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THE CONFIGURATION OF (-) TROPIC ACID AND OF ITS NATURALLY OCCURRING ESTERS

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(-) TROPIC acid is the acidic building stone of a number of important alkaloids, among others of hyoscyamine and hyoscine. In order to obtain a deeper insight into the biosynthesis and mode of physiological action of the latter compounds, establishing of the absolute configuration of (-)tropic acid was required.

β-chlorohydratropic acid (II) was resolved by McKenzie and Strathern[1] more than three decades ago, and the levorotatory acid was subsequently hydrolysed to (-)tropic acid (I) the reaction being accompanied by slight racemization; hydrolysis with ammonium hydroxide gave (-)tropamide in a still higher state of optical purity.

On the other hand, (+)α-methylphenylacetic acid (IIIb) was treated by the Curtius reaction to give (-)phenylethylamine[2] (IV), and the N-benzoyl derivative was oxidized, in turn,[3] to (+) alanine (V).

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[1] A. McKenzie and R. C. Strathern, J. Chem. Soc. 127, 86 (1925).

[2] H. I. Bernstein and F. C. Whitmore, J. Amer. Chem. Soc. 61, 1324 (1939).

[3] W. Leithe, Ber. Dtsch. Chem. Ges. 64, 2827 (1931).

According to the unequivocal convention of Cahn et al.,[4] (+)α-methylphenylacetic acid is designated as S (+)α-methylphenylacetic acid (IIIb), where the R configuration corresponds to the levorotatory form (IIIa).

The single missing link between tropic acid and alanine was now the establishment of the correlation of (-)β-chlorohydratropic acid (II) with either S or R α-methylphenylacetic acid. This work has been done recently in the laboratory of the authors.

β-chlorohydratropic acid obtained from atropic acid[5] was resolved by codeine instead of morphine used by McKenzie.[1] The codeine salt of (-)β-chlorohydratropic acid melted at 138° (decomp.), $[\alpha]_D^{20}$ -95° (c = 0.4, in methanol). (Found: C, 67.9; H, 6.3; N, 2.7. $C_{27}H_{30}O_5NCl$ requires C, 67.0; H, 6.2; N, 2.9%).

The levorotatory acid, m.p. 62°, gave correct[1] rotational values, $[\alpha]_D^{20}$ -115° (c = 0.4; in 96% ethanol).

Hydrogenolysis of this compound over a Pd-charcoal catalyst in ethyl acetate in the presence of barium hydroxide resulted in the formation of R (-)α-methylphenylacetic acid, b.p.$_{1-2}$ 115°, $[\alpha]_D^{20}$ = -76° (c = 0.794 in 96% ethanol). (Found: C, 72.2; H, 6.7. $C_9H_{10}O_2$ requires: C, 72.0; H, 6.7%.)

The Cahn - Ingold - Prelog convention,[4] gives the unequivocal configuration of S (-)tropic acid (I) for the levorotatory form.

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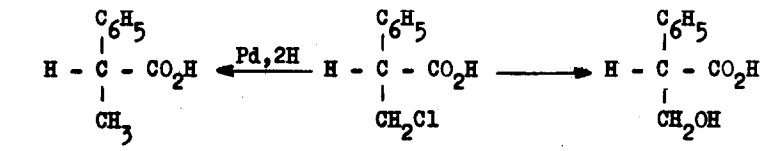
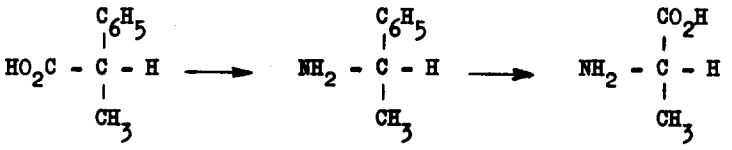
[4] R. S. Cahn, C. K. Ingold and V. Prelog, Experientia 12, 81 (1956).
[5] A. McKenzie and J. K. Wood, J. Chem. Soc. 115, 835 (1919).



IIIa (-) II (-) I (-)-Tropic acid



IIIb (+) IV (-) V (+)-Alanine

All these formulae are Fischer projection.

Accordingly, (-)hyoscyamine is S (-)tropoyl-tropan-3α-ol, and (-)hyoscine is S (-)tropoyl-3α-hydroxy-6,7 β-epoxy-tropane.