The Senecio *Alkaloids. Part XII.* The Synthesis of* (±)-erythro-3-*Hydroxy*-2-*methoxy*-4-*methylpentane*-3-*carboxylic Acid.*

By LEONARD J. DRY and FRANK L. WARREN.

[Reprint Order No. 5704.]

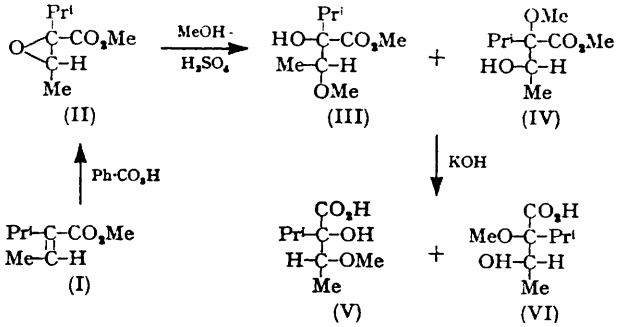
Methyl 4-methylpent-2-ene-3-carboxylate (I) is oxidised with perbenzoic acid and the epoxide (II) subjected to acid methanolysis to yield, after saponification, (±)-*erythro*-3-hydroxy-2-methoxy-4-methylpentane-3-carboxylic acid (V).

HELIOTRINIC ACID, m. p. 93—95°, $[\alpha]_D$ −12°, has been obtained by the hydrolysis of heliotrine (Menshikov, *Ber.*, 1932, **65**, 974) and *iso*heliotrine (Trautner and Neufeld, *Austral. J. Sci.*, 1949, **11**, 211) and was shown to be 3-hydroxy-2-methoxy-4-methylpentane-3-carboxylic acid (Menshikov, *J. Gen. Chem. U.S.S.R.*, 1939, **9**, 1851). Adams and van Duuren (*J. Amer. Chem. Soc.*, 1953, **75**, 4636) reported that on demethylation it yielded an acid, m. p. 89°, which showed no m. p. depression with trachelantic acid which we had shown was (+)-*threo*-2 : 3-dihydroxy-4-methylpentane-3-carboxylic acid, m. p. 92° (*J.*, 1952, 3445). We have synthesised (±)-*erythro*-3-hydroxy-2-methoxy-4-methylpentane-3-carboxylic acid (V), which we had expected to yield heliotrinic acid.

4-Methylpent-2-ene-3-carboxylic acid (see Dry and Warren, 1952, *loc. cit.*) was esterified by way of the acid chloride without isomerisation since the ester (I) yielded the original acid on hydrolysis. The ester with perbenzoic acid readily gave methyl 2 : 3-epoxy-4-methylpentane-3-carboxylate (II). In boiling methanolic sulphuric acid this yielded, after hydrolysis, an acid mixture which was shown, by quantitative oxidation with lead tetra-acetate (Leisegang and Warren, *J.*, 1950, 702), to contain about 80% of an α-hydroxy-acid (V). That a certain amount of the 2-hydroxy-ester (IV) should be formed during acid methanolysis follows from the reasoning applied to the acid methanolysis of methyl αβ-epoxybutyrate (Dry and Warren, *J. S. African Chem. Inst.*, 1953, **6**, 14), where the α-hydroxy-isomer was obtained in 77% yield. The *erythro*-configurations of (V) and (VI)

* Part XI, preceding paper.

follow from the *trans*-addition of methanol to the epoxide (II) (Dry and Warren, 1953, *loc. cit.*) with inversions at positions 2 and 3 respectively.



The mixture (V) + (VI) was obtained as an oil even after purification and prolonged desiccation. The acid (V) was readily separated by crystallising the morphine salts from water or acetone, the hydrated salt, m. p. 187—189°, of the racemic acid (V) being obtained. The salt yielded an oily, optically inactive α-hydroxy-acid which was not investigated further. The anhydrous morphine salt, m. p. 208—209°, of (V) was obtained from ethanol–ether and gave an α-hydroxy-acid which gradually crystallised. The acid, m. p. about 40°, characterised as the *p*-bromophenacyl ester, m. p. 138°, showed no rotation, was very hygroscopic, and appeared unlikely to be the racemic form of heliotrinic acid. Demethylation gave a product, m. p. 149°, showing no m. p. depression with (±)-*erythro*-2 : 3-dihydroxy-4-methylpentane-3-carboxylic acid, m. p. 150° (Dry and Warren, 1952, *loc. cit.*). Since the optically active form of this acid does not racemise under the conditions of demethylation, resolution of (V) had apparently not occurred and could not be achieved by fractional crystallisation of the morphine salts.

Experimental

Methyl 4-Methylpent-2-ene-3-carboxylate.—4-Methylpent-2-ene-3-carboxylic acid (30 g.) in ether (50 ml.) was refluxed for 90 min. with thionyl chloride (21 ml.), the ether evaporated, the residual liquid treated with methanol (20 ml.) at 0°, and the whole heated to 100°. The product (24 g.), b. p. 79—83°/45 mm., was redistilled to give *methyl 4-methylpent-2-ene-3-carboxylate* (23 g.), b. p. 74°/36 mm. (Found : C, 67·8; H, 9·9. $C_8H_{14}O_2$ requires C, 67·6; H, 9·9%). With boiling alcoholic potassium hydroxide it yielded immediately the pure acid, m. p. and mixed m. p. 54°.

Methyl (±)-2 : 3-*Epoxy-4-methylpentane-3-carboxylate.*—Methyl 4-methylpent-2-ene-3-carboxylate (21·4 g., 1·0 mol.) in dry N-chloroformic perbenzoic acid (400 ml., 1·3 mols.) was set aside for 15 days at 6—8°; oxidation was then complete. The solution was extracted with 2N-sodium hydroxide (180 ml.), washed with dilute hydrochloric acid and 10% aqueous sodium chloride, dried ($MgSO_4$), and distilled, to yield the (±)-*epoxy-ester* (20·5 g., 0·86 mol.), b. p. 98—99·5°/35 mm. (Found : C, 61·2; H, 8·8. $C_8H_{14}O_3$ requires C, 60·7; H, 8·9%).

(±)-erythro-3-*Hydroxy-2-methoxy-4-methylpentane-3-carboxylic Acid.*—The foregoing ester (17·8 g.), sulphuric acid (2·2 ml.), and methanol (60 ml.) were refluxed for 3 hr., anhydrous sodium acetate (8 g.) was added, the excess of methanol evaporated under reduced pressure, and the product worked up as above. The ester mixture (15 g.), b. p. 112—115°/31 mm., was hydrolysed by boiling potassium hydroxide (18 g.) in 70% ethanol (200 ml.) for 1 hr. The acid product, freed from a small quantity of unchanged ester, was extracted with chloroform and worked up in the usual way, all solvent being evaporated under reduced pressure, to give an oily acid mixture (11·1 g.) Found : equiv., 183; CO_2, 14·8 ml. at N.T.P. Calc. for $C_8H_{16}O_4$: equiv., 176; 17·8 ml. for 1 mol. of CO_2). It gave a barium salt (Found : OMe, 12·5. Calc. for $C_8H_{15}O_4Ba_{0·5}$: OMe, 12·7%).

The acid mixture (8·1 g., 1 mol.) in 50% ethanol (200 ml.) was warmed with morphine (1 mol.), and the solution evaporated under reduded pressure to 100 ml. and cooled to 0°. Large prisms (10 g.), m. p. 180—184°, separated. Evaporation of the mother-liquor to 40 ml. and cooling to 0° yielded a further crop (8·7 g.) of the same salt, m. p. 180—182°. After three

recrystallisations from water a *salt* (2·5 g.), m. p. 187—189°, not raised on further recrystallisation, was obtained (Found : C, 62·2; H, 7·7; OMe, 6·5. $C_{25}H_{35}O_7N,H_2O$ requires C, 62·6; H, 7·8; OMe, 6·5%). The salt (2·4 g.) yielded an oily acid, $[\alpha]_D$ ±0° (*c*, 1 in H_2O), which did not solidify after sublimation at 70°/0·1 mm. The same salt was obtained by recrystallisation from acetone, boiling out with small quantities of acetone, and by crystallising an aqueous solution containing equal parts of the sodium and the morphine salt. When twice recrystallised from ethanol–ether, however, a *salt*, m. p. 208—209°, was obtained (Found : C, 64·6; H, 8·0; OMe, 6·6. $C_{25}H_{35}O_7N$ requires C, 65·0; H, 7·6; OMe, 6·7%). The latter reverted to the former, m. p. 187—189°, on recrystallisation from water, and yielded a very hygroscopic acid, m. p. *ca.* 40°, $[\alpha]_D$ ±0° (*c*, 1 in H_2O), crystallising in needles after 4 months in a desiccator and giving an intense yellow colour with ferric chloride. The p-*bromophenacyl ester*, m. p. 138°, crystallised from aqueous alcohol in stout prisms (Found : C, 51·9; H, 6·0; Br, 21·7; OMe, 8·2. $C_{16}H_{21}O_5Br$ requires C, 51·5; H, 5·7; Br, 21·4; OMe, 8·3%).

Demethylation. The methoxy-acid (30 mg.) was heated at 100° with 48% hydrobromic acid (5 ml.) for 2 hr., and the solution diluted somewhat and extracted with ether. The washed and dried ether extracts were evaporated and the residue sublimed at 90°/0·5 mm.

The authors acknowledge a bursary (to L. J. D.) and a grant for equipment from the South African Council for Scientific and Industrial Research.

Department of Chemistry and Chemical Technology,
University of Natal, Pietermaritzburg, South Africa. [*Received, September 6th*, 1954.]