

**933.** “Stable” 2,4-Dihydroxy-2,4-dimethylglutaric Acid: a Re-investigation; and Some Derivatives of meso-2,4-Dihydroxy-2,4-dimethylglutaric Acid and Lactone.

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Two isomers of 2,4-dihydroxy-2,4-dimethylglutaric acid monolactone, (I) and (IV), have been re-investigated. The latter can exist as a stable monohydrate, which was formerly confused with the diacid (III). The authentic diacid (III) has now been prepared. The allocation of these two monolactones and related compounds to the *meso*- and ( $\pm$ )-series, respectively, formerly made from a study of models, has now been confirmed experimentally. Some derivatives of *meso*-2,4-dihydroxy-2,4-dimethylglutaric acid are described.

DERIVATIVES of 2,4-dihydroxy-2,4-dimethylglutaric acid were required in connexion with another problem. The monolactone (I), prepared in good yield from acetylacetone, was dry distilled to give a dilactone (II), as reported by Zelinsky.<sup>1</sup> By heating the dilactone (II) with alkali, and acidifying the solution, Zelinsky<sup>1</sup> obtained a compound, m. p. 103—104°, which he formulated as (III), and described as the “stable” diacid (as opposed to the isomeric diacid from (I), which could not be prepared). This compound was also described by Auwers and Jackson,<sup>2</sup> and by Auwers and Kauffmann.<sup>3</sup> In all cases, analysis figures agreed with the structure (III), yet Zelinsky<sup>1</sup> found that, when titrated with alkali, the compound behaved as a monobasic acid in the cold and a dibasic acid in hot solution, just as did the acid lactone (I). Auwers and Kauffmann<sup>3</sup> confirmed this, and suggested that the compound might be the acid lactone (IV), with one molecule of water of crystallisation. However, drying experiments were inconclusive, and the compound gave the same analysis whether recrystallised from water or ether,<sup>1</sup> or ligroin-acetic acid,<sup>3</sup> though the melting point varied from 98—99° to 106—107°.

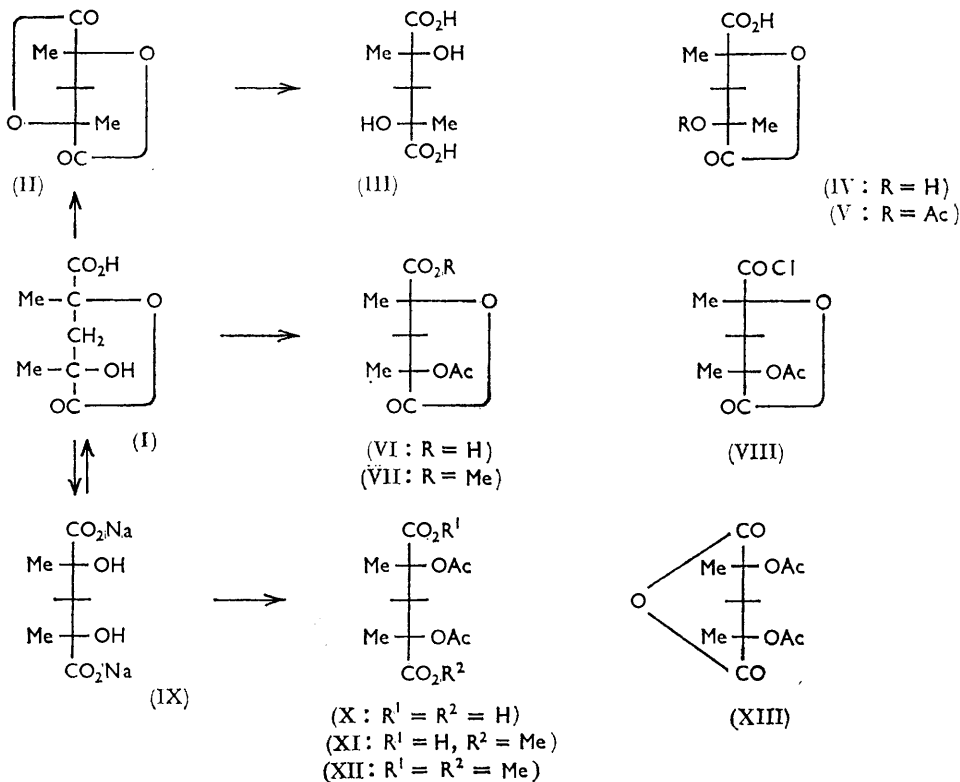
In the present work, this compound, prepared by Zelinsky's method, was shown to be

<sup>1</sup> Zelinsky *Ber.*, 1891, **24**, 4006.

<sup>2</sup> Auwers and Jackson, *Ber.*, 1890, **23**, 1614.

<sup>3</sup> Auwers and Kauffmann, *Ber.*, 1892, **25**, 3221.

the lactone acid (IV). After four recrystallisations from ether the analysis, in contrast with the early work, was correct for the lactone acid (IV). After two recrystallisations from water, the compound gave an analysis correct for the hydrate, even after being dried for 2 days *in vacuo* over phosphorus pentoxide. Thus Auwers and Kauffmann<sup>3</sup> were correct



in formulating their compound as the hydrate of (IV). The infrared spectrum of the compound (see Table) showed two carbonyl bands, corresponding with lactone and carboxylic groups, just as did the monolactone (I). On a paper chromatogram (as the ethylamine salt, see Table) it behaved like (I), and not like (III) (below), which had a low  $R_F$ , similar to that of glutaric acid. The compound (IV) gave a monoacetyl derivative (V), with retention of the lactone ring, as shown by analysis, and by the infrared spectrum (Table).

When either the dilactone (II), or the monolactone (IV), was treated with alkali in concentrated solution, and acidified with cooling, a different product, m. p. 133°, crystallised from the solution. This gave a single carbonyl absorption; it reacted with two equivalents of alkali at room temperature, and analysis confirmed that it was the authentic diacid (III). On being heated with dilute acid, (III) was converted into the lactone-acid (IV).

The stereochemistry of these compounds was discussed by Auwers and Kauffmann.<sup>3</sup> From a study of models, structure (IV) was assigned to the ( $\pm$ )-series, and structure (I) to the *meso*-series. The dilactone (II) could only belong to the ( $\pm$ )-series; it was also related to compound (IV) in that, with phenylhydrazine, it yielded the same diphenylhydrazide as that obtained from (IV), and not that given by compound (I). These conclusions are now confirmed as follows: (a) The lactone acid (I) was resolved through its brucine salt. When this (–)-acid was converted into the disodium salt (IX), and then recovered after acidification, all optical activity was lost. Hence compounds (I) and (IX)

Infrared spectra (C=O region) and  $R_F$ s of 2,4-dihydroxy-2,4-dimethylglutaric acid derivatives. ( $R_F$ s of acetic and glutaric acids were 0.18, and 0.01, respectively.)

Compound	Carbonyl bands (cm. <sup>-1</sup> )	Assignment	$R_F$ of EtNH <sub>2</sub> salt
(I)	* 1770 1740	Lactone Acid	0.36 (0.07) §
(II)	† 1812	Lactone	—
(III)	* 1745	Acid	0.02
(IV)	* 1773vs 1730s	Lactone Acid	0.325 (0.05) §
(V)	* 1783 1727	Lactone Ester/acid	0.405
(VI)	† 1795 1740	Lactone Ester/acid	0.42
(VII)	‡ 1785 1750, 1740	Lactone Esters	—
(VIII)	† 1802vs 1785 infl. 1745s	Acid chloride Lactone Esters	—
(X)	* 1740 1710	Ester Acid	0.05
(XI)	† 1727vs	Ester/acid	0.525
(XII)	† 1740vs	Ester	—
(XIII)	† 1818m, 1780s 1748s	Anhydride Ester	—

\* In KCl disc. † In chloroform solution. ‡ As film. § Broad, weak spot; probably due to some diacid ethylamine salt.

belong to the *meso*-series. (b) The (—)-form of (IV), prepared in the same way, retained its optical activity when recovered from the disodium salt. Thus compounds (III) and (IV) belong to the (±)-series. (Resolutions were not necessarily complete, since it was sufficient to show the presence or loss of optical activity.)

From the above it is clear that an inversion takes place when the dilactone (II) is formed from the monolactone (I). That the rings of compound (II) are under greater strain than in an ordinary  $\gamma$ -lactone is apparent, both from models (in which the planes of the rings are seen to be approximately at right angles), and from the infrared spectrum, in which the carbonyl absorption is at a higher frequency than is normal for a  $\gamma$ -lactone (Table). In spite of this, there is no evidence that compound (II) can react by alkyl-oxygen fission, like a  $\beta$ -lactone. Thus, when the dilactone (II) was treated with aqueous sodium acetate, only compound (IV) was obtained, and no acetyl derivative (VI) (cf.  $\beta$ -propiolactone, which, with sodium acetate, gives  $\beta$ -acetoxypropionic acid).<sup>4</sup>

With acetyl chloride, (I) gave the monoacetyl derivative (VI). This, with thionyl chloride, gave the acetyl-lactone acid chloride (VIII), which reacted normally with methanol and triethylamine, forming the methyl ester (VII); this was also prepared from compound (VI) and diazomethane.

When the disodium salt (IX) was acetylated, *meso*-2,4-diacetoxy-2,4-dimethylglutaric acid (X) was obtained. This, when refluxed with thionyl chloride, gave mainly the anhydride (XIII). The latter, with methanol and triethylamine, formed the monomethyl ester (XI), which, with diazomethane, gave the dimethyl ester (XII), also prepared from the acid (X) and diazomethane.

## EXPERIMENTAL

Infrared spectra were recorded with a Perkin-Elmer model 137 instrument.

*Paper Chromatography of Acids.*—Descending chromatograms of ethylamine salts were made on Whatman No. 1 paper, butanol-ethylamine-water being used as solvent.<sup>5</sup> The dried papers were sprayed with Chlorophenol Red (0.2% in ethanol).

<sup>4</sup> Gresham, Jansen, and Shaver, *J. Amer. Chem. Soc.*, 1948, **70**, 1003.

<sup>5</sup> Manganeli and Brofazi, *Analyt. Chem.*, 1957, **29**, 1441.

*Acetylacetone Dicyanohydrin*.—Zelinsky's method<sup>1</sup> was modified as follows. To a well stirred solution of potassium cyanide (65 g.) in water (100 ml.) was added acetylacetone (51 ml.) with cooling to 0—5°. A mixture of hydrochloric acid (100 ml.) and water (50 ml.) was then slowly added, the temperature being kept below 10°. The product was collected, washed with ice-cold water, and dried at once *in vacuo* (38—50 g.; 50—76%). The yield was greatly reduced if the potassium cyanide was impure, if the reaction temperature was allowed to rise, or if the product was not collected immediately. When recrystallised from ethanol, the dicyanohydrin had m. p. 133° (decomp.) (lit.,<sup>1</sup> 134—136°); the crude material was adequate for hydrolysis (below).

*meso-2,4-Dihydroxy-2,4-dimethylglutaric Acid Monolactone (I)*.—Acetylacetone dicyanohydrin was hydrolysed<sup>1</sup> with about five times its weight of hydrochloric acid at 100° for 3 hr. The liquor was evaporated to dryness under reduced pressure. The residue was mixed with half its volume of Hyflo Supacel and extracted overnight with ether (Soxhlet). The extract was concentrated and cooled, and the almost pure acid lactone collected (73%), m. p. 190—192° (lit.,<sup>1</sup> 189—190°). More product, less pure, was obtained from the mother-liquor.

This compound, with one equivalent of brucine in ethanol, gave a *brucine salt* which, after two recrystallisations from methanol, formed blades, m. p. 215—216° (Found: C, 61.2; H, 7.0.  $C_7H_{10}O_5, C_{23}H_{28}N_2O_4, CH_3 \cdot OH$  requires C, 62.0; H, 6.7%).

The (–)-acid-lactone, recovered from this salt, had m. p. 189°,  $[\alpha]_D - 25.3^\circ$  (*c* 8.4 in ethanol). This was warmed with 6*N*-sodium hydroxide; the disodium salt had zero optical rotation (in 6*N*-sodium hydroxide). The acid lactone, m. p. and mixed m. p. 190.5°, recovered from this salt, also had zero rotation (*c* 4.9 in ethanol).

(±)-*2,4-Dihydroxy-2,4-dimethylglutaric Acid Dilactone (II)*.—The above monolactone (10 g.) was melted, and distilled fairly quickly over a soft flame. Slow distillation gave a lower yield. The oily crystals were sucked dry and washed well with water (yield 2.9 g., 32%), m. p. 101—102° (lit.,<sup>1</sup> 104—105°; Auwers and Kauffmann<sup>3</sup> give 102—103°).

(±)-*2,4-Dihydroxy-2,4-dimethylglutaric Acid Monolactone (IV)*.—The dilactone (1.8 g.) was treated with 3*N*-sodium hydroxide at 100° for 15 min., cooled, washed with ether, and acidified (HCl). The lactone acid was extracted with ether and had m. p. 101—105° (1.8 g., 88%). Four recrystallisations from anhydrous ether gave prisms, m. p. 110°, dropping to 102—104° after being dried for 2 days *in vacuo* over phosphorus pentoxide (Found: C, 48.2; H, 5.7. Calc. for  $C_7H_{10}O_5$ : C, 48.25; H, 5.75%).

The crude material, recrystallised twice from water, formed prisms, m. p. 102—104°, unaltered after being dried as above (Found: C, 43.8; H, 6.4. Calc. for  $C_7H_{10}O_5, H_2O$ : C, 43.75; H, 6.25%).

When the dilactone (0.3 g.) was heated with sodium acetate (1.3 g.) in water (1.5 ml.) at 90—95° for 15 min., and worked up as before, the same product (0.29 g.) was obtained, m. p. 102—104°.

Acetylation of this compound with acetyl chloride gave prisms, m. p. 153—154° (from ethyl acetate), of (±)-*4-acetoxy-2-hydroxy-2,4-dimethylglutaric acid lactone (V)* (Found: C, 50.4; H, 5.75.  $C_9H_{12}O_6$  requires C, 50.0; H, 5.55%).

(±)-*2,4-Dihydroxy-2,4-dimethylglutaric Acid (III)*.—A solution of the dilactone (II), or the acid lactone (IV), in a minimum of 3*N*-sodium hydroxide was heated for 15 min. at 100°, cooled, washed with ether and cooled in ice, and hydrochloric acid added dropwise until the solution was just acid. The crystals were collected at once, and washed with a little ice-cold water. The *diacid* formed needles, m. p. 133° (from ethanol) (Found: C, 43.5; H, 6.2.  $C_7H_{12}O_6$  requires C, 43.75; H, 6.25%).

On titration, this compound required two equivalents of 0.1*N*-sodium hydroxide for neutralisation at room temperature (to phenolphthalein).

When this acid was heated with dilute hydrochloric acid for a few min., and re-extracted with ether, the lactone acid (IV) was obtained, m. p. and mixed m. p. 102—104°.

The diacid, with one equivalent of brucine, gave a salt; after two recrystallisations from methanol (the first crops being collected), it formed blades, m. p. 136—137°. This salt was warmed with dilute hydrochloric acid, and the lactone acid (IV) was extracted with ether,  $[\alpha]_D - 5.1^\circ$  (*c* 2.6 in ethanol). This acid was heated with excess of 6*N*-sodium hydroxide, acidified, and recovered as above,  $[\alpha]_D - 5.6^\circ$  (*c* 0.93 in ethanol).

*4-Acetoxy-2-hydroxy-2,4-dimethylglutaric Acid Lactone (VI)*.—The monolactone acid (I; 15 g.) was refluxed for 3 hr. with acetyl chloride (30 ml.). The excess of reagent was removed *in vacuo*,

and the product recrystallised from ether–light petroleum (b. p. 40–60°) to give the *acetoxy-lactone acid* (15 g., 80%) as needles, m. p. 119° (Found: C, 49.6; H, 5.55.  $C_9H_{12}O_6$  requires C, 50.0; H, 5.55%).

This compound (5 g.) was refluxed with thionyl chloride (12 ml.) for 2 hr., excess of reagent was removed *in vacuo*, and the residue recrystallised from ether–light petroleum (b. p. 40–60°) to give the *acid chloride* (VIII) (4.2 g.; 77%) as leaflets, m. p. 48° (Found: C, 46.0; H, 4.8; Cl, 14.8.  $C_9H_{11}ClO_5$  requires C, 46.05; H, 4.7; Cl, 15.15%).

*Methyl 4-Acetoxy-2-hydroxy-2,4-dimethylglutarate Lactone* (VII).—(a) The acetoxy-lactone acid (VI) with excess of diazomethane in ether gave the *methyl ester* as a syrup, which was distilled *in vacuo*, b. p. 130°/0.1 mm.,  $n_D^{20}$  1.4490 (Found: C, 51.8; H, 6.1.  $C_{10}H_{14}O_6$  requires C, 52.2; H, 6.1%).

(b) The acid chloride (VIII) (0.5 g.) was added gradually to a mixture of methanol (1.5 ml.) and triethylamine (0.5 ml.). After being kept for 10 min. at room temperature, the mixture, in ether (20 ml.), was shaken in turn with dilute hydrochloric acid, sodium bicarbonate solution, and water, and then dried ( $Na_2SO_4$ ) and concentrated to give the methyl ester (0.35 g., 71%),  $n_D^{20}$  1.4490, identical (infrared spectrum) with that described above.

*meso-2,4-Diacetoxy-2,4-dimethylglutaric Acid* (X).—The lactone acid (I) (15 g.) was dissolved in 6*N*-sodium hydroxide (30 ml.) and the solution concentrated to dryness under reduced pressure. Benzene (20 ml.) was added and then removed *in vacuo*. The residue was suspended in pyridine (45 ml.), and acetyl chloride (40 ml.) was added in small lots with vigorous stirring and water cooling. The mixture was stirred for 15 min. at room temperature, diluted with water (60 ml.), kept a further 15 min., acidified (HCl), and extracted eight times with ether. The dried ( $MgSO_4$ ) extract was concentrated, and acetic acid distilled off *in vacuo*. The residue was washed with ice-cold ether and recrystallisation from ethyl acetate to give the *diacetoxy-diacid* (8.0 g., 43%) as leaflets, m. p. 176° (Found: C, 47.6; H, 5.8.  $C_{11}H_{16}O_8$  requires C, 47.8; H, 5.8%).

The ether washings and recrystallised mother-liquors were concentrated and the residue (about 5 g.) incorporated in the starting material for a further preparation. In this way, the overall yield was raised to about 57% from four batches.

*meso-2,4-Diacetoxy-2,4-dimethylglutaric Anhydride* (XIII).—The diacid (X) (10 g.) was refluxed with thionyl chloride (75 ml.) for 2 hr. Excess of reagent was removed under reduced pressure. Benzene was added, and removed under reduced pressure; this was repeated twice. The residue was recrystallised from ether–light petroleum (b. p. 40–60°) to give the *anhydride* (6.2 g., 66.5%) as needles, m. p. 90° (Found: C, 50.6; H, 5.4.  $C_{11}H_{14}O_7$  requires C, 51.2; H, 5.4%).

*Methyl Hydrogen 2,4-Diacetoxy-2,4-dimethylglutarate* (XI).—The anhydride (XIII) (4 g.) was added gradually to a mixture of methanol (20 ml.) and triethylamine (6 ml.). After the mixture had been refluxed for 30 min., the excess of amine and methanol were removed under reduced pressure. The residue was dissolved in ether, washed (dilute hydrochloric acid, then water), and shaken with sodium bicarbonate solution (carbon dioxide evolved). The aqueous layer was acidified, and extracted with ether to give the *monomethyl ester* (3 g., 67%) as microscopic leaflets, m. p. 151° (from ethyl acetate) (Found: C, 50.0; H, 6.2.  $C_{12}H_{18}O_8$  requires C, 49.6 H, 6.2%).

This ester, with diazomethane, gave *dimethyl 2,4-diacetoxy-2,4-dimethylglutarate* (XII), which formed prisms, m. p. 78° (from ether–light petroleum), identical with material prepared from the diacid (X) and diazomethane (Found: C, 51.5; H, 6.9.  $C_{13}H_{20}O_8$  requires C, 51.3; H, 6.6%).

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