poured into the chromatographic column. The acids were eluted with 40 cc. of chloroform, followed by 40 cc. of 5% butanol in chloroform. A Packard automatic fraction collector was set for fractions containing 400 drops. Fractions 3 and 4 contained benzoylformic acid; fractions 10, 11 and 12 contained mandelic acid. The mandelic acid was isolated by evaporating the appropriate fractions to dryness. In a typical control experiment, a mixture of 35 mg. of benzoylformic acid and 21 mg. of mandelic acid was chromatographed; 30 mg. of benzoylformic acid and 19 mg. of mandelic acid were recovered.

In one reduction, 346 mg. of Hantzsch compound and 203 mg. of benzoylformic acid in 2 cc. of dimethoxyethane were allowed to react as described. After chromatography, 33.5 mg. of mandelic acid were found (by titration). The free acid was recovered by acidification of the titration mixture, and identified by comparing its infrared spectrum to that of an authentic sample of mandelic acid.

The reduction of 445 mg. of benzoylformic acid with 495 mg. of the Hantzsch compound in 3.5 cc. of ethanol gave 20 mg. of mandelic acid.

Direct Hydrogen Transfer.—Hantzsch compound (492 mg.) and benzoylformic acid (416 mg.) were allowed to react in 3.3 cc. of deuterioethanol. The reaction mixture was worked up as described. The mandelic acid obtained after chromatography was isolated directly without titration; 17 mg., m.p. 117–118°, was obtained. The compound was analyzed for deuterium.[4] and found to contain 0.21 atom % excess; for one deuterium atom per molecule, mandelic acid would contain 12.5 atom % excess deuterium. The deuterium atoms on the carboxyl group and on the hydroxyl group of mandelic acid are lost by equilibration with water and with the aqueous acid on the chromatographic column, during the "work-up" described above. The control experiment, below, shows that no such loss would have occurred from the α-carbon atom had the reduction process led to the introduction of deuterium at this site.

Control.—A control experiment was carried out to find out whether deuterium was introduced onto the α-carbon atom of mandelic acid, but subsequently lost during chromatography. For this purpose, a silicic acid column was prepared by mixing 7 g. of silicic acid with 4 cc. of D_2O and 0.05 cc. of concentrated sulfuric acid. The column was prepared in the usual way, but all solvents were equilibrated with D_2O rather than with water. Mandelic acid (20 mg.) was dissolved in 0.75 cc. of D_2O and one drop of HCl was added. This solution was then mixed with 1 g. of the specially prepared silicic acid, and the chromatography conducted as before. The mandelic acid was isolated directly by evaporation of the chloroform–butanol mixture (*i.e.*, without prior titration). The acid was dissolved in water to remove the exchangeable deuterium from the carboxyl and hydroxyl groups; the water was then removed in vacuum. The recovered acid (16 mg.) was analyzed for deuterium. It contained 0.00 atom % excess deuterium. Had deuterium been introduced into the α-carbon atom during the chromatographic procedure, it would have been found in this analysis. The only opportunity for loss of

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[1] Chemistry Department, The Ohio State University, Columbus, Ohio.

[2] B. Vennesland and F. H. Westheimer, "The Mechanism of Enzyme Action," McElroy and Glass, eds., The Johns Hopkins Press, Baltimore, Md., 1954, p. 357.

[3] D. Mauzerall and F. H. Westheimer, THIS JOURNAL, **77**, 2261 (1955).

[4] R. Abeles and F. H. Westheimer, *Fed. Proc.*, **15**, 675 (1956); R. Abeles, R. Hutton and F. H. Westheimer, THIS JOURNAL, **79**, 712 (1957).

[5] J. Hannah, Thesis, University of London, 1956.

[6] For proof of structure of these compounds, see R. F. Hutton and F. H. Westheimer, *Tetrahedron*, **3**, 73 (1958).

[7] "Organic Syntheses," Vol. III, John Wiley and Sons, Inc., New York, N. Y., p. 114.

[8] H. Meyer and H. Tropsch, *Monatsh.*, **35**, 207 (1914).

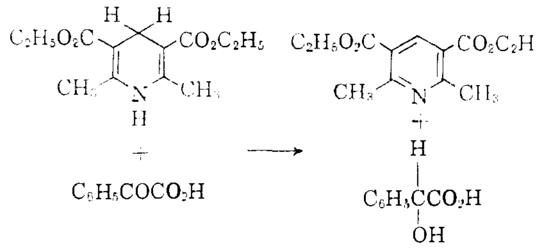
[9] C. S. Marvel and R. D. Rands, Jr., THIS JOURNAL, **72**, 2642 (1950).

deuterium occurred when the mandelic acid was dissolved in water. But optically active mandelic acid does not readily racemize in water, and the α-hydrogen atom is therefore not exchanged. In fact, mandelic acid is quite stable in acid solution even at 96°, and racemizes only slowly at that temperature in strong alkali.[10]

Reduction of Pyruvic Acid.—The reduction of pyruvic acid by the Hantzsch compound already has been reported.[3] The reaction was repeated in ethanol and in glycol dimethyl ether as solvents; low yields (*ca.* 5%) of lactic acid could be identified, after chromatography, in each case.

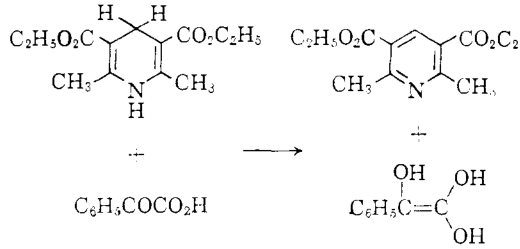
Discussion

The reduction of benzoylformic acid might take place by either of two mechanisms, which are represented schematically as shown.



(1)

or



(2)

If the reaction had taken place by way of the enol of mandelic acid (scheme 2) then the hydrogen atoms of the enol would have exchanged with those of the solvent and, in the deuterated solvent, the product would have contained an atom of deuterium per molecule, or at least a large fraction of an atom of deuterium per molecule. Since no appreciable amount of deuterium was in fact transferred to the mandelic acid, the reduction must have taken place by a direct hydrogen transfer from the reducing agent to the α-carbon atom of the benzoylformic acid.

The yield in this reduction is very low, and the reducing agent is not really comparable in structure to reduced diphosphopyridine nucleotide, since the Hantzsch compound has a hydrogen atom, rather than an alkyl group, attached to the nitrogen atom of the pyridine ring. However, the work does show that a non-enzymatic reduction of a ketoacid by a derivative of 1,4-dihydropyridine can occur with direct hydrogen transfer.

Acknowledgment.—The authors wish to thank the National Institutes of Health for a grant in support of this work.

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[10] A. N. Campbell and A. J. R. Campbell, This Journal, **54**, 4581 (1932).

[Contribution from the Development Department, Union Carbide Chemicals Co., Division of Union Carbide Corp.]

The Chemistry of α,β-Unsaturated Ethers. III. Self Condensation[1]

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Received April 23, 1958

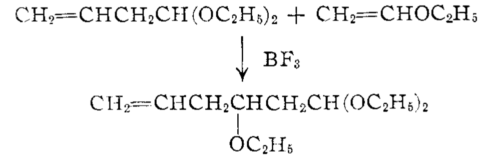
The novel self condensation of α,β-unsaturated ethers in the presence of boron trifluoride and mercuric acetate to yield dimers, trimers and tetramers is reported. The primary products are acetals or ketals of β,γ-unsaturated aldehydes or ketones. The higher condensation products are acetals and probably result from the condensation of the lower acetal or ketal products with the starting ether. Attempts to isolate the free vinylacetaldehyde from 1,1-diethoxy-3-butene (dimer of vinyl ethyl ether) were unsuccessful, but this aldehyde was isolated as its 2,4-dinitrophenylhydrazone. The mechanism of the reaction is discussed.

α,β-Unsaturated ethers are polymerized readily by strongly acidic catalysts, particularly those of the Friedel–Crafts type.[2] Inasmuch as most of the known reactions of these ethers are also acid-catalyzed, this marked tendency to polymerize is often the most important reason for the failure when these ethers do not react well with other compounds.

During our studies of the chemistry of α,β-unsaturated ethers we learned that the catalyst combination of mercuric acetate and boron trifluoride is effective for controlling the polymerization of these ethers to yield dimers, trimers and tetramers. Higher condensation products were formed but in insufficient yields to permit their isolation and identification.

The dimeric products of this reaction are acetals or ketals of β,γ-unsaturated aldehydes or ketones. The trimers and tetramers appear to be the acetal–vinyl ether condensation products of the dimers and trimers, respectively, with the starting ether.[3] These may be expressed for the self condensation of vinyl ethyl ether by

$$2CH_2{=}CHOC_2H_5 \xrightarrow[BF_3]{Hg(OAc)_2} CH_2{=}CHCH_2CH(OC_2H_5)_2 \quad (1a)$$



$$CH_2{=}CHCH_2CH(OC_2H_5)_2 + CH_2{=}CHOC_2H_5 \xrightarrow{BF_3} CH_2{=}CHCH_2\underset{\displaystyle OC_2H_5}{\underset{|}{CH}}CH_2CH(OC_2H_5)_2 \quad (1b)$$

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[1] For the previous paper of this series see R. I. Hoaglin, D. G. Kubler and R. E. Leech, This Journal, **80**, 3069 (1958).

[2] C. E. Schildknecht, A. O. Zoss and C. McKinley, *Ind. Eng. Chem.*, **39**, 180 (1947).

[3] R. I. Hoaglin and D. H. Hirsh, This Journal, **71**, 3468 (1949).