

283. 4-Hydroxycyclohexane-1-carboxylic Acid.

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The form of 4-hydroxycyclohexane-1-carboxylic acid hitherto assigned the *trans*-configuration is shown to contain both the *cis*- and the *trans*-isomer. The authentic *trans*-acid has been prepared, and also the previously unknown *cis*-4-acetoxycyclohexanecarboxylic acid.

4-HYDROXYCYCLOHEXANE-1-CARBOXYLIC ACID (I) was first prepared, by reduction of 4-ketocyclohexane-1-carboxylic acid with sodium amalgam, by W. H. Perkin, jun. (*J.*, 1904, **85**, 416), who described it as a solid of melting point 120—121°. Since distillation yielded a product which was completely soluble in sodium carbonate solution, this material was assumed to have

the *trans*-configuration. The same acid has been made more recently by Hardegger, Plattner, and Blank (*Helv. Chim. Acta*, 1944, **27**, 793), using essentially the same method; they record m. p. 119—120° and also assume that the product has the *trans*-configuration.

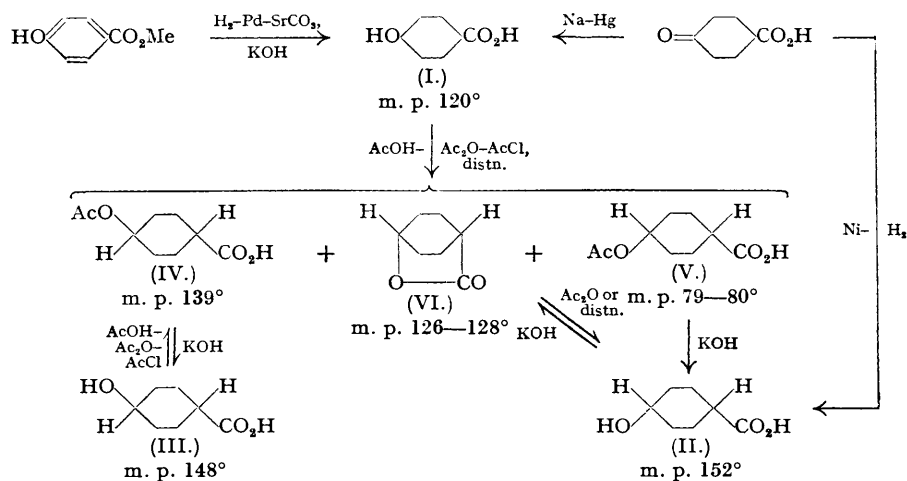
Martin and Robinson (*J.*, 1943, 497), who prepared 4-hydroxycyclohexane-1-carboxylic acid by hydrolysis of the ester obtained by hydrogenation of ethyl *p*-hydroxybenzoate, state that the pure *trans*-acid melts at 121°. This method was also used, with slight modification, by Hardegger, Heusser, and Blank (*Helv. Chim. Acta*, 1946, **29**, 477), who did not record the melting point of their product.

Balaš and Šrol (*Coll. Trav. Chim. Czech.*, 1929, **1**, 658), by hydrogenation of *p*-hydroxybenzoic acid, obtained an acid melting at 152°, which readily lactonised on distillation and was accordingly assumed to be the *cis*-isomer (II). They also obtained a small quantity of the acid melting at 119—120°. This work has been repeated by Owen and Robins (*J.*, 1949, 326), who also obtained, as a principal product, the acid of m. p. 152°.

On repeating the work of Hardegger, Plattner, and Blank (*loc. cit.*) we obtained the acid (I), m. p. 119—120°, which gave a 44% yield of the acetoxy-acid (IV), m. p. 139°. Hardegger *et al.* (*loc. cit.*) had obtained this acid in 50% yield, with the same melting point.

The aqueous mother-liquors from the recrystallisation of the acetoxy-acid were saturated with ammonium sulphate and the separated oil distilled. The product, which was equivalent to a yield of 42% of acetoxy-acid, deposited a small quantity of crystalline material, which, after exhaustive recrystallisation from chloroform and from ethyl acetate, melted at 148°. The acid value and ultimate analysis indicated that this was a hydroxycyclohexanecarboxylic acid, which was initially assumed to be identical with the *cis*-acid described by Balaš and Šrol (*loc. cit.*). However, when it was acetylated, the product proved to be, not the expected lactone, but an acid which melted at 139° and did not depress the melting point of the acetoxy-acid (IV). Hydrolysis of (IV) gave a hydroxy-acid which showed no depression of melting point on admixture with the new hydroxy-acid (m. p. 148°). A 50% mixture of the new hydroxy-acid with an authentic specimen of the known *cis*-acid (Hardegger *et al.*, *loc. cit.*) melted over the range 119—134°, but, after resolidifying, the mixture melted at 118—120° and after recrystallisation from ethyl acetate still melted at 120°, not depressing the melting point of the hydroxy-acid (I) hitherto regarded as the *trans*-isomer. It was then found that mixtures of the new hydroxy-acid with 40—60% of the authentic *cis*-acid melt within the range 118—121°.

The new hydroxy-acid distilled virtually unchanged at atmospheric pressure, no lactone being formed. Under these conditions, the *cis*-acid readily lactonises (Balaš and Šrol, *loc. cit.*). On distillation the hydroxy-acid (I) gave a first fraction containing mostly the lactone (VI) derived from the *cis*-acid (II), and a later, acidic fraction which was largely unsaturated but from which it was possible to isolate a small quantity of the new hydroxy-acid, m. p. 148°. That the small yield of the new hydroxy-acid may have been caused by dehydration under the conditions of rather prolonged heating was indicated by the preparation, from the unsaturated fraction, of a dibromo-acid melting at 84°, which was evidently 3:4-dibromocyclohexanecarboxylic acid (cf. Perkin, *J.*, 1904, **85**, 433).



It is evident that the hydroxy-acid of m. p. 148° is the authentic *trans*-4-hydroxycyclohexane-1-carboxylic acid (III) and that the previously accepted *trans*-acid (I), m. p. 120°, contains both isomers, probably in equal proportions. The latter conclusion is confirmed by the fact that the hydroxy-acid (I) gives no more than 50% of pure acetoxy-acid. We have repeated the work of Hardegger, Heusser, and Blank (*loc. cit.*), who claimed a 75% yield of acetoxy-acid, of unstated m. p., from a specimen of hydroxy-acid, presumably (I); we obtained a 79% yield of crude crystalline material (m. p. 102—118°), but no more than 40% of the pure acetoxy-acid (IV).

Further treatment of the oil, from which the new *trans*-hydroxy-acid had been separated, yielded a small quantity of a lactone (VI), m. p. 127—128° (cf. Hardegger, Plattner, and Blank, *loc. cit.*), together with an acetoxy-cyclohexanecarboxylic acid of m. p. 79—80°. Hydrolysis of both the lactone and the new acetoxy-acid yielded the *cis*-hydroxy-acid (II) (mixed m. p.). Accordingly, the new acetoxy-acid must be the hitherto unknown *cis*-4-acetoxy-acid (V).

These results throw light on observations by Owen and Robins (*loc. cit.*). These authors assumed the *trans*-configuration for the hydroxy-acid (I), melting at 120°, and have shown that the solid product obtained by Perkin (*loc. cit.*) by distillation of that acid was the lactone (VI), which may also be obtained from the pure *cis*-acid; they supposed this to be evidence of inversion under the conditions of experiment. Furthermore, they report that on Bouveault-Blanc reduction of the ethyl ester of the supposed *trans*-hydroxy-acid (I) a mixture of stereoisomeric glycols was obtained, partial inversion being again invoked. Our results make these assumptions no longer necessary, since Owen and Robins's starting material contained both isomers.

Balaš and Šrol (*loc. cit.*) found the melting point of the lactone obtained by distillation of the pure *cis*-hydroxy-acid (II) to be 109—110° and Owen and Robins (*loc. cit.*) found that of the lactone obtained similarly from the supposed *trans*-hydroxy-acid (I) to be between 108° and 112°, with no alteration on recrystallisation from ether. Hardegger, Plattner, and Blank (*loc. cit.*), however, found the lactone prepared by dehydration of the *cis*-hydroxy-acid (II) under acetylating conditions to melt at 128°. Specimens of the lactone have been obtained by us by all of the above methods, as well as by treating the hydroxy-acid (I) with a mixture of acetic acid, acetic anhydride, and acetyl chloride. In a Thiele tube they all melted between 126° and 128° and exhibited no mutual depression of the melting point. However, further investigation showed that, on very much slower heating, melting occurred over the range 123—128° and alterations in appearance were observed during the cooling of the melts. Since these phenomena persisted after repeated recrystallisation from different solvents and after sublimation, the presence of polymorphic forms was suspected. Dilatometry indicated changes between 83° and 87° and between 126° and 129°. Thermal analysis showed that the lower transition temperature was 84—85°, corresponding, apparently, to a change in crystal structure. The higher transition, the melting-point, was 127—129°. No evidence was obtained for any change between 108° and 112°, in purified specimens of the lactone (VI).

EXPERIMENTAL.

4-Hydroxycyclohexane-1-carboxylic Acid (I) (m. p. 120°).—This was prepared from 4-ketocyclohexane-1-carboxylic acid by reduction with sodium amalgam (Hardegger, Plattner, and Blank, *loc. cit.*) and by hydrolysis of the product obtained by hydrogenation of methyl *p*-hydroxybenzoate at 150°/130 atm. using palladium on strontium carbonate (Robinson *et al.*, *loc. cit.*, and Hardegger, Heusser, and Blank, *loc. cit.*). The products appeared to be identical.

trans-4-Acetoxy-cyclohexanecarboxylic Acid (IV).—4-Hydroxycyclohexane-1-carboxylic acid (I) (60 g.) was refluxed for 4 hours with acetic acid (460 ml.), acetic anhydride (46 ml.), and acetyl chloride (4.6 ml.). Excess of the reagents was distilled off under reduced pressure and the residual oil recrystallised several times from water, yielding the required acetoxy-acid (34 g.), m. p. 139° (Hardegger, Plattner, and Blank, *loc. cit.*) (Found: C, 58.3; H, 7.6. Calc. for $C_8H_{14}O_4$: C, 58.05; H, 7.6%).

trans-4-Hydroxycyclohexane-1-carboxylic Acid (III).—(a) The aqueous mother-liquors from the preparation of the above acetoxy-acid were saturated with ammonium sulphate and extracted with ether. The oil remaining after evaporation of the ether was distilled, a fraction being collected boiling at 146—152°/0.4 mm. (32 g.). The distillate deposited a small amount of crystalline material, which was collected and washed with carbon tetrachloride. The crude product (2.3 g.) had m. p. 131°, raised to 148° by three recrystallisations from chloroform and one from ethyl acetate (Found: C, 58.0; H, 8.3; acid value, 396. $C_7H_{12}O_3$ requires C, 58.3; H, 8.4%; acid value, 390). The mixed m. p. with *cis*-4-hydroxycyclohexane-1-carboxylic acid (II) (m. p. 152°) (Balaš and Šrol, *loc. cit.*) was 119—134°.

(b) The acetoxy-acid (IV) (0.5 g.) was hydrolysed by being kept overnight with 20% potassium hydroxide solution (10 ml.). The mixture was then acidified (Congo-red) with dilute sulphuric acid and extracted with ethyl acetate. The extract was dried ($MgSO_4$) and evaporated, yielding crystals (0.3 g.) which on recrystallisation from ethyl acetate had m. p. 149°, not depressed on admixture with the hydroxy-acid (III) obtained as described under (a).

Reacylation of the Hydroxy-acid (III).—Under the conditions described above this gave an almost quantitative yield of the acetoxy-acid (IV), m. p. 139° after one recrystallisation from ethyl acetate–light petroleum (b. p. 60–80°).

Distillation of the Hydroxy-acid (III).—When distilled, (III) (20 mg.) gave an oil which completely solidified and had m. p. 139°. Recrystallisation from ethyl acetate raised the m. p. to 147°, unchanged on admixture with the original hydroxy-acid (III).

cis-4-Acetoxy-cyclohexanecarboxylic Acid (V).—The oil remaining after separation of the hydroxy-acid (III) in the preparation (a) above failed to crystallise and was hydrolysed by heating on the water-bath with 10% potassium hydroxide solution for 2 hours. The crude acid (26 g.; m. p. 112°) extracted from the acidified solution was reacylated under the same conditions as before and the product distilled. The distillate (24 g.; m. p. 60–90°) was dissolved in ether and extracted with potassium hydrogen carbonate solution. The ethereal solution (A) was reserved for further treatment and the aqueous extract acidified. Next morning a small quantity of crystalline material had been deposited, having m. p. 50–60°, raised to 139° after three recrystallisations from water. This gave no depression of the m. p. of the *trans*-acetoxy-acid (IV). The aqueous mother-liquors were extracted with ether, and the sticky product so obtained was crystallised from water. The m. p. (53°) of this crude product was unaffected by further crystallisation from water, but separation was effected by fractional crystallisation from cyclohexane. By recrystallisation from ethyl acetate–light petroleum (b. p. 40–60°) the tail fraction yielded *cis-4-acetoxy-cyclohexanecarboxylic acid*, m. p. 79–80° (Found: C, 58.1; H, 7.4. $C_9H_{14}O_4$ requires: C, 58.05; H, 7.6%).

Methyl cis-4-acetoxy-cyclohexanecarboxylate, prepared by diazomethane, had b. p. 83°/0.7 mm., n_D^{20} 1.4539 (Found: C, 59.7; H, 8.0. $C_{10}H_{16}O_4$ requires C, 60.0; H, 8.0%).

cis-4-Hydroxycyclohexane-1-carboxylic Acid Lactone (VI).—The ethereal solution (A) of the neutral products above was evaporated, yielding a syrup which crystallised on storage. The crystals melted at 117–126°, raised to 126–128° on recrystallisation from light petroleum (b. p. 40–60°). This substance caused no depression of the m. p. of the lactone prepared from *cis-4-hydroxycyclohexane-1-carboxylic acid* (II) (Balaš and Šrol, and Hardegger *et al.*, *loc. cit.*) (Found: C, 66.9; H, 8.0. Calc. for $C_7H_{10}O_2$: C, 66.7; H, 8.0%). Thermal and dilatometric analyses of the lactone were carried out by standard methods. The lactone used was recrystallised once from ether and twice from light petroleum (b. p. 40–60°), and finally sublimed in a high vacuum. When slowly heated the substance shrank and sintered at 123°, and then rapidly melted at 126.5° and cleared at 128°. On cooling, crystallisation commenced sharply at 126.5° and the appearance of the crystal mass changed at 71.5°. Owing to the solubility of the lactone in most organic liquids, near to its melting point, mercury was used, in a dilatometer having an upturned bulb.

cis-4-Hydroxycyclohexane-1-carboxylic Acid (II).—(a) 4-Ketocyclohexane-1-carboxylic acid was reduced in sodium hydroxide solution by shaking it with hydrogen in the presence of Raney nickel (Hardegger, Plattner, and Blank, *loc. cit.*). The purified product, as reported, had m. p. 152° and on distillation (Balaš and Šrol, *loc. cit.*) or on heating with acetic anhydride (Hardegger *et al.*), yielded identical lactones, m. p. 126–128°. This acid was assumed to be the authentic *cis-4-hydroxycyclohexane-1-carboxylic acid*.

(b) *cis-4-Acetoxy-cyclohexanecarboxylic acid* (V) (0.5 g.) was hydrolysed by being kept for 16 hours at room temperature with 20% potassium hydroxide solution (10 ml.). The mixture was extracted once with ether (rejected) and acidified with dilute sulphuric acid (Congo-red). Extraction with ethyl acetate yielded on evaporation an acid, m. p. 144–150°, raised to 152° after two recrystallisations from ethyl acetate (Found: C, 58.8; H, 8.3. Calc. for $C_7H_{10}O_3$: C, 58.3; H, 8.4%). The m. p. was unchanged on admixture of the substance with the authentic *cis*-hydroxy-acid, prepared as described under (a).

(c) The lactone (VI), hydrolysed under the same conditions as above, yielded *cis-4-hydroxycyclohexane-1-carboxylic acid* (II), m. p. 152°.

Distillation of 4-Hydroxycyclohexane-1-carboxylic Acid (I).—Distillation of this acid at atmospheric pressure yielded a fraction, b. p. 260°, which solidified, and a second, oily fraction boiling between 290° and 350°. The total distillate was dissolved in ether, and the acidic substances were extracted with 10% potassium hydrogen carbonate solution. Evaporation of the ethereal solution yielded *cis-4-hydroxycyclohexane-1-carboxylic acid* lactone (0.76 g.), m. p. 100–110°, raised to 126–128° on recrystallisation from light petroleum (b. p. 40–60°) and from ether. The aqueous extract, after acidification with dilute sulphuric acid, was extracted twice with ether and thrice with ethyl acetate. The former extract, on evaporation, yielded an oil (0.74 g.), which decolorised a solution of bromine in carbon tetrachloride. The ethyl acetate extract gave a small yield of crude *trans-4-hydroxycyclohexane-1-carboxylic acid* (0.13 g.), m. p. 140–144°, raised to 147° on recrystallisation from ethyl acetate. A dibromo-acid, prepared from the unsaturated fraction in carbon tetrachloride, melted at 84° (Perkin, *loc. cit.*, gives m. p. 86° for 3:4-dibromocyclohexanecarboxylic acid).

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