THE ABSOLUTE CONFIGURATION OF PANTOTHENIC ACID

R. K. Hill and T. H. Chan*
Department of Chemistry, University of Georgia, Athens, Georgia, 30601

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Summary: The absolute configuration of pantothenic acid has been defined as (R) by conversion of (-)-pantolactone to (S)-(+)-pinacolyl ethyl ether.

Pantothenic acid (Vitamin B_3), a member of the B complex vitamins (1), plays a crucial role in carbohydrate and lipid metabolism as a component of coenzyme A, the acyl transfer coenzyme. The structure (I) contains a single asymmetric center, so that the vitamin is optically active; only the natural dextrorotatory isomer possesses vitamin activity. Assignment of absolute configuration has up until now been based only on application of Hudson's rules (2); since the amide (3) and phenylhydrazide (4) of pantoic acid (II) are both more dextrorotatory than the acid, the chiral center was assigned the D_g (or, in modern notation, R) configuration. Because of the fallibility of empirical rules relating rotation with configuration (5) and the biochemical importance of pantothenic acid, it appeared desirable to provide a sounder basis for the configurational assignment. We report an unambiguous correlation of (-)-pantolactone (III) with (S)-(+)-lactic acid via pinacolyl ethyl ether (VII).

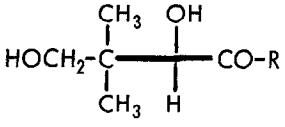
Methods and Results

(-)-Pantolactone (III) (Fluka A. G.), $[\alpha]_D^{25}$ -17.2° ($c = 0.9$, $CHCl_3$), was converted to the ethyl ether (IV), b.p. 117° (25 mm.), $[\alpha]_D^{25}$ $+35.8^\circ$ ($c = 1.25$, $CHCl_3$), by reaction with ethyl iodide and silver oxide in dimethylformamide for 16 hr. at 60°, a procedure (6) known not to affect the configuration at the chiral carbinol carbon. The ir spectrum showed the disappearance of the hydroxyl band at 3400 cm^{-1} and the retention of the γ-lactone carbonyl at 1795 cm^{-1},

* Department of Chemistry, McGill University, Montreal, Quebec

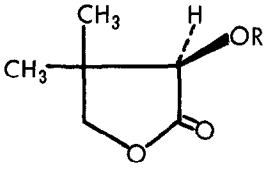
while the nmr spectrum showed the characteristic ethoxyl peaks. Lithium aluminum hydride reduction of IV in ether led to 2-ethoxy-3, 3-dimethyl-1,4-butanediol (V), $[\alpha]_D^{25}$ +11.0° (c = 1.0, $CHCl_3$); nmr ($CDCl_3$): 1.0, s, 6H (CH_3-C-CH_3); 1.25, t (J = 7 Hz), 3H (CH_3-CH_2); 3.2, q, 1H (CHOEt), 3.4-4.0, m, 6H (3 CH_2-O).

Treatment of V with methanesulfonyl chloride in pyridine at 0°, then 5 hr. at 25°, afforded the bis-methanesulfonate (VI), which without purification was reduced with lithium aluminum hydride. Pinacolyl ethyl ether (VII) was collected in a fraction of b.p. 100-120° and purified by preparative vapor-phase chromatography, using a 10-ft. column of 20% SE-30 at 90°. The pure ether had infrared and nmr spectra identical with those of a synthetic sample, prepared from pinacolyl alcohol and triethyloxonium fluoroborate (7), and showed



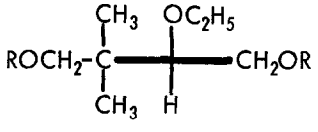
I. R = NH-CH_2CH_2COOH

II. R = OH



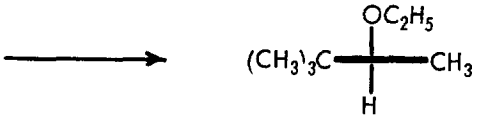
III. R = H

IV. R = C_2H_5



V. R = H

VI. R = SO_2CH_3



(S)-(+)-VII

$[\alpha]_D^{25}$ $+19^\circ$ ($c = 0.28$, CCl_4); the rotation calculated for optically pure VII is $+22.4^\circ$ (7).

(+)-Pinacolyl ethyl ether (VII) has recently been assigned the (S) configuration by direct synthesis from (S)-(+)-lactic acid (7). Consequently, the conversion outlined above constitutes rigorous proof that the asymmetric center in (-)-III and in the natural (+)-pantothenic acid has the (R)-configuration.

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