Tetrahedron Vol. 29, pp 683 to 690 Pergamon Press 1973 Printed in Great Britain

CONFORMATIONAL EFFECTS IN THE HYDROGENATION OF HEMIMELLITIC AND CYCLOHEX-1-ENE-1,2,3-TRICARBOXYLIC ACIDS*

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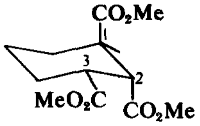
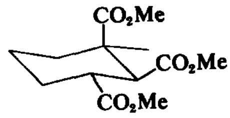
(*Received in the UK* 12 *September* 1972; *Accepted for publication* 1 *November* 1972)

Abstract—The three possible isomers of cyclohexane-1,2,3-tricarboxylic acid were synthesised and separated in order to study the regiospecificity and stereoselectivity of the α-C alkylation of their trimethyl esters. No definitive conclusions could be reached on this aspect for reasons which became apparent in the course of the work. However, the three independent methods adopted for the synthesis of the isomeric tricarboxylic acids have given dramatically different isomer compositions. The reasons are explored in this paper.

We have previously demonstrated[1] that the methylation of two of the isomers of trimethyl 1-methylcyclohexane-1,2,3-tricarboxylate, (**1a** and **1b**), having the conformations shown predominant, is highly stereoselective and regiospecific at C_3. While the stereoselectivity could be attributed to certain conformational effects operative in these highly substituted systems[2] the reason for the regiospecificity was less clear. The nonformation of the C_2-methylation products in these cases was originally attributed[1] to the inhibition of anion formation at that centre by the electron release effect of the C_1-Me, analogy for such an effect being available.[1] However, it was possible that assumption of coplanarity by the relevant atoms necessary for the continuous interaction of the CO π-orbital with the p-orbital of the incipient carbanion during the removal of the C_2-proton would give rise to severe $A^{1,3}$ interaction[3] between lone-pairs of the O atoms and the carbons of the flanking equatorial substituents (Fig 1), thus inhibiting the formation of the C_2-anion. It seemed therefore that a study of the anion formation in the case of the isomers of trimethyl cyclohexane-1,2,3-tricarboxylate (**2a**), a system in which the possible role of the electron-release effect of the Me group at C_1 has been eliminated while retaining the possibility of generating $A^{1,3}$ interaction on C_2-anion formation, would be of interest. The preparation and the separation of the stereoisomeric acids (**2A**, **B** and **Ca**) have not been reported. We attempted obtaining these acids by three methods each of which has given products differing in isomer composition. The possible reasons for this result are explored in this paper.



1a



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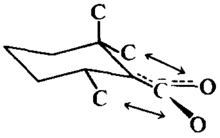

Fig 1.

The first was the direct hydrogenation of hemimellitic acid (**3**) in aqueous medium employing 5% rhodium-on-carbon catalyst, following Freifelder *et al.*[4] The product was esterified with diazomethane and shown by GLC analysis to consist of two components present in the approximate ratio of 1 : 12. On the presumption that hydrogenation of hemimellitic acid occurred from one side (See Sequel), the predominant component was thought to be trimethyl *cis,cis*-cyclohexane-1,2,3-tricarboxylate (**2Cb**). The triacid corresponding to this was isolated by fractional crystallisation of the total hydrogenation product from ethyl acetate and shown to consist of a single isomer by GLC analysis of the corresponding trimethyl ester.

The configuration of the carboxyl groups and the position of the double bonds in the intermediate stages of hydrogenation of hemimellitic acid not being known, it seemed worthwhile to compare the stereoisomeric composition of the product of its hydrogenation with that of a cyclohexene-1,2,3-tricarboxylic acid system with a double bond at a known position. We attempted to prepare one such system, cyclohex-1-ene-1,2,3-tricarboxylic acid (**4a**; R=H) by hydrolysis of the product of dehydration of the cyanohydrin (**5b**) obtained from dimethyl cyclohexanone-2,6-dicarboxylate[5] (**5a**).

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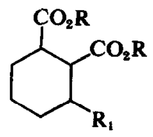
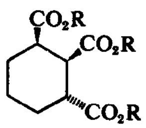
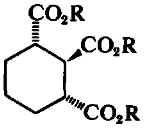
*Abstracted from the thesis of M. Balasubramanian submitted to the Indian Institute of Science for the Ph.D. degree (1971); presented at the Convention of Chemists—1970 held at the Indian Institute of Technology, Madras, Nov. 30–Dec. 4, 1970.



2a: $R=Me; R_1=CO_2Me$
b: $R=Me; R_1=CN$
c: $R=H; R_1=CO_2H$

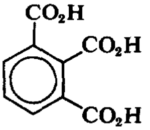


2A



a: R=H
b: R=Me
c: R=Et

2B



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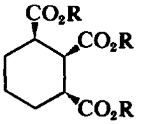
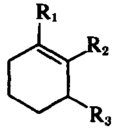
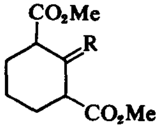


2C

Optimised conditions for realising this synthetic sequence were found to be: (1) preparation of the cyanohydrin (**5b**) by an exchange reaction with acetone cyanohydrin, since attempted direct addition of hydrogen cyanide gave poor yields; (2) dehydration employing phosphorus oxychloride, since employment of thionyl chloride resulted in a mixture of the unsaturated cyanodiester (**4b**; R=Me) and a chloro compound [possibly dimethyl 2-cyano-2-chlorocyclohexane-1,3-dicarboxylate (**5c**), formed by displacement of the hydroxy group[6]]; (3) hydrolysis followed by hydrogenation, rather than the reverse sequence, to obtain the tricarboxylic acid (**2c**), since clean catalytic hydrogenation of the unsaturated cyanodiester (**4b**; R=Me) could not be realised.



4a: $R_1=R_2=R_3=CO_2R$
b: $R_1=R_3=CO_2R; R_2=CN$
c: $R_1=H; R_2=R_3=CO_2R$
d: $R_1=R_2=CO_2R; R_3=H$
e: $R_1=CO_2Et; R_2=CN; R_3=H$
f: $R_1=H; R_2=CN; R_3=CO_2Et$



5a: R=O
b: R=OH,CN
c: R=Cl,CN

The unsaturated triester (**4a**; R=Me) exhibited UV absorption* and NMR spectra consistent with the assigned structure. The corresponding triacid (**4a**; R=H) was hydrogenated by the method indicated for hemimellitic acid. The esterified product was proved to consist of a *single* stereoisomer (GLC analysis) of the triester (**2a**), identical with the ester of the predominant isomer obtained from the hydrogenation of hemimellitic acid. This stereospecificity in hydrogenation is commented upon in the sequel.

In order to obtain the other two possible isomers of the acid (**2c**) in quantity recourse had to be had to an *a priori* synthesis not involving stereoselective steps, since attempted base catalysed equilibration of the product of hydrogenation of hemimellitic acid failed. Success was achieved by a procedure involving base catalysed addition of hydrogen cyanide to dimethyl cyclohex-1-ene-1,6-dicarboxylate (**4c**; R=Me). The preponderant non-crystalline acidic fraction of the product had infrared absorption characteristic of a cyano-acid. GLC analysis of this product after hydrolysis and esterification with diazomethane showed it to be a mixture of three components, A, **B** and C, present in the approximate ratio of 22 : 18 : 1; A and C corresponded with the triesters of the two isomeric acids obtained by the saturation of hemimellitic acid, the major product in that case being the minor product, C, of the present case. These isomers were separated by GLC and characterised by their IR spectra.

The asymmetric *cis,trans*-configuration (**2A**) could be readily assigned to isomer A since it exhibited two singlets of unequal half-widths and approximately equal heights in the 220 Hz region of its 60 MHz NMR spectrum. The unequal widths of these signals, which integrated together to nine protons, indicated that this isomer had three non-equivalent ester groups, two of which were imperfectly resolved.†

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*The UV max of this triester (216 nm) and that of the analogous diester **4c** (R=Me; 215 nm) seem to indicate that $A^{1,3}$ interaction between the allylic and vinylic methoxycarbonyl groups prevents their assuming the rotameric configuration necessary for extension of conjugation (1-methoxycarbonylcyclohexene absorbs maximally at 219 nm). In apparent confirmation of this it has been found that the unsaturated cyanodiester **4b** (R=Me) and its mono-ester analogue (**4e**), in which $A^{1,3}$ interaction between the lone-pairs on one of the O atoms of the ester group (the ether oxygen in the transoid configuration of the ester group) and the laterally extending π-orbital of the cyano group may not be of the same order as in the diester case, absorb maximally at 233 nm. This max, ascribable to the extension of conjugation of an α,β-disubstituted acrylic ester by a cyano group (cyclohex-1-enecarbonitrile absorbs maximally at 211 nm) is probably unique to such a system and its ethynyl analogue in that, in most trienic systems with a central *cis*-double bond coplanarity cannot be attained if the end group is not a linear array (*cf cis*-stilbene). Though rules resembling "Woodward's Rules" have been proposed [O. H. Wheeler, *J. Am. Chem. Soc.* **78**, 3216 (1956); R. Heilmann, J. Bonnier and G. de Gaudemaris, *C.R. Acad. Sci. Paris* **244**, 1787 (1957); O. H. Wheeler, *J Org. Chem.* **26**, 4755 (1961)] for conjugated nitriles, a study of unsaturated nitriles with the conjugation extended has yet to appear.

†The 100 MHz NMR spectrum of the triethyl ester corresponding to this isomer showed three sets of quartets and triplets for the $—OCH_2CH_3$ groups, supporting the assignment of the asymmetric configuration (2A). The resonances of the protons α to the ethoxycarbonyl groups were ill-defined multiplets.

Since the other two isomers should possess symmetric configurations (*cis,cis* and *trans,trans*), their OMe resonances were expected to consist of two signals of equal widths, one having twice the height of the other, and integrating together to nine protons.* However, while isomer **B** exhibited such a set, isomer C, identical with the major product derived from the hydrogenation of hemimellitic acid and the sole product of the hydrogenation of the acid (**4a**; R=H), and tentatively assigned the *cis, cis*-configuration (**2C**), exhibited an apparently similar set but integrating to ten protons, the C_2-proton resonance having evidently been obscured by the OMe signals. This resonance could, however, be seen separately as a triplet-like envelope† centred at *ca* 353 Hz and upfield of the $—OCH_2—$ resonances in the 100 MHz NMR spectrum (Fig 2) of the corresponding triethyl ester (**2Cc**) prepared by diazoethane esterification of the crystalline tricarboxylic acid derived from isomer C.

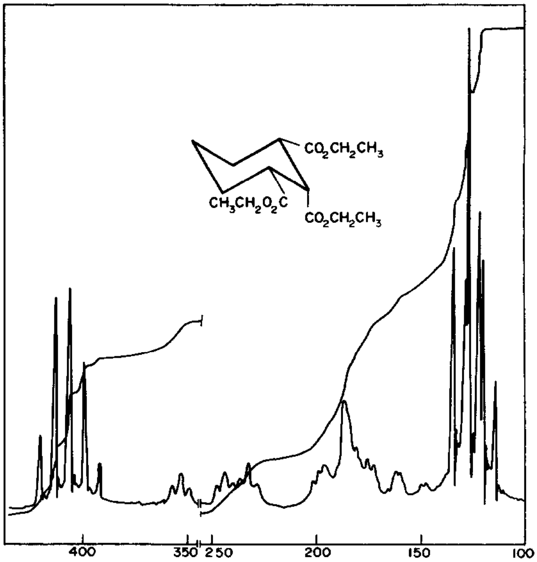

Fig 2. 100 MHz NMR spectrum of the triethyl ester **6** in carbon tetrachloride solution (footnote †).

One of us has shown that AB-nonequivalence of the $—OCH_2—$ protons of the diethyl esters of *cis*-cyclohexane-1,3-dicarboxylic acids can be diagnostic of *syn*-axial conformation of the ester groups.[9] The $—OCH_2—$ proton signals of the triethyl ester (**2Cc**) consisted of five prominant lines (Fig 2) interpreted as indicating that two pairs of these protons were equivalent, implying a symmetric configuration, and that the third was displaced downfield by just about the methylene-methyl coupling of *ca* 7 Hz. Absence of AB-nonequivalence indicated that the equivalent pair of ethoxy-carbonyl groups was not *syn*-axial.

The triethyl ester of isomer **B**, similarly prepared, also did not exhibit AB-nonequivalence of O-methylene protons, the signal complex in the 415 Hz region consisting of two sets of quartets with an intensity ratio of 1 : 2 (Fig 3). The signals assignable to the three α-protons appeared as a complex envelope in the 220–290 Hz region.‡ Since the equatorial conformation could be assigned to the C_1- and C_3-ester groups of both isomers **B** and **C** on the basis of absence of AB-nonequivalence of the $—OCH_2—$ protons, assignment of conformation to the C_2-ester groups depended simply on the relative chemical shifts of the C_2-protons.§ Accordingly, isomer C, with the more highly deshielded, and hence equatorial, C_2-proton was assigned the *cis,cis*-configuration [**2Cc**; conformation (**6**)] and isomer **B** the *trans,trans*-configuration [**2Bc**; conformation (**7**)].

In accordance with the analysis of Johnson and Malhotra,[3] of two quasi-chair forms **8** and **9**, contributing to the conformational equilibrium of cyclohex-1-ene-1,2,3-tricarboxylic acid (**4a**; R=H), the latter, with the quasi-axial carboxyl group at C_3 is likely to predominate (~ 90%) since, in it, the larger dihedral angle between the car-

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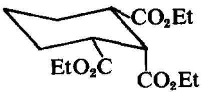
**cf* the case of the isomeric 2-acetoxyamino-1,3-cyclohexanediol diacetates.[7]

†The signal due to the C_1— and C_3—protons appears as a pair of triplets centred at 236 Hz. In considering the analogous cases of *cis,cis*-1,2,3-cyclohexanetriol and its tribenzoate McCasland[8] *et al.* found the signal due to the C_2-proton to be a sharp triplet and that due to the C_1- and C_3-protons in the case of the tribenzoate to be a triplet of doublets; the small spacing in this signal pattern was equal to the spacing in the C_2-proton triplet. The triplet-like appearance of this signal was attributed to strong coupling with the C_2-proton and the tendency of the chemical shifts of the axial and equatorial protons at C_4 and C_6, with which the C_1- and C_3-protons can additionally couple, to be equalised under the influence of the axial benzoate group at C_2. In the present case, however, the C_2,C_3-proton signal is a *doublet* of triplets with spacings roughly equal to that in the triplet-like signal due to the C_2-proton, raising the possibility that the "triplets" can be individually assigned to the C_1- and C_3-protons and the spin system can be treated virtually as an ABX system [with $J_{AB} \simeq J_{AX} = |J_{BX}|$, F. A. Bovey, *Nuclear Magnetic Resonance Spectroscopy* p. 285. Academic Press, New York & London (1969) computed spectra Nos. 18 and 19]. Such a possibility of individual assignment would imply that ring has a permanent asymmetric distortion by which the C_1- and C_3-protons are in non-equivalent environments.

‡Even though the three relatively sharp lines centred at 275 Hz assigned to the C_2-proton have spacings (11 Hz) characteristic of diaxial coupling, a direct conformational conclusion has not been drawn because the lines are probably part of an AB_2M_n system. This ester also bears close analogy to *trans,trans*-cyclohexanetriol and its tribenzoate discussed by McCasland *et al.* refered to in footnote † above.

§Both protons are subject to the similar paramagnetic influences, due to symmetry, of two ring $C—CO_2Et$ polarized bonds in *gauche*-relationship; Reference 2 has a comment on a situation where a vicinal ring $C—CO_2Et$ bond apparently exerts a strong paramagnetic effect.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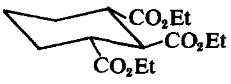
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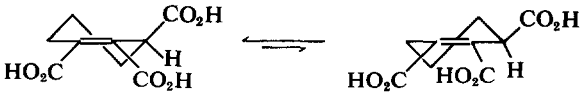
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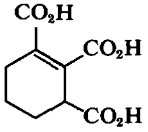
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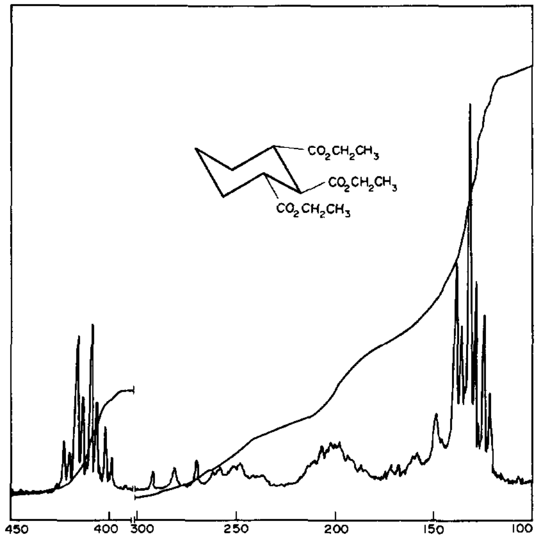

Fig 3. 100 MHz NMR spectrum of the triethyl ester 7 in carbon tetrachloride solution (footnotes † and ‡ on p. 685).

boxyl groups at C_2 and C_3 compared with that in the ring inverted form (8) relieves Pitzer strain ($A^{1,2}$-strain). In order to take account of the Curtin-Hammett Principle, we have to consider the likely difference in the transition state energies to account for the isomer composition of the product mixture when the reactants are in rapid equilibrium.[10] It appears reasonable to assume that $A^{1,2}$ strain operates in the transition state leading to the hydrogenation of the adsorbed molecules of the acid (4a; R=H). The most favoured transition state is then the one with the C_1-carboxyl group *quasi*-axial and, since hydrogenation is likely to occur from the less hindered side, the product of *cis,cis*-configuration (2Ca) would be formed predominantly. Also, the product of *trans,trans*-configuration (2Ba) is unlikely to be produced at all. This is in accordance with the results of our hydrogenation experiments. The lesser degree of stereoselectivity in the case of hydrogenation of hemimellitic acid may imply that a dihydrobenzene tricarboxylic acid (10) in which $A^{1,2}$ strain would play a modified role, intervenes. We wish to reserve our comments on this for the present.

The most easily accessible isomer of the triester (2a), that of *cis,cis*-configuration (2Cb), was chosen for the anion formation studies. We proposed to quench the anion with methyl iodide since three of the four possible isomers of the C_1-methylation product were available[2] to us for direct comparison with the reaction products. The formation of the anion was attempted employing tritylsodium in ether slightly in excess of 1 mol equiv; immediate discharge of the red colour of the trityl anion was noticed. Methyl iodide was added at the end of 15 min. The product was analysed by GLC after removal of aromatic hydrocarbons by preliminary TLC. It was found to consist of the starting *cis,cis*-triester (2Cb) admixed with some of the triester of *cis,trans*-configuration (2Ab); no methylation products and none of the *trans,trans*-triester (2Bb) were detectable. We have interpreted these results to mean that: (a) the C_1-anion of the *cis,cis*-isomer (2Cb) is formed in a facile manner; (b) this undergoes configurational inversion at the anionic centre to give the *cis,trans*-product (2Ab) on work-up; (c) sufficient time might not have been allowed for attainment of the configurational equilibrium at C_1 ($2C \rightarrow 2A$);* (d) methylation of the anions may be slow on account of ion aggregation in the ether medium,[11] hence our inability to detect methylation products; (e) the *trans,trans*-isomer (2Bb) is not

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*That such equilibria are attained only slowly has been demonstrated.[2]

detected since its formation involves either direct configurational inversion of the C_2-anion of the *cis,cis*-ester (**2Ca**) or the formation of a *bis*-anion at C_1 and C_2 of the *cis,trans*-triester (**2Ab**). The former is unlikely because formation of a C_2-anion and rehybridisation at that centre as the proton is pulled away generates increasing $A^{1,3}$ interaction with the ester groups at C_1 and C_2 (Fig 1). The *cis, trans*-triester (**2Ca**) is involved in the reaction only as its C_1-anion and not as the free ester. Hence for a second configurational change [to the *trans,trans*-form (**2Bb**)] to occur, the formation of a C_1, C_3-bis-anion is necessary. Since no opportunity exists for this to happen no *trans,trans*-triester is formed.

EXPERIMENTAL

M.ps and b.ps are uncorrected, the former being determined with a micro hot-stage. IR spectra were recorded with a Perkin-Elmer Model 137 "Infracord" spectrophotometer. UV spectra were recorded for samples dissolved in purified 95% EtOH with a Unicam Model SP700A recording spectrophotometer. NMR spectra were recorded with Varian Model A-60 and HA 100D spectrometers using TMS as internal standard. As a routine organic extracts were washed with saturated brine and dried with $NaSO_4$ prior to being concentrated. TLC tests and separations were carried out on glass plates (20 × 5 cm and 20 × 20 cm) coated with silica gel (*ca* 0·2 mm; from the National Chemical Laboratory, Poona) and activated at 100° for 4–6 hr prior to use; spots and bands were rendered visible with iodine vapour. GLC analyses were performed with a Willy Giede Model GCHF 18·3 gas chromatograph employing a thermal conductivity detector and hydrogen as the carrier gas under the stated conditions. 'Celite' refers to the product of 30–80 mesh supplied by British Drug Houses, U.K.; 'Porolit' refers to the product of 60 mesh supplied by the manufacturers of the GLC instrument. The rhodium-on-carbon catalyst (5%) was procured from the Baker Platinum Division of Engelhard Industries Ltd., U.K. Esterification of acids with diazomethane or diazoethane was invariably carried out employing distilled ethereal solns of the reagent. All the reactions involving the use of triphenylmethylsodium (tritylsodium) were carried out under a continuous stream of oxygen-free dry N_2. Hexane refers to the petroleum fraction boiling in the range 60–80°. The ratios of isomeric tricarboxylic acids (**2a A, B** and **C**) given are averages of three independent hydrogenation experiments in every case.

Hydrogenation of benzene-1,2,3-*tricarboxylic acid* (*Hemimellitic acid*) (**3**). A suspension of **3** (0·60 g) in water (50 ml) and 5% rhodium-on-carbon catalyst (0·25 g) was stirred under H_2.[4] Though absorption of H_2 practically ceased at the end of 2 hr stirring was continued for a further period of 8 hr. The catalyst was filtered off and washed with hot water (3 × 25 ml). The filtrate was rendered acidic with conc HCl (since the hydrogenated acid was found to exist as an inorganic salt) and evaporated to dryness to obtain **2c** isomer mixture (0·58 g); m.p. 168–173°.

The product was esterified with diazomethane. GLC analysis of the ester indicated the presence of two isomers (**2Cb** and **2Ab**) in the approximate ratio of 12 : 1 [R_t (**2Ab**) 3·1 and (**2Cb**) 4·4 min; 2 m × 4 mm column packed with 10% 'Carbowax' on 'Celite' (aged column); oven temp 216°; flow rate 150 ml/min; R_t (**2Ab**) 11·6 and (**2Cb**) 16·3 min; 2 m × 4 mm column packed with 10% 'Carbowax' on 'Celite' (column not aged); oven temp 200°; flow rate 120 ml/min].

Recrystallisation of the hydrogenated product from EtOAc containing a drop of MeOH furnished the analytically pure **2Ca**; m.p. 172·5–175·5°; ν_{max} (mineral oil mull) 3700–2330 (OH; CO_2H), 1727 (monomer; CO_2H), 1701 and 1689 (dimer; CO_2H), 1312, 1267 (C—O), 1227, 1148, 1007, 962, 917, 877, 813 and 726 cm^{-1}. The IR spectrum of the melt showed the formation of an anhydride; ν_{max} (mineral oil mull) 2560–3770 (OH; CO_2H), 1848 and 1776 (C—O; anhydride), and 1701 (CO_2H) cm^{-1}. (Found: C, 49·87; H, 5·56. $C_9H_{12}O_6$ requires: C, 50·0; H, 5·6%).

The acid **2Ca** was esterified with diazomethane in order to obtain **2Cb**; b.p. 100° (bath)/0·017 mm; ν_{max} (liquid film) 1751, 1739 and 1718 (CO_2Me), 1302, 1205 (broad, C—O), 1140, 1121, 1093, 1037, 1009, 871, 826, 787 and 772 cm^{-1}; $\Delta\nu$ (CCl_4) 218·5 (singlet, C_1— & C_3—$CO_2\underline{Me}$) 215 (singlet, C_2—$CO_2\underline{Me}$), *ca* 212 (multiplet, C_2—H (?); these three signals integrated together to 10 protons), 160–130 (2H, multiplet, C_1— & C_3—H) and 100–75 (6H, multiplet, ring methylene protons) Hz (at 60 MHz). The 100 MHz NMR spectrum of the corresponding triethyl ester is given in Fig 2. (Found: C, 55·67; H, 6·9. $C_{12}H_{18}O_6$ requires: C, 55·80; H, 7·03%).

Trimethyl cyclohex-1-*ene*-1,2,3-*tricarboxylate* (**4a**; R=Me). Compound **5a** (11 g)[5] was allowed to react with acetone cyanohydrin (52 ml) in the presence of 10% NaOH aq (1 ml) for 2 days at room temp. The mixture was diluted with water (50 ml) and acidified with 2N HCl (10 ml) and extracted with ether. Removal of the solvent under reduced pressure after washing and drying furnished **5b** (11 g). When liquid HCN was employed in place of acetone cyanohydrin in the preparation described above, the yield was lower and the product was contaminated by a dark solid.

To a cooled soln of the crude **5b** (1·6 g) in pyridine (27 ml) was added $POCl_3$ (9 ml) and the mixture was allowed to stand overnight. After heating in an oil bath (*ca* 110°) for 2·5 hr the mixture was poured onto crushed ice and the organic materials taken up in ether; the phases were then filtered together to remove black solids. The filtrate (aqueous phase acidic to Congo Red) was separated into its phases and the organic layer was washed and dried. Removal of the solvent gave a residue (1·12 g) which was subjected to short-path distillation to yield **4b** (R=Me; 0·75 g) as a colourless oil. TLC (20% EtOAc–80% hexane) and GLC analyses [R_t 2·3 min; 1 m × 4 mm column packed with 10% 'Fluhysol' on 'Porolit'; oven temp 198°; flow rate 120 ml/min] indicated slight contamination of the product by a low boiling component. The analytical sample was obtained by preparative TLC; b.p. 125° (bath)/0·3 mm; ν_{max} (liquid film) 2247 (unsaturated CN), 1739 (CO_2Me), 1661 (weak) and 1629 (medium) (C=C), 1258 (C—O), 1205, 1166, 1105, 1045, 1000, 980, 943, 840, 798 and 755 cm^{-1}; λ_{max}^{EtOH} 233 nm (ϵ 9,153).[7] (Found: C, 58·97; H, 5·83; N, 6·10. $C_{11}H_{13}NO_4$ requires: C, 59·18; H, 5·87; N, 6·28%).

Since attempted dehydration of **5b** with $SOCl_2$ and pyridine gave a mixture of products, presumably the required **4b** (R=Me) admixed with **5c** as indicated by elemental, GLC and NMR spectral analyses, only the first described method was followed when additional material was required.

A soln of **4b** (R=Me; 0·19 g) in EtOH (50 ml) was stirred under H_2 in the presence of 10% Pd-C (0·05 g) for 10 hr. No significant absorption of H_2 was noticed. Removal of the solvent, after filtration, gave the unchanged starting material as indicated by its IR spectrum.

Compound **4b** (R=Me; 0·6 g) was hydrolysed by refluxing with conc HCl (75 ml) for 9 hr. Compound **4a**; (R=H; 0·43 g) was isolated as a gummy product by exhaustive extraction with EtOAc for 10 hr in a liquid-liquid extraction apparatus since the acid was found to be highly soluble in water. All attempts to obtain the acid as a crystalline solid failed. On one occasion, a low melting crystalline product, presumably an anhydride of the unsaturated triacid was obtained. The anhydride structure for the solid was supported by its IR spectrum which had absorption bands at 2560–3770 (OH, CO_2H), 1848 and 1776 (C—O, anhydride), 1701 (CO_2H), 1259 (C—O), 891, 729 and 695 cm^{-1}.

Compound **4a** (R—H; 0·6 g) was esterified with diazomethane. The product **4a** (R=Me; 0·6 g) was purified by TLC (25% EtOAc–75% hexane) followed by short-path distillation [b.p. (bath) 140°/1–2 mm] and was shown to be homogeneous by GLC (R_t 24·2 min; 2 m × 4 mm column packed with 10% Carbowax on Celite; oven temp 206°; flow rate 60 ml/min); ν_{max} (liquid film) 1724 (CO_2Me), 1621 (weak, C=O), 1256 (C—O), 1195, 1166, 1096, 1047, 1010, 864, 810 and 766 cm^{-1}; λ_{max}^{EtOH} 216 nm (ϵ 7,470); $\Delta\nu$ (CCl_4) 218·5, 220 and 222·5 (9H, singlets, C_1—, C_2—, and C_3—$CO_2\underline{Me}$), 176·5 [1H, singlet, (low coupling with vicinal methylene protons), C_3—$\underline{H}$] and 90–150 (6H, multiplet, ring methylenes) Hz (at 60 MHz). (Found: C, 56·11; H, 6·48. $C_{12}H_{16}O_6$ requires: C, 56·24; H, 6·29%).

Hydrogenation of cyclohex-1-*ene*-1,2,3-*tricarboxylic acid* (**4a**; R=H). A suspension of 5% rhodium-on-carbon catalyst (0·39 g) in an aqueous soln of **4a** (R=H; 0·82 g) was stirred under H_2. Though H_2 uptake practically ceased at the end of 4 hr, stirring was continued for another 10 hr. The product, **2Ca** (0·32 g), was isolated in the manner described earlier for the hydrogenation product of hemimellitic acid. The acid was recrystallised from EtOAc containing some MeOH; m.p. 172·5–175·5°. The IR spectra of the acid and its melt were found to be identical with those of the acid and the melt of the major product of hydrogenation of hemimellitic acid.

Samples of the corresponding trimethyl ester, obtained by esterification of the crude acid as well as the recrystallised acid were shown to consist of **2Ca** only and identical with the triester of the major product of the hydrogenation of hemimellitic acid by GLC [R_t 13·1 min; 2 m × 4 mm column packed with 10% 'Carbowax' on 'Celite'; oven temp 207°; flow rate 90 ml/min] and IR spectral comparison.

Attempted equilibration of cis,cis-*cyclohexane*-1,2,3-*tricarboxylic acid* (**2Ca**). Compound **2Ca** (0·04 g) was heated under reflux with methanolic MeONa (0·5 g Na metal dissolved in 9·5 ml dry MeOH) for 4 hr. After removal of the MeOH under reduced pressure the residue was acidified with conc HCl (4 ml), diluted with water (10 ml) and extracted with EtOAc. The extract was washed with brine and dried. Removal of the solvent *in vacuo* gave a pasty residue (0·04 g) which was directly esterified with diazomethane. GLC analysis of the ester thus obtained (0·05 g) indicated the presence of **2Cb** only. (R_t 11·3 min; 2 m × 4 mm column packed with 10% 'Carbowax' on 'Celite'; oven temp 220°; flow rate 60 ml/min).

Mixture of dimethyl cyclohex-1-*ene*-1,2- *and* -1,6-*dicarboxylates* **4d** and **4c** (R=Me). A soln of 2-ethoxycarbonylcyclohexanone (31 g), acetone cyanohydrin (100 ml) and 10% NaOH aq (1 ml) was allowed to stand at room temp. At the end of 2 days the mixture was acidified with 2N HCl (5 ml) and extracted with ether. The extract was washed, dried, concentrated and the residue distilled under reduced pressure in order to obtain 2-2-ethoxycarbonyl-1-cyanocyclohexan-1-ol* (25·8 g); b.p. 130–135°/1–2 mm; $n_D^{26°}$ 1·4645 (Reported b.p. 147–150°/10 mm); ν_{max} (liquid film) 3450 (OH), 2250 (CN), and 1735 (CO_2Et) cm^{-1}.

To a cooled soln of this cyanohydrin (25·8 g) in pyridine (135 ml) was added dropwise $POCl_3$ (45 ml) with stirring. The mixture was heated in an oil bath (110°) for 30 min and worked up in the usual way. GLC analysis of the product indicated the presence of 3 components later identified as cyclohex-1- necarbonitrile, **4e** and **4f** in the ratio *ca* 4:12:11; [R_t 0·5, 4·7 and 5·2 min respectively; 2 m × 4 mm column packed with 10% 'Carbowax' on 'Celite'; oven temp 190°; flow rate 75 ml/min]. Fractional distillation of the product gave the mixture of the two unsaturated cyano-esters (12 g) free from cyclohexene carbonitrile; b.p. 115–118°/1–2 mm. Components of this mixture were separated by preparative TLC. The faster moving one was shown to be **4e** from its UV absorption spectrum;† b.p. 110° (bath)/1–2 mm; ν_{max} (liquid film) 2232 (unsaturated CN), 1715 (unsaturated ester), 1629 (C=C), 1277, 1245, 1179, 1103, 1070, 1045, 1005, 858 and 759 cm^{-1}; λ_{max}^{EtOH} 233 nm (ϵ 9,100). (Found: C, 67·04; H, 7·28; N, 7·98. $C_{10}H_{13}NO_2$ requires: C, 67·02; H, 7·31; N, 7·82%).

The slower moving component was identified as **4f** from its spectral data; b.p. 110° (bath)/1–2 mm; ν_{max} (liquid film) 2237 (unsaturated CN), 1730 (saturated ester), 1626 (C=C), 1305, 1250, 1175, 1026, 924 and 861 cm^{-1}; λ_{max}^{EtOH} 211 nm (ϵ 10,600). (Found: C, 67·05; H, 7·26; N, 7·92. $C_{10}H_{13}NO_2$ requires: C, 67·02; H, 7·31; N, 7·82%).

Alkaline hydrolysis of the mixture of the unsaturated cyano-esters. To a soln of the mixture of **4e** and **4f** (11·4 g) in MeOH (50 ml) was added 30% KOH aq (50 ml) and the mixture was heated under reflux for 25 hr. After the removal of the MeOH under reduced pressure, the residue was diluted and acidified with conc HCl. The crystalline product which separated (6·15 g) was isolated by filtration; m.p. 190–193°. The filtrate was extracted with EtOAc after saturation with ammonium sulphate. The dried extract, on removal of the solvent, furnished an additional quantity (1·67 g) of the product as a crystalline solid; m.p. 180–200°. These two materials were shown to be mixtures of the two unsaturated diacids, **4c** (R=H) and **4d** (R=H) (see below).

This mixture of the unsaturated diacids (5·1 g) was added to dry acetone (250 ml) containing redistilled dimethyl sulphate (9·2 g) and anhydrous K_2CO_3 (13·3 g) and heated under reflux for 36 hr. Most of the solvent was then distilled off *in vacuo* and the residue, after dilution with water, was extracted with ether, the extract being washed with sat $NaHCO_3$ aq. Removal of the solvent furnished a liquid residue (4·8 g) which was shown to be a mixture of **4c** (R=Me) and **4d** (R=Me) by GLC in the ratio of 1:7 [R_t 1·4 **4c** (R=Me) and 2·3 **4d** (R=Me) min;

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*The preparation of this cyanohydrin and its dehydration differ in many details from the description given in the literature: G. A. R. Kon and B. L. Nandi, *J. Chem. Soc.* 1628 (1933); these authors claim the formation of **4e** as the *sole* product of dehydration.

†See footnote * p. 685.

2 m × 4 mm column packed with 10% 'Carbowax' on 'Celite'; oven temp 200°; flow rate 120 ml/min].

The two unsaturated esters were separated by TLC (25% EtOAc–75% hexane). The minor fraction with the higher R_f value was found to be **4c** (R=Me), b.p. 110° (bath)/1–2 mm; ν_{max} (liquid film) 1733 (CO_2Me), 1639 (weak, C=C), 1307, 1259, 1192, 1096, 1042, 912 and 782 cm^{-1}; λ_{max}^{EtOH} 205 nm (ϵ 2,700). (Found: C, 60·40; H, 7·25. $C_{10}H_{14}O_4$ requires: C, 60·59; H, 7·12%).

The other, and major, fraction was shown to be **4d** (R=Me) from its spectral properties; b.p. 120° (bath)/1–2 mm; ν_{max} (liquid film) 1718 (unsaturated CO_2Me), 1647 (C=C), 1337, 1250, 1167, 1095, 1065, 1011, 922 and 764 cm^{-1}; λ_{max}^{EtOH} 215 nm (ϵ 9,300). (Found: C, 60·36; H, 7·54. $C_{10}H_{14}O_4$ requires: C, 60·59; H, 7·12%).

The mixture of acids **4c** (R=H) and **4d** (R=H) on diazomethane esterification gave a solid product containing nitrogen, m.p. 118·5–119·5° in addition to the two diesters **4c** (R=Me) and **4d** (R=Me). The structure of the solid product was not investigated.

Isomers of dimethyl 3-*cyanocyclohexane*-1,2-*dicarboxylate* (**2b**). To a soln of the mixture of **4c** and **4d** (2·45 g) in MeOH (13 ml), NaCN aq (1·85 g in 3·5 ml of water) was added and the mixture was heated under reflux for 16 hr. Most of the solvent was removed under reduced pressure and the residue was freed from neutral material (0·15 g) by extraction with ether after dilution with water. The aqueous phase was then acidified with conc HCl and the acidic material (2·3 g) isolated by extraction with a mixture of EtOAc and ether after saturation with ammonium sulphate. The IR spectrum of the product showed the presence of the CN group; ν_{max} (liquid film) 3500–2700 (CO_2H), 2273 (CN), and 1706 (broad, CO_2H/CO_2Me) cm^{-1}. It (2·3 g) was then esterified with diazomethane and the ester (2·3 g) subjected to separation by preparative TLC (20% EtOAc–80% hexane) in order to isolate the mixture of stereoisomers of **2b**. This material was not further resolved either by TLC or by GLC (R_t 17·3 min; 2 m × 4 mm, column packed with 10% 'Carbowax' on 'Celite'; oven temp 220°; flow rate 55 ml/min). Its IR spectrum was consistent with the assigned plane structure **2b**: ν_{max} (liquid film) 2278 (saturated CN) and 1736 (saturated CO_2Me) cm^{-1}. Its NMR spectrum however confirmed that the cyano-diester was a mixture of isomers: $\Delta\nu$ (CCl_4) 219, 220 and 224·5 ($CO_2\underline{Me}$ protons) Hz (at 60 MHz). (Found: C, 58·69; H, 6·83, N, 6·38. $C_{11}H_{15}NO_4$ requires: C, 58·65, H, 6·71; N, 6·22%).

Mixture of isomers of trimethyl cyclohexane-1,2,3-*tricarboxylate* (**2a**). The crude **2b** (1·24 g) obtained in the previous experiment was hydrolysed by refluxing with conc HCl (100 ml) for 15 hr. Attempts to separate the stereoisomers of this triacid **2c** by fractional crystallisation failed as successive crops differing only slightly in isomer composition could be obtained.

The mixture of isomers of **2c** (0·92 g) was esterified with diazomethane. The isomeric components of the product (0·72 g) could not be resolved by TLC (25% EtOAc–75% hexane).

An analytical sample of the triester isomer mixture was obtained by purification by TLC followed by short-path distillation; b.p. 105° (bath)/0·002 mm. (Found: C, 55·75; H, 7·04. $C_{12}H_{18}O_6$ requires: C, 55·8; H, 7·04%).

Separation of the stereoisomers of trimethyl cyclohexane-1,2,3-*tricarboxylate* (**2a**). GLC analysis of the crude mixture of isomers of **2a** showed the presence of three components, besides the starting unsaturated diesters **4c** (R=Me) and **4d** (R=Me), in the ratio 22:18:1 [R_t 2·0 **4c** (R=Me), 3·2 **4d** (R=Me), 8·5 (**2Ab**), 9·2 (**2Bb**) and 10·6 (**2Cb**) min; 2 m × 4 mm, column packed with 10% 'Carbowax' on 'Celite'; oven temp 224°; flow rate 60 ml/min]. The last component was found to correspond with the *cis,cis*-isomer of **2a**. The first component corresponded with the triester of the minor product obtained in the hydrogenation of hemimellitic acid.

The three components were separated by semimicro-preparative GLC. The first component, A, b.p. 140° (bath)/1–2 mm, solidified on letting stand; m.p. 64–65·5°; ν_{max} (liquid film) 1733 (CO_2Me), 1202, 1071, 1032, 907, 883, 861, 844, 825, and 751 cm^{-1}; ν_{max} (mineral oil mull) 1724 (CO_2Me), 1247, 1178, 1094, 1072, 1034, 910, 886, 847, 826, 788 and 745 cm^{-1}. It was shown to be the **2Ab** by its NMR spectrum; $\Delta\nu$ (CCl_4) 217·2 and 219·2 (9H, singlets of unequal widths, C_1—, C_2—, and C_3—$CO_2\underline{Me}$), 169–195 (3H, multiplet, C_1—, C_2—, and C_3—$\underline{H}$), 78–130 (6H, multiplet, ring methylenes) Hz (at 60 MHz).

The second component, B, b.p. 150° (bath)/1–2 mm, was shown to be **2Bb** by its NMR: $\Delta\nu$ (CCl_4) 218·5 and 215 (9H, singlets of equal widths, C_1—, C_3— and C_2—$CO_2\underline{Me}$), 180–135 (3H, multiplet, C_1—, C_2—, and C_3—$\underline{H}$), 130–70 (6H, multiplet, ring methylenes) Hz (at 60 MHz). The 100 MHz NMR spectrum of the corresponding triethyl ester (**2Bc**) obtained by esterification of the corresponding acid (see below) with diazoethane is shown in Fig 3; ν_{max} (liquid film) 1733 (CO_2Me), 1253, 1198, 1163, 1035, 1010, 973, 847, 758 and 719 cm^{-1}.

The third component, C, was identical with the triester of the major product of hydrogenation of **3** and the *sole* product of hydrogenation of **4a** (R=H) to which the *cis,cis*-configuration (**2C**) has been assigned.

cis,trans-*Cyclohexane*-1,2,3-*tricarboxylic acid* (**2Aa**). Compound **2Ab** (0·124 g) (separated by GLC) was hydrolysed by refluxing with conc HCl (10 ml) for 10 hr. The soln was evaporated to dryness on a steam bath and the residue was extracted with EtOAc containing a few drops of MeOH. Removal of the solvent after filtration left a gummy residue. Trituration with acetonitrile (2 ml) furnished the crystalline **2Aa** (0·065 g); recrystallisation from the same solvent furnished the analytical sample, melting in the range, 166–183° (clear liquid formation at 183°); ν_{max} (mineral oil mull) 3570–2500 (CO_2H), 1698 (CO_2H, dimer), 1294, 1188, 1145, 930, 837, 769, and 714 cm^{-1}. (Found: C, 49·98; H, 5·79. $C_9H_{12}O_6$ requires: C, 50·0; H, 5·6%).

The IR spectrum of the melt of the acid indicated the formation of an anhydride; ν_{max} (mineral oil mull) 3700–2500 (CO_2H), 1855 and 1783 (C—O; anhydride), and 1706 (CO_2H) cm^{-1}.

trans,trans-*Cyclohexane*-1,2,3-*tricarboxylic acid* (**2Ba**). Compound **2Bb** (0·056 g) (separated by GLC) was hydrolysed with conc HCl (7 ml) as described in the previous experiment. The product (0·042 g) was recrystallised from acetonitrile to obtain the analytical sample; melting in the range 191–200° (clear liquid formation at 200°); ν_{max} (mineral oil mull) 3570–2500 (CO_2H), 1698 (CO_2H, dimer), 1259, 1225, 1212, 1189, 1100, 935 and 704 cm^{-1}. (Found: C, 50·02; H, 5·78. $C_9H_{12}O_6$ requires: C, 50·0; H, 5·6%).

The formation of an anhydride on melting was in this case also indicated by the IR spectrum of the melt, ν_{max} (smear) 3700–2500 (CO_2H), 1855 and 1773 (C—O, anhydride) and 1704 (CO_2H) cm^{-1}.

Attempted methylation of trimethyl cis,cis-*cyclohexane*-1,2,3-*tricarboxylate* (**2Cb**). To a soln of trimethyl *cis,cis*-cyclohexane-1,2,3-tricarboxylate (0·162 g) in dry ether (75 ml) was added an ethereal soln of tritylsodium (0·0773N, 9 ml; 1·1 molar equivalent) with stirring after displacing the air in the system with N_2. Immediate discharge of the red colour of the trityl ion was noticed. MeI (5 ml) was added at the end of 10 min and stirring was continued for 2 hr. The mixture was then allowed to stand overnight. It was then quenched with acidulated water (20 ml containing a few drops AcOH) and the ether layer was separated, washed with brine and dried. Distillation of the solvent *in vacuo* furnished a residue (0·75 g) which was subjected to TLC separation (10% ethyl acetate–90% hexane). The ester portion (0·16 g) on GLC analysis exhibited two peaks corresponding to the starting **2Cb** and **2Ab** formed by isomerisation (ratio *ca* 4 : 1); none of the methylation product(s) of the *cis,cis*-triester was detected [R_t 9·5 (**2Ab**) and 12 (**2Cb**) min; 2 m × 4 mm, column packed with 10% 'Carbowax' on 'Celite'; oven temp 220°; flow rate 60 ml/min]. The two components were separated by GLC and were identified by their IR spectra.

Acknowledgement—The authors wish to express their thanks to Professor D. K. Banerjee for his keen interest, to Dr. T. R. Govindachari for the 60 MHz NMR spectra and to Messrs. B. R. Seetharamia and H. S. Thyagarajan for the microanalyses. They are grateful to Professor W. von Philipsborn for his comments on their interpretation of the NMR spectral data. They are also indebted to Messrs. Koch-Light Laboratories, U.K., for a gift of hemimellitic acid.

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