

662. *The Senecio Alkaloids. Part IX.* The Synthesis and Resolution of 3 : 4-Dihydroxy-2-methylpentane-3-carboxylic Acids: Viridifloric and Trachelantic Acids.*

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4-Methylpent-2-ene-3-carboxylic acid (I) is oxidised by perbenzoic acid and the product hydrolysed to (\pm)-*erythro*-3 : 4-dihydroxy-2-methylpentane-3-carboxylic acid (IV), m. p. 148—150°. This is resolved into its optical components which shows no measurable rotation. The acid (I) is also oxidised by dilute potassium permanganate, giving (\pm)-*threo*-3 : 4-dihydroxy-2-methylpentane-3-carboxylic acid (II), m. p. 119—121°, which is resolved into the (+)-form, $[\alpha]_D^{20} + 2.2^\circ$, and the less pure (–)-form, $[\alpha]_D^{20} - 1^\circ$.

The significance of these results is discussed in relation to the configurational relations of trachelantic and viridifloric acids.

TRACHELANTIC ACID, m. p. 93—95°, has been obtained by the alkaline hydrolysis of trachelantine (Menshikov, *J. Gen. Chem., U.S.S.R.*, 1941, **11**, 209; cf. also Menshikov and Borodina, *ibid.*, 1945, **15**, 225), lindifoline (Menshikov, *ibid.*, 1948, **18**, 1836), and supinine (Menshikov and Gurevich, *ibid.*, 1949, **19**, 1382). Menshikov (*ibid.*, 1947, **17**, 343) reported the acid as inactive and showed it to be 3 : 4-dihydroxy-2-methylpentane-3-carboxylic acid. The same author (*loc. cit.*, 1949) was able to isolate (+)-trachelantic acid, m. p. 93—94°, $[\alpha]_D + 1.3^\circ$ (in water), by catalytic hydrogenolysis of supinine. An isomeric acid, viridifloric acid, m. p. 119—121°, was obtained by the hydrolysis of viridiflorine (Menshikov, *ibid.*, 1948, **18**, 1736).

Adams and Herz (*J. Amer. Chem. Soc.*, 1950, **72**, 155) synthesised one form of (\pm)-3 : 4-dihydroxy-2-methylpentane-3-carboxylic acid (II), m. p. 119°, by the oxidation of 4-methylpent-2-ene-3-carboxylic acid (I) with dilute potassium permanganate. They naturally concluded that their synthetic acid (II) was identical with viridifloric acid which Menshikov had reported was optically inactive. They indicated that they were unable to obtain the other form of the dihydroxy-acid, and were not prepared to assign a configuration to their synthetic acid. It would seem, however, from Braun's studies (*ibid.*, 1929, **51**, 228) that the acid (II) was the *threo*-form.†

* Part VIII, *J.*, 1951, 66.

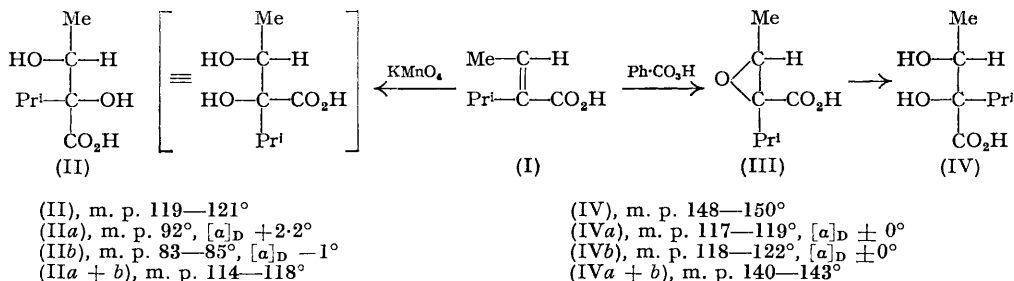
† Throughout this paper the stereochemical designations refer to the four-carbon chain shown vertically in the formulae. The formulae refer to the form shown, its mirror image, or the optically inactive form, as the case may require.

The other modification of this dihydroxy-acid has now been synthesised. The unsaturated acid (I) was converted by perbenzoic acid into the epoxide (III), which was not isolated but was hydrolysed to give, by *trans*-addition, (\pm)-*erythro*-3 : 4-dihydroxy-2-methylpentane-3-carboxylic acid (IV), m. p. 148—150°. This acid was certainly not identical with natural trachelantic acid. The validity of the structure followed not only from the synthesis. The synthetic acid showed the characteristics of an α -hydroxy-acid, and oxidation with lead tetra-acetate gave acetaldehyde, identified and estimated as the dimedone derivative, m. p. 138°, and its anhydro-form, m. p. 174°, in 68% yield.

Menshikov's trachelantic acid could be the (+)-form of this *erythro*-acid (IV). Accordingly the brucine salt of the pure (\pm)-acid (IV) was crystallised from absolute alcohol; the less soluble salt, m. p. 184—186°, yielded an acid (IVa), m. p. 117—119°. The more soluble brucine salts, recovered from the alcoholic solution by evaporation, were extracted many times with acetone, to leave a salt, m. p. 207—210°, which gave the enantiomorphous acid (IVb), m. p. 114—115°.

The brucine salts remaining in the acetone were recrystallised from this solvent, to give a less pure brucine salt, which yielded an acid, m. p. 120—130°, showing after sublimation, m. p. 118—122°. The melting points of both optical forms (IVa) and (IVb) were depressed about 30° on admixture with the (\pm)-*threo*-form (II). Neither of the enantiomorphs showed measurable rotation; but a mixture of the two showed a melting-point elevation to 140—143°. Addition of the (\pm)-modification (IV) to either of its optical components always showed a melting-point rise, the amount of which increased with increasing amounts of the (\pm)-form. This observation implied that the racemic form (IV) formed solid solutions with its enantiomorphs so that trachelantic acid could be neither a pure, nor a partly racemised, enantiomorph of the *erythro*-acid (IV).

Reinvestigation of Adams and Herz's synthesis (*loc. cit.*) confirmed the formation of an acid, m. p. 119—121°, which is formulated as (\pm)-*threo*-3 : 4-dihydroxy-2-methylpentane-3-carboxylic acid (II). Resolution of this acid through the brucine salt gave the (+)-acid (IIa), m. p. 92°, and a slightly optically impure (—)-acid (IIb), m. p. 84°. A mixture of the (+)- and the (—)-acid showed m. p. 114—118°. The melting points of both (IIa) and (IIb) were depressed on admixture with a small amount of (II).



In the absence of an authentic specimen the identification of viridifloric acid with Adams and Herz's synthetic acid (II) (*loc. cit.*) is not completely satisfactory. Viridifloric acid could be either one of the *erythro*-acids (IVa or b). It seems, however, in the light of our findings tabulated above, that trachelantic acid, m. p. 93—95°, is (+)-*threo*-3 : 4-dihydroxy-2-methylpentane-3-carboxylic acid (IIa).

It follows from configurational studies on $\alpha\beta$ -unsaturated acids by Auwers and Weissbach (*Ber.*, 1923, 56, 715; cf. also Auwers *et al.*, *Annalen*, 1923, 432, 46) that our unsaturated acid (I) is almost certainly the stable *cis*-modification with respect to the carbon chain (cf. tiglic acid, Titov, *J. Gen. Chem.*, U.S.S.R., 1948, 18, 1467). The configuration of the two acids, *threo* (II) and *erythro* (IV), follows from the *cis*- and *trans*-addition respectively of the hydroxyl groups across the double bond. These findings parallel those of the oxidation by potassium permanganate (*i.e.*, *cis*-addition) of the geometrical isomers of both but-2-ene-2-carboxylic acid (Fittig and Penschuck, *Annalen*, 1894, 283, 109, 114) and pent-2-ene-3-carboxylic acid (Fittig, *ibid.*, 1892, 263, 22) : the stable forms of these

acids give the lower-melting dihydroxy-acids whilst the labile forms yield the dihydroxy-acids with the higher melting point.

The preparation of acid (I) was essentially that used by Adams and Herz (*loc. cit.*). The yield, however, of the mixed unsaturated esters formed from the dehydration of ethyl 4-hydroxy-2-methylpentane-3-carboxylate is now raised to over 80% whilst the time required for the operation is decreased to less than an hour and charring is nearly completely avoided by a simple modification of Kon and Nargund's method (*J.*, 1932, 2461). Furthermore, an ultra-violet extinction curve showed that the mixed unsaturated acids (λ_{\max} . 213; ϵ_{\max} . 5100 in alcohol) contained only about 60% of the pure $\alpha\beta$ -unsaturated acid (λ_{\max} . 213; ϵ 8600) at equilibrium. The method of separation of the required $\alpha\beta$ -unsaturated acid (I) by partial esterification (cf. Eccott and Linstead, *J.*, 1929, 2160) did not readily give a separation. The $\alpha\beta$ -acid was readily separated by initially freezing out and then removing the liquid $\beta\gamma$ -form by differential extraction with a calculated quantity of sodium hydrogen carbonate. The derived mixture of $\alpha\beta$ - and $\beta\gamma$ -unsaturated acids was then heated with potassium hydroxide solution, and the $\alpha\beta$ -unsaturated acid separated as above. This process was repeated twice.

EXPERIMENTAL

Analyses are by Drs. Weiler and Strauss, Oxford, and spectroscopic data by M. E. von Klemperer of these laboratories. M. p.s are uncorrected.

Dehydration of Ethyl 4-Hydroxy-2-methylpentane-3-carboxylate.—The ester (143 g., 0.82 mol.) in pure dry benzene (200 ml.) was heated to boiling and vigorously stirred whilst phosphoric oxide (118 g., 0.83 mol.), mixed to a paste with benzene (150 ml.), was added during 30 minutes. The mixture was refluxed for a further 20 minutes and cooled. The supernatant liquid was poured off and the metaphosphoric acid residue washed with benzene. The combined solution and washings gave a mixture of unsaturated esters (70 g.), b. p. 75—80°/22 mm. The phosphoric acid residues were taken up with hot water, and the solution was extracted with benzene which, after being washed and dried, gave a further quantity of ester (34 g.). The total yield was 81%.

4-Methylpent-2-ene-3-carboxylic Acid (I).—The mixture of unsaturated esters (104 g.) was heated under reflux for 45 minutes with potassium hydroxide (93 g.) in 85% ethanol (500 ml.). The solvent was removed under reduced pressure and the residue acidified with dilute sulphuric acid, an oily layer, which partly solidified on chilling, then separating. The $\alpha\beta$ -unsaturated acid was filtered off and the residual acid layer was taken up in ether. The ethereal solution was re-extracted with a calculated volume of a solution of sodium hydrogen carbonate to remove two-thirds of the total remaining acids. The remaining ethereal layer contained a further quantity of predominantly $\alpha\beta$ -unsaturated acid which, combined with the first batch, crystallised from 25% ethanol, to give 4-methylpent-2-ene-3-carboxylic acid (31 g.), m. p. 54° (Found: C, 65.6; H, 9.6. Calc. for $C_7H_{12}O_2$: C, 65.6; H, 9.4%).

The liquid acid mixture (1 mol.) obtained from the sodium hydrogen carbonate extract was heated for 16 hours at 97° with 20% alcoholic potassium hydroxide (10 mols.). The acidified solution was worked up as above to give a further quantity of pure $\alpha\beta$ -unsaturated acid (15 g.). By repeating this equilibration it was possible to isolate a total of 60 g. of pure acid.

(\pm)-erythro-3 : 4-Dihydroxy-2-methylpentane-3-carboxylic Acid.—4-Methylpent-2-ene-3-carboxylic acid (25 g., 1 mol.) was dissolved in 0.92N-perbenzoic acid in dry chloroform (1.1 mols.). After 22 days at 8° the oxidation was practically complete, whereupon water (200 ml.) and 2N-sulphuric acid (20 ml.) was added. The chloroform was partly removed by evaporation, and the residual mixture refluxed for 3 hours. The aqueous layer was separated, washed twice with benzene to remove benzoic acid and a little unchanged unsaturated acid, neutralised with sodium carbonate, and evaporated under reduced pressure. The concentrate, acidified with concentrated hydrochloric acid, was extracted with ether. The ethereal solution, washed twice with a little saturated sodium chloride solution and dried (Na_2SO_4), gave a crude acid (9.2 g.). This acid was boiled out with benzene, and the insoluble material (7.2 g.) crystallised from ether—light petroleum in granules. Sublimation at 93—94°/6 μ gave (\pm)-erythro-3 : 4-dihydroxy-2-methylpentane-3-carboxylic acid, m. p. 148—150° (Found: C, 51.8; H, 8.7. $C_7H_{14}O_4$ requires C, 51.8; H, 8.7%). The p-phenylphenacyl ester crystallised from dilute ethanol and then from benzene—light petroleum in small stout prisms, m. p. 123—124° (Found: C, 70.35; H, 6.75. $C_{21}H_{24}O_5$ requires C, 70.75; H, 6.8%).

(\pm)-threo-3 : 4-Dihydroxy-2-methylpentane-3-carboxylic Acid.—4-Methylpent-2-ene-3-carboxylic acid (12.8 g.) was oxidised by potassium permanganate as described by Adams and Herz

(*loc. cit.*), to yield crude (\pm)-*threo*-acid (5.8 g.) whilst some unsaturated acid (2.7 g.) was recovered. The crude acid solidified when stirred with light petroleum and crystallised from ethyl acetate–light petroleum or chloroform–light petroleum, giving the (\pm)-*threo*-acid, m. p. 116–119°. When sublimed at 80°/0.2 mm., it had m. p. 119–121°. Adams and Herz (*loc. cit.*) give m. p. 119°. The *p*-phenylphenacyl ester crystallised from benzene–light petroleum in needles, m. p. 96–97° (Found, after drying at 72°/0.2 mm. : C, 71.0; H, 6.9%).

Resolution of (\pm)-threo-Acid.—The brucine salt from recrystallised acid (6.9 g.) in absolute ethanol (160 ml.) was kept for 12 hours at room temperature and finally cooled to 8°. The crystalline salt (11 g.) was recrystallised four times from ethanol, to give the *brucine* (+)-*acid* salt (7 g.), m. p. 225° (Found : C, 64.4; H, 7.3. $C_{30}H_{40}O_8N_2$ requires C, 64.7; H, 7.2%). The regenerated acid, crystallised from chloroform–light petroleum, gave the (+)-*acid*, m. p. 89–90°, $[\alpha]_D^{20} + 2.2^\circ \pm 0.2^\circ$ (*c*, 1 in ethanol), $[\alpha]_D^{20} + 2^\circ \pm 0.5^\circ$ (*c*, 1 in water) (Found : C, 51.8; H, 8.5%). Sublimation at 60°/0.2 mm. gave the (+)-*acid*, m. p. 92° (Found : C, 51.7; H, 8.5%). The unsublimed acid slowly became sticky but the sublimed acid was stable. A solution of the soluble brucine salt, concentrated to 100 ml. and cooled to 0° for 48 hours, gave crystals, m. p. 196–198°. The regenerated (–)-*acid*, crystallised from chloroform–light petroleum, had m. p. 70–75°, $[\alpha]_D^{20} - 0.75^\circ$ (*c*, 1 in water). Sublimation at 58°/0.2 mm. gave the (–)-*acid*, m. p. 83–85° (Found : C, 52.4; H, 8.9%).

Resolution of (\pm)-erythro-Acid.—The brucine salt (26 g.) was crystallised four times from absolute ethanol, to yield a *salt*, m. p. 184–186° (Found : C, 65.2; H, 7.2%). This yielded an acid, which, twice sublimed, gave the *erythro-acid* (IVa), m. p. 117–119°, $[\alpha]_D \pm 0^\circ$ (*c*, 1 in water) (Found : C, 51.65; H, 8.5%). The remaining brucine salts (B) were extracted with boiling acetone (100 ml.) for 20 minutes and the solution filtered hot. This process was repeated ten times with decreasing volumes of acetone, the final volume being 8 ml., to leave a salt, m. p. 207–210° (Found : C, 64.9; H, 7.2%). This yielded an acid which, crystallised from ethyl acetate–light petroleum, gave the *erythro-acid* (IVb), m. p. 114–115°, $[\alpha]_D \pm 0^\circ$ (*c*, 1 in water) (Found : C, 51.5; H, 8.55%). On another occasion, the brucine salts (B) were crystallised from acetone three times and the derived salt, m. p. 195–200°, gave an acid, m. p. *ca.* 120–130°, which on sublimation gave m. p. 119–122°.

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