[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY]

A New Synthesis of D-Erythrose Derivatives from D-Arabinose[1]

BY CLINTON E. BALLOU

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A preparation of D-erythrose, 2,3-isopropylidene-D-erythrose and methyl 2,3-isopropylidene-D-erythroside from D-arabinose is described. Intermediates in the synthesis are benzyl β-D-arabinoside, benzyl 3,4-isopropylidene-β-D-arabinoside, and 3,4-isopropylidene-D-arabinose.

Interest in the 4-carbon sugar D-erythrose has been stimulated by the recent recognition of the role played by D-erythrose 4-phosphate in carbohydrate metabolism.[2] A synthesis of the latter compound has been reported,[3] and this synthetic material has been found to behave qualitatively and quantitatively like the tetrose phosphate prepared enzymatically from D-fructose 6-phosphate.[4]

In experiments carried out for the purpose of obtaining a D-erythrose derivative blocked in the 2- and 3-positions for use as a possible intermediate in the synthesis of D-erythrose 4-phosphate, we accomplished the new synthesis of D-erythrose described in this paper. D-Arabinose was converted to benzyl β-D-arabinoside,[5] which was in turn acetonated to benzyl 3,4-O-isopropylidene-β-D-arabinoside. Hydrogenolysis of the latter removed the benzyl group to give 3,4-O-isopropylidene-D-arabinose, which could be reduced with sodium borohydride to 3,4-O-isopropylidene-D-arabitol. On cleavage with periodate, the latter yielded 2,3-O-isopropylidene-D-erythrose. This compound could be hydrolyzed in 20% acetic acid to give free D-erythrose.

On treatment with methanolic hydrogen chloride, the 2,3-O-isopropylidene-D-erythrose retained its acetone group, and was converted to methyl 2,3-O-isopropylidene-D-erythroside, which had a specific rotation of −137°. This rotation, which differs significantly from the value reported for the methyl isopropylidene-D-erythroside resulting from the simultaneous action on D-erythrose of a mixture of acetone and methanol containing sulfuric acid and copper sulfate,[6] indicates that our preparation may be the β-isomer. In contrast with the product described by Overend, Wiggins and Stacey,[6] our preparation is not reducing toward Fehling solution.

The 2,3-O-isopropylidene-D-erythrose was converted to 2,3-di-O-acetyl-4-O-trityl-D-erythrose diethyl mercaptal, the intermediate previously employed in the synthesis of D-erythrose 4-phosphate.[3] However, this route has no advantage over that starting with 2,4-O-ethylidene-D-erythrose obtained from 4,6-O-ethylidene-D-glucose.[7]

Experimental

Benzyl β-D-Arabinoside.—A mixture of 100 g. of D-arabinose in 500 ml. of benzyl alcohol was cooled in an ice-salt-bath and saturated with hydrogen chloride by bubbling the gas through for about 20 minutes. The mixture was shaken overnight at room temperature during which crystallization occurred. One liter of ethyl ether was then added slowly with constant mixing, and the mixture was left at 5° for 4 hours to complete crystallization. The crystals were collected by filtration, washed on the funnel with ether and dried in air. The yield was 145 g. (91%). Recrystallization was carried out from absolute ethanol (50 g./liter) to give 140 g. with m.p. 165–169°. The pure substance melts at 169–171°.[5]

Benzyl 3,4-O-Isopropylidene-β-D-arabinoside.—A mixture of 20 g. of benzyl β-D-arabinoside, 1 liter of dry acetone, 60 g. of anhydrous copper sulfate and 1 ml. of concd. sulfuric acid was shaken for 18 hours. Ammonia gas was then bubbled into the mixture until it was neutral. The solid was filtered off, and the filtrate was concentrated to a sirup. The sirup was dissolved in 150 ml. of ether, and the insoluble unreacted arabinoside was filtered off. The ether filtrate was concentrated to a thick sirup that was distilled in a high vacuum. The main fraction had b.p. 135–145° at 0.15 mm. (bath 175°), and amounted to 16.8 g. It solidified on standing, and could be crystallized from ethyl ether. The crystals showed m.p. 55–58°, and $[\alpha]_D$ −209° (*c* 2, ethanol). The substance analyzed correctly for an acetone derivative.

Anal. Calcd. for $C_{15}H_{20}O_5$ (280): C, 64.7; H, 7.15; acetone, 20.8. Found: C, 64.5; H, 7.57; acetone, 21.4.

3,4-O-Isopropylidene-D-arabinose.—The palladium-on-carbon catalyst was reduced and washed just before use as described previously.[5a] It must be washed free of acid, and the last washing is with dry ethyl ether. The catalyst was re-suspended in 200 ml. of ether and shaken with hydrogen until the volume remained constant.

Ten grams of benzyl isopropylidene-β-D-arabinoside was then introduced into the reduction chamber and the shaking was resumed until the hydrogen uptake almost ceased (820 ml. in 2.5 hours). The theoretical hydrogen uptake was 805 ml. The catalyst was centrifuged off and the ether solution was concentrated to a dry crystalline residue that weighed 6.0 g. This 3,4-O-isopropylidene-D-arabinose came out of most solvents a gel, but could be crystallized in a 50% yield from chloroform. It was strongly reducing and melted at 82–85°.

Anal. Calcd. for $C_8H_{14}O_5$ (190): C, 50.5; H, 7.37. Found: C, 49.1; H, 7.70.

2,3-O-Isopropylidene-D-erythrose and Methyl 2,3-O-Isopropylidene-β-D-erythroside.—To the ether solution of isopropylidene-D-arabinose resulting from reductive debenzylation of 10 g. of the arabinoside was added a solution of 1 g. of sodium borohydride in 50 ml. of ethanol. After 2 hours, when the aldehyde was reduced, the solution was neutralized to about *p*H 7 with glacial acetic acid and concentrated to remove the ether. About 50 ml. of water was added to the remaining alcoholic solution, followed by 10 g. of finely powdered sodium periodate. The mixture was swirled to facilitate the reaction which took about 15 minutes. The precipitated salt (sodium iodate) was then filtered off and the filtrate was concentrated to dryness. The solid residue was extracted with 100 ml. of ether, the

(1) Presented in part before The Division of Carbohydrate Chemistry at the 128th Meeting of The American Chemical Society, Minneapolis, Minn., Sept., 1955.

(2) B. L. Horecker and P. A. Smyrniotis, THIS JOURNAL, **75**, 2021 (1953); E. Racker, G. de la Haba and I. G. Leder, *Arch. Biochem. Biophys.*, **48**, 238 (1954).

(3) C. E. Ballou, H. O. L. Fischer and D. L. MacDonald, THIS JOURNAL, **77**, 2658, 5967 (1955).

(4) H. L. Kornberg and E. Racker, *Biochem. J.*, **61**, iii (1955).

(5) C. E. Ballou, S. Roseman and K. P. Link, THIS JOURNAL, **73**, 1140 (1951); E. Fischer and L. Beensch, *Ber.*, **27**, 2478 (1894).

(6) W. G. Overend, M. Stacey and L. F. Wiggins, *J. Chem. Soc.*, 1358 (1949).

(7) D. A. Rappoport and W. Z. Hassid, THIS JOURNAL, **73**, 5524 (1951).

ether extract was dried over sodium sulfate, and concentrated to the sirupy 2,3-O-isopropylidene-D-erythrose. The yield was 4.4 g. (77%). The substance did not reduce hot Fehling solution, but gave the theoretical oxidation equivalent in the Willstätter-Schudel titration.

A solution of 3.9 g. of 2,3-O-isopropylidene-D-erythrose in 50 ml. of dry methanol had a rotation of −6.13°, $[\alpha]_D$ −78°. Hydrogen chloride gas (0.5 g.) was bubbled into the solution, and the rotation was observed until it became constant in 2 hours, when the α was −9.98°. The solution was neutralized with 5 g. of silver carbonate, the silver chloride was filtered off, and the filtrate was treated with hydrogen sulfide. After filtration to remove silver sulfide, the solution was concentrated to a sirup that was distilled at 7.5 mm. The main fraction had b.p. 66–67°, and weighed 2.0 g. It showed $[\alpha]_D$ −137° (*c* 1, chloroform). The analysis agrees with that of methyl isopropylidene-erythroside.

Anal. Calcd. for $C_8H_{14}O_4$ (174): C, 55.1; H, 8.0; OCH_3, 17.8. Found: C, 55.0; H, 8.2; OCH_3, 20.1.

The product did not react with periodate. It was non-reducing to Fehling solution even after a long period of heating. This is contrary to the result found by Overend, Stacy and Wiggins,[6] who report that the methyl isopropylidene-erythroside prepared by the action of methanol, acetone and sulfuric acid on D-erythrose suddenly reduced Fehling solution after prolonged heating. Their product showed $[\alpha]_D$ −55° (chloroform), and is probably an α,β-mixture. The substance described here may represent the pure β-form.

2,3-Di-O-acetyl-4-O-trityl-D-erythrose Diethyl Mercaptal.—A preparation of crude 2,3-O-isopropylidene-D-erythrose (2.1 g.) was mercaptalated, as described for the mercaptalation of 2,4-O-ethylidene-D-erythrose,[3] to give 2.0 g. of a mercaptal. Tritylation followed by acetylation, yielded 3.8 g. of the desired product with m.p. 102–103° after recrystallization from methanol. The melting point was not depressed on admixture with authentic 2,3-di-O-acetyl-4-O-trityl-D-erythrose diethyl mercaptal.

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BERKELEY 4, CALIF.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Senecio Alkaloids: Mikanoidine, the Alkaloid from *Senecio mikanoides*

BY ROGER ADAMS AND MAURIZIO GIANTURCO

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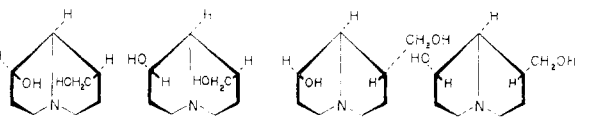
Mikanoidine, the alkaloid in *Senecio mikanoides* (Walp) Otto, is hydrolyzed to the base mikanecine, now identified as platynecine, and to mikanecic acid which proved to be a dehydrated seneciphyllic acid.

Manske[1] reported the isolation from *Senecio mikanoides* (Walp), Otto, of an amorphous alkaloid, mikanoidine. This yielded upon alkaline hydrolysis a base, mikanecine ($C_8H_{15}NO_2$), characterized as its picrate, and mikanecic acid which gave a poor analysis for $C_{13}H_{16}O_5$. This empirical formula for the acid was supported by molecular weight values of 254 and 260 in comparison with the theoretical value of 252. Manske deduced from the data that the alkaloid should have the formula $C_{21}H_{29}NO_6$. Since the great majority of the alkaloids obtained from Senecio species contain 18 carbon atoms and the corresponding acid moieties ten carbon atoms, mikanecine picrate and mikanecic acid were reinvestigated in this Laboratory. The materials for this work were kindly supplied by Dr. Manske.

It was suggested by Leonard[2] in his review article on Senecio alkaloids that mikanecine picrate might be identical with platynecine picrate. This suggestion has been tested experimentally and by determination of the melting point, melting point of a mixture, and comparison of the infrared spectra the identity of the two compounds was established.

With the stereochemical formulas of platynecine and dihydroxyheliotridane[3] definite (I and II), it was proposed that mikanecine from *Senecio mikanoides* and hastanecine from *Cacalia hastata*[4] were probably two stereoisomeric forms of 1-hydroxymethyl-7-hydroxypyrrolizidine, III and IV. Since mikanecine is identical with platynecine, the fourth isomeric form may be turneforcidine,[5] m.p. 118.5–120°, $[\alpha]_D$ −10.5° (MeOH), obtained from *Turneforcia sibirica*. Turneforcidine[5] was shown not to be identical with hastanecine, m.p. 113–114°, $[\alpha]_D$ −9.1° (MeOH), by determination of the melting point of a mixture; depression was observed. The paper describing turneforcidine was overlooked at the time the Communication on the stereochemistry of pyrrolizidine bases[3] was written.



I II III IV

Upon reinvestigation of mikanecic acid it was observed that the analytical values for carbon and hydrogen reported by Manske and checked in this Laboratory agree closely with the formula $C_{10}H_{12}O_4$ and only poorly with the one previously proposed $C_{13}H_{16}O_5$.[1] The infrared spectrum of the acid and its dimethyl ester showed the presence of two conjugated carboxylic acid and ester groups, respectively, 1690 and 1680 cm.$^{-1}$ (Nujol mull) for the acid; 1735, 1730 cm.$^{-1}$ and importantly 1260 cm.$^{-1}$ (very strong) for the ester ($CHCl_3$), two or more carbon–carbon double bonds, (1650 cm.$^{-1}$ (strong) and 1638 cm.$^{-1}$ (shoulder) and carbon–methyl groups. The determination of the neutralization equivalent gave consistently the value 100 ± 2, which, in the light of the infrared spectral data, corresponds to a molecular weight of

(1) R. H. F. Manske, *Can. J. Research*, **14B**, 6 (1936).

(2) N. J. Leonard in "The Alkaloids" by R. H. F. Manske and H. L. Holmes, Vol. I, Academic Press, Inc., New York, N. Y., 1949, p. 137.

(3) R. Adams and B. L. Van Duuren, THIS JOURNAL, **76**, 6379 (1954).

(4) V. S. Konovalov and G. P. Menshikov, *J. Gen. Chem. U.S.S.R.*, **15**, 328 (1945).

(5) G. P. Menshikov, S. O. Denisova and P. G. Massagetov, *ibid.*, **22**, 1465 (1952).