413. *Configuration of the* cyclo*Hexan-2-ol-1-carboxylic Acids and their Derivatives.*

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The configuration of the two *cyclo*hexan-2-ol-1-carboxylic acids has been established (*cis*, m. p. 80—81°; *trans*, m. p. 111°) by chemical reactions and physical properties, and various known and new derivatives have been stereochemically related to the acids. Differences in reactivity have been observed for each pair of isomerides, the *cis*-forms being always the more reactive. In almost all such instances the *cis*-compound can form an intramolecular hydrogen bridge.

A *cyclo*HEXAN-2-OL-1-CARBOXYLIC ACID, m. p. 111°, was obtained simultaneously by Einhorn and Meyerberg (*Ber.*, 1894, **27**, 2472), who treated 2-amino*cyclo*hexane-1-carboxylic acid with nitrous acid, and by Dieckmann (*ibid.*, p. 2476), who reduced ethyl *cyclo*hexan-2-one-1-carboxylate with sodium amalgam, and later by Gardner, Perkin, and Watson (*J.*, 1910, **97**, 1764), who reduced *cyclo*hexan-2-one-1-carboxylic acid also with sodium amalgam. Still later, catalytic hydrogenation of salicylic acid and its esters was repeatedly used (Houben and Pfau, *Ber.*, 1916, **49**, 2295; Díaz Aguirreche, *Anal. Fís. Quím.*, 1927, **25**, 313; I.G. Farbenind. A.-G., B.P. 286,201; Connor and Adkins, *J. Amer. Chem. Soc.*, 1932, **54**, 4678; Edson, *J. Soc. Chem. Ind.*, 1934, **53**, 138T; Packendorff, *Ber.*, 1935, **66**, 1251; Mitsui, *Mem. Coll. Sci. Kyoto Imp. Univ.*, 1935, *A*, 329) to prepare the corresponding hexahydro-derivatives, but was often complicated by hydrogenolysis of the hydroxyl and even of the carboxyl group.

Special mention should be made of the work of Balaš and Šrol (*Coll. Trav. chim. Czech.*, 1929, **1**, 658), who hydrogenated *o*-, *m*-, and *p*-hydroxybenzoic acid in presence of platinum black, obtaining the hexahydro-derivatives in two geometrically isomeric forms in each case. Salicylic acid yielded the *cyclo*hexan-2-ol-1-carboxylic acid, m. p. 111°, mentioned above, and a small proportion of an isomeride, m. p. 70—71°. Boeseken and his collaborators (*Rec. Trav. chim.*, 1933, **52**, 881) obtained the second isomeride in a still less pure form (m. p. 57—63°). Then Marshall, Kuck, and Elderfield (*J. Org. Chem.*, 1942, **7**, 454) isolated the second acid as the main product of high-pressure hydrogenation and subsequent hydrolysis of methyl salicylate, and gave its melting point as 76—78°. The same product resulted predominantly when ethyl *cyclo*hexan-2-one-1-carboxylate was hydrogenated in presence of platinum oxide and then hydrolysed (Pascual and Sistaré, *Anal. Fís. Quím.*, 1946, **42**, 667), and we now find its melting point to be somewhat higher (80—81°) than that given by the American authors.

Balaš and Šrol believed that the 111° acid was the *cis*-form, as for *cyclo*hexan-3- and -4-ol-1-carboxylic acid the *cis*- were the higher-melting forms. On the other hand, Boeseken *et al.* (*loc. cit.*) ascribed the *cis*-configuration to the lower-melting isomeride, as it alone increased the conductivity of boric acid.

We believe that the 81° acid is the *cis*-, and the 111° acid is the *trans*-form, for the following reasons.

(1) Reduction of ethyl *cyclo*hexan-2-one-1-carboxylate in a neutral medium (with sodium amalgam; Dieckmann) yields mostly the 111° acid, whereas reduction with platinum oxide gives almost wholly the ethyl ester of the 81° acid. The general rule, similar to Skita's, connecting these conditions with configuration has been repeatedly stated by Vavon and Godchot (cf. Godchot, *Bull. Soc. chim.*, 1934, [v], **1**, 1186). That reduction of ethyl *cyclo*hexan-2-one-1-carboxylate in presence of platinum oxide yields almost exclusively the ester of the 81° acid follows because hydrolysis of the product gives the latter acid directly in spite of its higher solubility.

(2) The same conclusion is reached by comparing the viscosities of the ethyl esters; Pascual and Sistaré (*loc. cit.*) obtained for those viscosities a ratio similar to that which has now been found for the methyl esters. The physical constants of the two pure methyl esters, which we prepared from the pure acids by diazomethane, support these configurations. In accordance with von Auwers and Skita's rule, the methyl ester of the 81° acid has the higher density, higher refractive index, and lower molecular refractivity. The relative viscosities are still more decisive. According to Thole (cf. Gough, Huntress, and Kenyon, *J.*, 1926, 2052), when groups in the 1 : 2-positions have a large residual affinity for each other, proximity of the groups can cause intramolecular neutralisation of affinities (in the present case probably with formation of a hydrogen bridge between the carbonyl oxygen of the acid group and the hydrogen of the hydroxyl group), so that the *cis*-compound, being less associated, has the lower viscosity; for the methyl esters now under consideration the viscosity of the 81° derivative is approximately

half of that of the 111° derivative. The boiling points of the methyl esters also accord with the configurations assigned; according to Hunter (*Ann. Reports*, 1946, **43**, 144), " in the case of isomeric compounds, that isomer which can achieve intramolecular hydrogen-bond structure is markedly more volatile than that which cannot."

Besides some liquid esters, which are probably mixtures of isomerides, the following derivatives of the *cyclo*hexan-2-ol-1-carboxylic acids are recorded (*cis* and *trans* refer to the 81° and 111° acid, respectively).

Derivatives of known configuration : ethyl *cis*-2-nitrobenzoyloxy*cyclo*hexane-1-carboxylate, m. p. 71—72° (Pascual and Sistaré, *loc. cit.*) ; ethyl *trans*-*cyclo*hexan-2-ol-1-carboxylate (obtained from the *trans*-acid by alcohol and sulphuric acid), b. p. 120—121°/30 mm. (Einhorn and Meyerberg, *loc. cit.*), 130—132°/25 mm. (Pascual and Sistaré).

Derivatives of unknown configuration : an amide, m. p. 113·7—114·7° (Marshall *et al.*, *loc. cit.*) ; two acetyl derivatives, m. p. 96—101° (Eason and Pyman, *J. Soc. Chem. Ind.*, 1933, **52**, 97T) and 66·1—66·7° (Marshall *et al.*), respectively; two *p*-toluidide acetates, m. p. 154·5—155·9° and 124—143°, respectively (Marshall *et al.*).

Our work has established the configuration of some of these compounds and added a few more, as shown in the following table :

	Melting points.	
	cis.	*trans.*
(i) *cyclo*Hexan-2-ol-1-carboxylic acid	81°	111°
(ii) 2-Acetoxy-acid, from (i)	65·5—66·5 *	104·5—105·3 *
(iii) 2-Acetoxy-*p*-toluidide, from (ii)	155—156 *	154·5—155·5 *
(iv) p-*Toluidide* of (i), from (i), (iii), or (v)...	190·6—191·4 *	178·3—178·9 *
(v) *Methyl* ester, from (i)	(b. p. 105°/14 mm.)	(b. p. 115°/14 mm.)
(vi) Amide of (i), from (v)	113—115	—

* Corr.

The relations of these substances to those described in the literature will be apparent.

The differing reactivity of the hydroxyl and carboxyl groups, observed in several of the pairs of compounds under consideration, must be related to the configuration. Thus, the *cis*-acid gives the acetyl derivative when boiled with acetyl chloride in ether, whereas the *trans*-form requires the presence of pyridine; similarly, Pascual and Sistaré (*loc. cit.*) obtained a *p*-nitrobenzoyl derivative of the *cis*- but not of the *trans*-ethyl ester. In reactions affecting the carboxyl and carbomethoxy-group, when the hydroxyl group is free, the *cis*-derivative is also the more reactive : the *cis*-acid and its methyl ester yield a *p*-toluidide when boiled with *p*-toluidine, whereas the *trans*-compounds react with difficulty; the *trans*-amide could not be obtained from the ester; and hydrolysis of the acetylated *p*-toluidide is much easier in the *cis*- than in the *trans*-series.

These differing reactivities are caused by the ability of the *cis*-forms to form internal hydrogen bridges. Intermolecular association of the *trans*-forms is shown in, *e.g.*, the higher viscosity of its methyl ester. Further work is in hand to decide whether the differences, *e.g.*, in the formation of amides, persist when the hydroxyl groups are methylated.

EXPERIMENTAL.

Ethyl cyclo*Hexan-2-one-1-carboxylate.*—This was prepared by the method of *Org. Synth.*, Coll. Vol. II, 531, or of Pascual and Sistaré (*loc. cit.*). .

Hydrogenation of Ethyl cyclo*Hexan-2-one-1-carboxylate. Preparation of* cis- *and* trans-cyclo*Hexan-2-ol-1-carboxylic Acid.*—An apparatus similar to that described by Adams and Voorhees (*Org. Synth.*, Coll. Vol. I, 2nd. Edn., p. 61) was used. Ethyl *cyclo*hexanonecarboxylate (150 g.) was hydrogenated in its own volume of absolute alcohol containing platinic oxide (2·2 g.) at room temperature and 5 atmospheres; after 20 hours' stirring the pressure had dropped to 2 atmospheres and then remained constant. After filtration and removal of the solvent, the product was distilled through a Vigreux column, to give methyl *cyclo*hexanolcarboxylate (120 g.), b. p. 117—118°/17 mm. This ester was mixed with hot 25% sodium hydroxide solution (400 ml.), stirred while cooling, and set aside at room temperature; next day, the sodium salt (120 g.) which had separated was filtered off, washed with a little alcohol, and dried. This salt was dissolved in the smallest possible amount of water and decomposed by 10% hydrochloric acid, and the solution saturated with amonium sulphate and extracted with ether. The ethereal layer was dried and, on evaporation in a vacuum, gave the acid (80 g.), m. p. 78°, which after crystallisation from ether had m. p. 80—81° (corr.).

The *cis*-acid remaining in solution, probably with some of the *trans*-form, was recovered as the latter after boiling it with alkali which set up an equilibrium (see below).

The mother-liquors from the sodium salt were mixed with the alcoholic washings, the alcohol was removed, more alkali added, and the whole boiled for 30 hours. The cold solution was made acid to Congo-red, saturated with ammonium sulphate, and extracted with ether. The ethereal solution was dried and the solvent distilled off, giving 10 g. of an acid, m. p. 106—110°.

The total yield of the two acids was 90%, the ratio of *cis*- and *trans*-forms being 8 : 1.

Transformation of the cis- *into the* trans-*Acid by boiling it in Alkaline Solution.*—The acid, m. p. 78° (15 g.), was heated under reflux in 7·5N-potassium hydroxide (150 ml.) for *ca.* 35 hours. The cold liquid was made acid to Congo-red, saturated with ammonium sulphate, and extracted with ether. 9·8 G. of an acid, m. p. 102°, were obtained which, when recrystallised from ethyl acetate, had m. p. 110—111°.

Methyl cis-cyclo*Hexan-2-ol-1-carboxylate.*—The *cis*-acid (10 g., 0·069 mol.) in absolute ether (*ca.* 55 ml.) was treated in the cold with a 2·95% solution (100 ml., 0·07 mol.) of diazomethane in ether. The resulting solution was treated as usual, and the extract was distilled in a vacuum, to give the *methyl* ester, b. p. 105°/14 mm., d_{25}^{25} 1·0989, n_D^{25} 1·4645, η^{25} 9·50 (yield, almost quantitative) (Found : C, 61·1; H, 8·7. $C_8H_{14}O_3$ requires C, 60·8; H, 8·9%).

cis-cyclo*Hexan-2-ol-1-carboxyamide.*—An alcoholic solution of the methyl ester, saturated with dry ammonia, was heated in a sealed tube at 100° for 12 hours, the alcohol distilled off, and the residue treated with absolute ether. In a short while, the amide crystallised; m. p. 113—115°.

cis-cyclo*Hexan-2-ol-1-carboxy*-p-*toluidide.*—(a) *From the acid.* 1 G. of acid was heated under reflux with 2 g. of *p*-toluidine at 150° for 2 hours; the resulting product, when cold, was treated with an excess of 25% sulphuric acid, and the residue filtered off, washed several times with a little water, and dried. The p-*toluidide* (1 g.), recrystallised twice from methanol, melted at 190·6—191·4° (corr.).

(b) *From the methyl ester.* The methyl ester (1 g.) and *p*-toluidine (2 g.) were heated for approx. 3 hours at 150°. The product, when cold, was treated as above, the same *p*-toluidide being obtained (Found : N, 6·2. $C_{14}H_{19}O_2N$ requires N, 6·0%).

cis-2-*Acetoxy*cyclo*hexanecarboxylic Acid.*—A procedure similar to that of Marshall *et al.* (*loc. cit.*) was used. The acid, m. p. 80° (1 g.), ether (25 ml.), and acetyl chloride (10 g.) were heated under reflux for 4 hours. The ether and excess of acetyl chloride were removed by distillation, first at atmospheric pressure and then in a vacuum, giving an oil which did not crystallise. When distilled at 175—180°/15 mm., it crystallised in a few hours. The product was recrystallised from ether–light petroleum, forming prisms, m. p. 65·5—66·5° (corr.).

cis-2-*Acetoxy*cyclo*hexane-1-carboxy*-p-*toluidide.*—The above acetyl derivative (0·5 g.) was heated under reflux with thionyl chloride (2—3 ml.) for 1 hour. The excess of chloride was then distilled off, finally in a vacuum. The residue was dissolved in a little absolute ether and poured on a solution of *p*-toluidine (1 g.) in ether (a few ml.), with cooling, and set aside for a few hours. The ethereal solution was shaken twice with 2N-sulphuric acid, twice with water, and then dried. Removal of the solvent gave a crystalline residue which, recrystallised from ether–light petroleum, had m. p. 155—156° (corr.).

This *p*-toluidide acetate (0·1 g.) was kept for a few hours in 0·5N-methanolic potassium hydroxide (5 ml.). The insoluble material was then filtered off, washed several times with water, and dried. It was identified as *cis-cyclo*hexan-2-ol-1-carboxy-*p*-toluidide by its m. p. (190—191·5°) and mixed m. p.

Methyl trans-cyclo*Hexan-2-ol-1-carboxylate.*—This *ester*, prepared from the *trans*-acid by the method used for the *cis*-isomeride, had b.p. 115°/14 mm., m.p. 35—36° (corr.), d_{25}^{25} (supercooled) 1·0899, n_D^{25} 1·4640, η^{25} 18·5 (Found : C, 60·8; H, 8·6. $C_8H_{14}O_3$ requires C, 60·8; H, 8·9%).

trans-cyclo*Hexan-2-ol-1-carboxy*-p-*toluidide.*—(a) *From the acid.* Prepared in the same way as was its *cis*-isomeride, but with heating at 160° for 3 hours, the p-*toluidide*, m. p. 173—174°, was obtained in poor yield.

(b) *From the methyl ester.* The procedure used for the *cis*-isomeride, but with heating for about 6 hours at 180—200°, gave a very dark product (0·7 g. from 1·4 g.), m. p. 166—167°, which after repeated crystallisation from methyl alcohol formed fine needles, m. p. 178·3—178·9° (Found : N, 6·1. $C_{18}H_{19}O_2N$ requires N, 6·0%).

trans-2-*Acetoxy*cyclo*hexane-1-carboxylic Acid.*—To 5 g. of acid, m. p. 111°, dissolved in 50 g. of pure pyridine, were added 15 g. of acetyl chloride, with stirring and efficient cooling. After 5 hours the mixture was treated, while cooling, with 30% sulphuric acid until acid to Congo-red, and extracted several times with ether. The ethereal extract was washed twice with cold water, dried, and distilled, first at atmospheric pressure and finally in a vacuum. The resulting oil crystallised on addition of a little ether and light petroleum, and when recrystallised from ether–light petroleum yielded prisms, m. p. 104·5—105·5° (corr.) (4·8 g.).

trans-2-*Acetoxy*cyclo*hexane-1-carboxy*-p-*toluidide.*—5 G. of the above acetyl derivative, dissolved in 30 ml. of benzene, were mixed with thionyl chloride, and the whole heated on a steam-bath for *ca.* 1 hour. The solvent and the thionyl chloride were removed by distillation, first at ordinary pressure and then in a vacuum. The residue was dissolved in ether (*ca.* 15 ml.), and *p*-toluidine (10 g.) in ether (*ca.* 50 ml.) was added with cooling. The mixture was set aside for a few hours, and the ethereal solution then treated with 10% hydrochloric acid and twice with water (if necessary, more ether was added, as the product is sparingly soluble in that solvent), decolorised with a little carbon black, filtered, and dried. The crystalline p-*toluidide* (*ca.* 4 g.) obtained on removal of the solvent was recrystallised several times from absolute methyl alcohol and then had m. p. 154·5—155·5° (corr.) (mixed m. p. with the *cis*-form, 124—145°) (Found : N, 5·3. $C_{16}H_{21}O_3N$ requires N, 5·1%).

The above compound (1·9 g.) was added to 5N-methanolic potassium hydroxide (50 ml.) and set aside overnight. The mixture was then diluted with the same volume of water, and the resulting precipitate filtered off, repeatedly washed with water, and recrystallised from absolute methyl alcohol. The product was shown by its m. p. and mixed m. p. to be *trans-cyclo*hexan-2-ol-1-carboxy-*p*-toluidide.

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