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CONFORMATIONAL EFFECTS IN COMPOUNDS WITH SIX-MEMBERED RINGS—I

SYNTHESIS OF THE STEREOISOMERS OF 5-ALKYLCYCLOHEXANE-1,3-DICARBOXYLIC ACIDS

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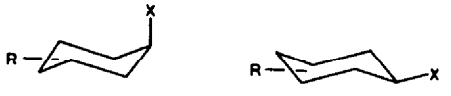
Abstract—Syntheses and proofs of configuration and conformation are described for stereoisomeric 5-alkylcyclohexane-1,3-dicarboxylic acids and their esters, in which the alkyl group varies in complexity from methyl to 1,1-diethylpropyl. A preparatively useful hydrogenolysis of alkoxyl substituents during Raney nickel hydrogenation is described.

THIS series of papers is concerned primarily with determining the nature and magnitude of steric interactions in non-aromatic six-membered ring compounds. For this purpose we have preferred to use equilibrium constants for the interconversion of pairs of stereoisomers used as models for pairs of conformations, rather than compare the properties of conformationally ambiguous compounds with analogous compounds of known conformation.

The conformational equilibrium constant, $K = [\text{Ie};\ R = H]/[\text{Ia};\ R = H]$, for a derivative, for example I (R = H), of cyclohexane or an analogous system may in principle be determined directly by, say, electron diffraction, but in practice less



Ia Ie

direct methods have been used. In the method devised by Winstein and Holness[1] the numerical value, k, of some property of I (R = H), which is dependent on the axial or equatorial situation of the group X, is compared with the values k_a and k_e for model compounds Ia (R ≠ H) and Ie (R ≠ H) respectively. If these compounds are exact models for Ia (R = H) and Ie (R = H) then $K = (k_a - k)/(k - k_e)$. It is immediately apparent that unless k_a is considerably larger than k or k_e, the observed value of K, which is usually considerably greater than 1, will be particularly sensitive to both random experimental errors in k and k_e and to any systematic errors resulting from the assumption that R is simply ". . . . a compelling but remote control of conformation".[1] This method was first applied by Winstein and Holness[1] to reaction rate constants, but essentially similar use has been made of IR[2] and NMR

[1] S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.* **77**, 5562 (1955).
[2] R. A. Pickering and C. C. Price, *J. Amer. Chem. Soc.* **80**, 4931 (1958).

spectra,[3–6] and of acid[7,8] and base[6,7,9] dissociation constants. The properties which have commonly been used are usually rather sensitive to polar and steric effects and it is not always easy to devise tests to detect the possible errors. A further, purely practical, difficulty is that even moderately accurate values of K at single temperatures require considerable labour, and in no instance, so far as we know, has the temperature dependence of K been determined from rate or dissociation constant measurements, although the value of entropy differences for interpreting conformational equilibria has been demonstrated by Allinger.[10]

The use of equilibrium constants, or equivalent thermodynamic data, is much older but apart from the notable series of papers by Allinger[11] this method has not been widely used recently in conformational analysis. In using equilibrium constants it is assumed that the substituents R affect the thermodynamic functions of Ia ($R \neq H$) and Ie ($R \neq H$) equally, so that

$$\begin{aligned} -RT \ln K &\equiv F(Ia;\ R = H) - F(Ie;\ R = H) \\ &= F(Ia;\ R \neq H) - F(Ie;\ R \neq H) \\ &= \Delta F(Ie \rightarrow Ia) \end{aligned}$$

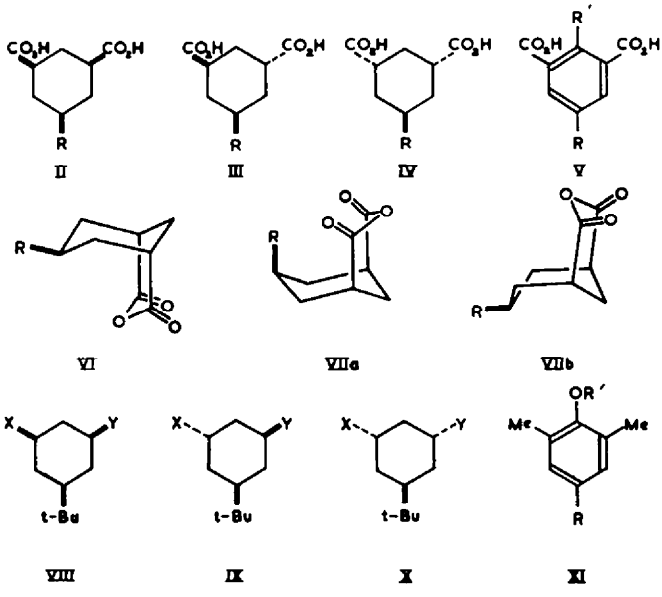
The errors caused by making this assumption may be regarded as due to differences in the polar and the steric interactions between R and X, and between R and the ring, in the two conformations. If R and X are not attached to neighbouring ring atoms steric interactions should be negligible, while the importance of polar interactions may be checked by measuring properties, such as acid dissociation constants, which are sensitive to electrostatic effects, of geometrically similar compounds. Differences in interactions between R and the ring should be negligible, when only chair conformations are involved, but some differences in steric interactions between R and boat and chair conformations of the ring are likely, particularly if R is one or more very bulky groups such as t-butyl. In this method the principal limitation is the scarcity of reversible epimerisations without side reactions if alkyl groups alone are considered for the conformation holding group R, but substituents such as alkoxycarbonyl can be used.

Because we wished to study the conformational properties of alkyl groups and other substituents by epimerisation of stereoisomers, we required a series of alkyl-substituted cyclohexane derivatives with functional groups which would serve three main purposes. Firstly, it was desirable to have readily epimerisable groups which would allow stereoisomers to be interconverted smoothly in, for example, a hydroxylic solvent between 0 and 100° or under comparable conditions. Secondly, the functional groups had to allow the use of physical methods for determining preferred conformations in solution. Finally, the functional groups had to be large enough to force

[3] A. H. Lewin and S. Winstein, *J. Amer. Chem. Soc.* **84**, 2464 (1962).
[4] F. A. L. Anet, *J. Amer. Chem. Soc.* **84**, 1053 (1962).
[5] E. L. Eliel, M. H. Gianni, T. H. Williams and J. B. Stothers, *Tetrahedron Letters* 741 (1962).
[6] E. L. Eliel, E. W. Della and T. H. Williams, *Tetrahedron Letters* 831 (1963).
[7] M. Tichy, J. Jonáš and J. Sicher, *Coll. Czech. Chem. Comm.* **24**, 3434 (1959).
[8] R. D. Stolow, *J. Amer. Chem. Soc.* **81**, 5806 (1959).
[9] J. Sicher, J. Jonáš and M. Tichy, *Tetrahedron Letters* 825 (1963).
[10] N. L. Allinger and L. A. Freiberg, *J. Amer. Chem. Soc.* **82**, 2393 (1960).
[11] N. L. Allinger, L. A. Freiberg and S-E. Hu, *J. Amer. Chem. Soc.* **84**, 2836 (1962), and earlier papers.

even large alkyl groups to become axial or to force the ring into a boat conformation. Because no single functional group seemed likely to satisfy this last requirement as well as the other two, we considered that it was necessary to use *cis*-1,3-difunctional cyclohexane derivatives, relying on the large repulsion between *cis*-1,3-diaxial groups to help those functional groups remain equatorial. The most accessible compounds satisfying these requirements were esters of 5-alkylcyclohexane-1,3-dicarboxylic acids (II, III and IV). Since this work was completed the use of a single alkoxycarbonyl group has been described[11] but this is not very satisfactory since these groups have a smaller effective size than any alkyl group. The free acids (II, III and IV), furthermore, are geometrically very good models for the esters and therefore the measurement of acid dissociation constants allows significant polar interactions between the 5-alkyl and the 1- and 3-alkoxycarbonyl groups to be detected. This paper deals with synthesis of these compounds and assignment of configurations to the stereoisomers. Conformational deductions are the subject of the following paper.

When this work began the only cyclohexane-1,3-dicarboxylic acids known were the *cis* and *trans* isomers of the parent acid, which is most conveniently prepared by hydrogenation of isophthalic acid or its esters. This appeared to be the most suitable route for the 5-alkyl acids, in spite of the inaccessibility of some of the aromatic acids, and has been explored in detail for the 5-t-butyl acids because these acids and their derivatives have been the most important in this work. The preparation and properties of the acids with t-alkyl groups were similar, but different methods had to be employed for the acids with smaller alkyl groups, and these will be discussed later.



5-t-Butyl-*m*-xylene, unlike *m*-xylene itself, was inert to potassium permanganate in water but when aqueous t-butyl alcohol was used as a solvent 5-t-butylbenzene-1,3-dicarboxylic acid (V; R = t-Bu) was formed in excellent yield. The yields in seven similar oxidations (Table 1) were better than 50% and aqueous t-butyl alcohol appears to be much superior to aqueous pyridine.[12] Hydrogenation of the dicarboxylic

[12] D. S. Noyce and L. J. Dolby, *J. Org. Chem.* **26**, 3619 (1961).

TABLE 1. ALKYL- AND ALKOXY-ISOPHTHALIC ACIDS (I)

Substituents R	R′	M.p.	Yield[a] (%)	Found (%) C	H	Misc.[b,c,d]		Required (%) C	H	Misc.[b,c,d]
H	OEt	180–183	82	57·2	5·0	21·3[c]	$C_{10}H_{10}O_5$	57·1	4·8	21·4[c]
e		154–155		51·6	3·5	7·4[c] 26·4[d]	$C_{26}H_{20}O_7Br_2$	51·7	3·3	7·5[c] 26·4[d]
OMe	H	267–269[f]	54							
CMe_2OH	OMe	178	83	56·6	5·6	12·5[b]	$C_{13}H_{14}O_6$	56·7	5·6	12·2[b]
e		130		51·8	3·9	4·7[b] 24·9[d]	$C_{28}H_{24}O_8Br_2$	51·9	3·7	4·8[b] 24·7[d]
CMe_2OH	OEt	151–152	35	58·1	6·1	16·8[c]	$C_{13}H_{16}O_6$	58·2	6·0	16·8[c]
e		119–120		52·4	4·2	23·9[d]	$C_{29}H_{26}O_8Br_2$	52·6	4·0	24·1[d]
t-Bu	H	340–342[g]	88							
e		193–194		54·6	4·0	26·1[d]	$C_{28}H_{24}O_6Br_2$	54·6	3·9	25·9[d]
t-Bu	OMe	192–193	84	61·9	6·7	12·5[b]	$C_{13}H_{16}O_5$	61·9	6·4	12·3[b]
e		149–150		53·9	4·3	24·6[d]	$C_{29}H_{26}O_7Br_2$	53·9	4·1	24·7[d]
CMe_2Et	H	318–320	70	66·4	6·8	—	$C_{13}H_{16}O_4$	66·1	6·8	—
CEt_3	OMe	158–160	65	65·2	7·6	10·6[b]	$C_{16}H_{22}O_5$	65·3	7·5	10·5[b]
e		121–124		55·6	4·8	4·6[b] 23·1[d]	$C_{32}H_{32}O_7Br_2$	55·8	4·7	4·5[b] 23·2[d]
CO_2H	OEt	242–244	48[h]	51·7	4·3	17·8[b]	$C_{11}H_{10}O_7$	52·0	4·0	17·7[c]
e		73–74		50·0	2·9	5·2[c] 28·4[d]	$C_{25}H_{25}O_{10}Br_3$	49·7	3·0	5·3[c] 28·4[d]

[a] Yield from potassium permanganate oxidation of appropriate derivative of m-xylene, [b] OMe, [c] OEt, [d] Br, [e] *p*-Bromophenacyl ester, [f] lit.[17] m.p. 267–268°, [g] lit.[18] m.p. 343°, [h] From the $KMnO_4$ oxidation of 2-methyl-2-(3,5-dimethyl-4-ethoxyphenyl)dioxolane.

[17] J. C. Calandra and J. J. Svarz, *J. Amer. Chem. Soc.* **72**, 1027 (1950).

[18] D. Nightingale, H. D. Radford and O. G. Shanholtzer, *J. Amer. Chem. Soc.* **64**, 1662 (1942).

acid (V; R = t-Bu) in alkaline solution over nickel was very slow, even when it had been very carefully purified. Crystallization of the resulting mixture of acids (II, III and IV; R = t-Bu) gave one pure stereoisomer, m.p. 236–238°. This acid appeared to have *cis* carboxyl groups since only one monomethyl ester was isolated after partial hydrolysis of the dimethyl ester, but the acid did not form a cyclic anhydride in cold acetyl chloride.[13] However, a single cyclic anhydride was readily obtained from the acid, m.p. 236–238°, or from the mixture of acids in the mother liquors, when they were heated with acetic anhydride and a basic catalyst. The anhydride was hydrolysed by hot water to an acid, m.p. 172–173°, from which it was reformed with cold acetyl chloride. The anhydride reacted with boiling methanol to give a monomethyl ester of the acid, m.p. 172–173°, which must have *cis* carboxyl groups. When the anhydride was treated with sodium alkoxides, the initially formed monoesters were epimerized to the monomethyl and mono-t-butyl esters of a third acid, m.p. 209–210°, obtained by acidic hydrolysis of either mono-ester. Since the anhydride must give initially derivatives of a *cis*-diacid and ester but not carboxylate groups should be epimerised by an alkoxide, the acid, m.p. 209–210°, was expected to have *trans* carboxyl groups. This was confirmed by the following preparation of a second monomethyl ester of this acid; the mono-t-butyl ester was treated with diazomethane and the t-butyl ester group was cleaved with hydrogen chloride to give a monomethyl ester. Hydrolysis of this second ester also gave the acid, m.p. 209- 210°, which must have *trans* carboxyl groups. Although it does not form an anhydride without change in configuration the acid, m.p. 236–238°, must have *cis* carboxyl groups and it only remains to determine whether it is II (R = t-Bu) or IV (R = t-Bu). The acid (IV; R = t-Bu) can form the strainless anhydride (VI; R = t-Bu) but the acid (II; R = t-Bu) would give an anhydride which is severely strained in both of the conformations (VIIa; R = t-Bu and VIIb R = t-Bu); the acid, m.p. 236–238°, must be II (R = t-Bu) and the acid, m.p. 172–173°, must be IV (R = t-Bu). These configurations were confirmed by base catalysed epimerizations of the esters (IVa; R = t-Bu and IIIa; R = t-Bu) to IIa (R = t-Bu), which alone can exist in a conformation with all the substituents equatorial and which should therefore be the most stable stereoisomer. Furthermore, the anhydride (VI; R = t-Bu) will form the mono-esters (X; X = CO_2H, Y = CO_2Me or —CO_2 t-Bu) which by epimerization will give the esters (IX; X = CO_2H, Y = CO_2Me or CO_2 t-Bu); the second monomethyl ester of the acid (III; R = t-Bu) must therefore be IX (X = CO_2Me, Y = CO_2H). For studies to be reported in the following paper the acids (II; R = t-Bu), III; R = t-Bu and IV; R = t-Bu) were converted into all the possible dimethyl, methyl ethyl and diethyl esters.

The acids (II; R = CMe_2Et and IV; R = CMe_2Et) and their dimethyl esters were obtained from 5-t-pentyl-*m*-xylene by reactions analogous to those used for the corresponding 5-t-butyl compounds described above. When attempts were made to alkylate *m*-xylene with 1-ethyl-1-methylpropyl and 1,1-diethylpropyl alcohols the alkyl groups were partly rearranged and inseparable mixtures resulted. Since this route is not suitable for primary or secondary alkyl groups anyway, it was necessary to find a removable activating group such that a 5-alkyl group, or a suitable precursor, could be introduced into a *m*-xylene derivative under mild conditions. In model

[13] K. Alder, H-H. Mölls and R. Reeber, *Liebigs Ann.* **611**, 7 (1958).

experiments it was found that 2-ethoxy- and 5-methoxy-*m*-xylene could be oxidized to 2-ethoxy- and 5-methoxybenzene-1,3-dicarboxylic acids by potassium permanganate, showing that hydroxyl or alkoxyl substituents could be used as activating groups. These acids, and, incidentally, 5-aminobenzene-1,3-dicarboxylic acid, were reduced by hydrogen over Raney nickel to cyclohexane-1,3-dicarboxylic acid, with quantitative removal of the alkoxyl or amino substituent. These reactions established that 2,6-dimethylphenol and its ethers would be suitable starting materials for alkylation or acylation *meta* to the methyl groups. Because we suspected that methanol formed by hydrogenolysis of methyl ethers was acting as a catalyst poison during the hydrogenations we also prepared some ethyl ethers.

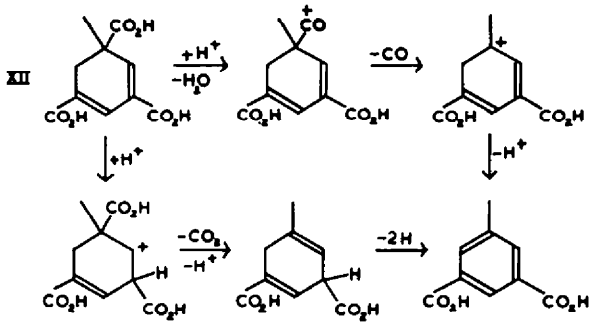
2,6-Dimethylphenol reacted with t-butyl or 1,1-diethylpropyl alcohol in phosphoric acid[14] to give good yields of the phenols (XI; R = t-Bu, R′ = H and XI; R = CEt_3, R′ = H). The latter was shown conclusively to have the required t-alkyl group by its PMR spectrum, the three equivalent ethyl groups giving a triplet at 9·33τ (9 protons) and a quadruplet at 8·41τ (6 protons). Molecular models show that at least one of the ethyl groups must be bent round into the strongly shielding regions on each side of the benzene ring and this presumably accounts for the comparatively wide separation of the methyl and methylene absorptions. Successive methylation, oxidation, and reduction with hydrogenolysis converted the phenols into the required 5-alkylcyclohexane-1,3-dicarboxylic acids. The reductions of the acid (V; R = CEt_3, R′ = OMe) were exceptionally slow. Although the preparation of the 5-t-butylcyclohexane-1,3-dicarboxylic acids by this route was primarily a model for the 1,1-diethylpropyl analogues, the method was not much less convenient than that described earlier.

The synthesis of the 5-methyl-, 5-ethyl-, and 5-isopropylcyclohexane-1,3-dicarboxylic acids were substantially different from one another, and will be discussed separately, but the subsequent interconversions of stereoisomers were similar.

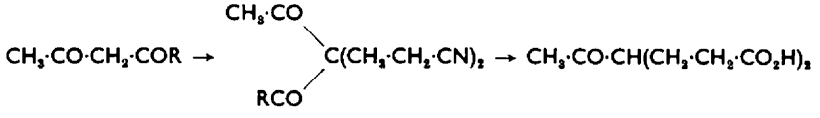
Although 5-methylbenzene-1,3-dicarboxylic acid, uvitic acid, has usually been prepared by partial oxidation of mesitylene, the alkaline self-condensation of pyruvic acid to the acid XII[15] appeared to offer a more convenient route for large scale work. The acid XII has been reported[15] to form uvitic acid when heated with concentrated sulphuric acid, but in our hands this reaction gave an extremely impure product in poor yield and large amounts of sulphur dioxide were evolved. We interpreted this reaction as an acid catalysed decarboxylation followed by oxidation of the acid sensitive intermediate cyclohexadiene; it seemed likely that in stronger acid decarbonylation giving uvitic acid directly would occur. In fact the use of dilute fuming sulphuric acid resulted in a clean reaction at room temperature, although carbon and sulphur dioxides, as well as carbon monoxide, were still detected in the evolved gas. Uvitic acid in alkaline solution was readily reduced over Raney nickel to a mixture of 5-methylcyclohexane-1,3-dicarboxylic acids.

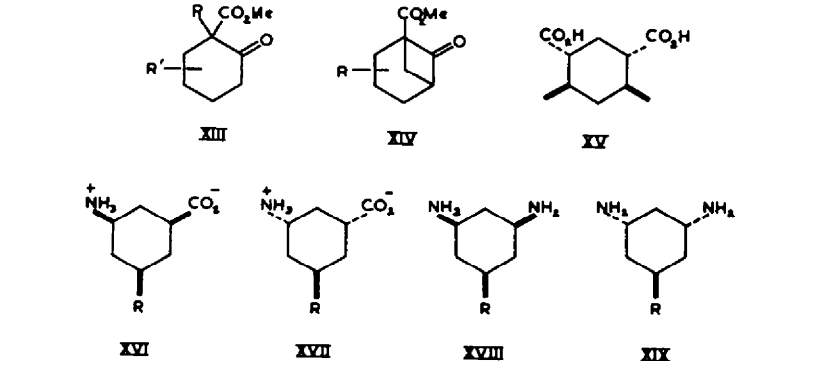
Because the method to be described for the preparation of the 5-isopropyl acids failed for the 5-ethyl analogues, we devised the following method for converting alkyl cyclohexanones into cyclohexane-1,3-dicarboxylic acids. Cyclohexanones are readily converted into the β-oxoesters (XIII; R = H) and we expected that alkylation of such esters with methylene iodide would give the iodomethyl derivatives

[14] A. Tchitchibabine, *C. R. Acad Sci., Paris* **198,** 1239 (1934).
[15] L. Wolff and F. Heip, *Liebigs Ann.* **305,** 135 (1899).



(XIII; R = CH_2I). These iodides are analogous to neopentyl halides and would therefore be unlikely to react further by intermolecular nucleophilic displacement of the iodine. We expected that such compounds would lose a proton from the active methylene group when treated with a strong base such as t-butoxide and that the resulting anion would readily cyclise by intramolecular displacement of the iodine atom to form the 2-oxobicyclo[3,1,1]heptane-1-carboxylic esters (XIV). The four membered ring in the latter should be rapidly and exclusively opened by potassium t-butoxide to esters of the required acids, because the alternative reaction leading to a bicyclo[3,1,1]heptanone and a carbonic ester would contravene Bredt's rule. This synthesis was successfully used in three examples. The 2-oxocyclohexane carboxylic esters (XIII; R = H, R′ = H and XIII; R = H, R′ = *cis*-4,-6-Me_2) were obtained from the corresponding cyclohexanone, dimethyl carbonate and sodium hydride. Methyl 5-ethyl-2-oxocyclohexane carboxylate (XIII; R = H, R′ = 5-Et) was prepared in five steps from acetylacetone and from ethyl acetoacetate:





Although in some experiments the iodomethyl derivatives were isolated, the presumed bicyclic intermediates could not be detected and the best yields (10–12%) of the cyclohexane-1,3-dicarboxylic acids were obtained when no attempt was made to isolate intermediates, the acids (II; R = H, II; R = Et, IV; R = Et and XV (were

separated from other acidic products by conversion to cyclic anhydrides which were distilled and hydrolysed. The acid (XV) has also been prepared by catalytic reduction of 4,6-dimethylbenzene-1,3-dicarboxylic acid.

Although primary and secondary alkyl groups attached to a benzene ring were expected to be rapidly oxidised by alkaline potassium permanganate, we hoped that suitable two and three carbon side chains containing oxygen and stable to potassium permanganate could be introduced into the 5-position in a *m*-xylene derivative, and that after oxidation of the methyl groups to carboxyl groups the longer side chains could be converted into ethyl and isopropyl groups by hydrogenolysis. This scheme was successfully realised for the isopropyl group only. 2-Methoxy- and 2-ethoxy-*m*-xylene were acetylated with acetyl chloride and aluminium chloride. The resulting 4-methoxy and 4-ethoxy-3,5-dimethylacetophenones (XI; R = COMe, R′ = Me and XI; R = COMe, R′ = Et) were converted into the dioxolane (XI; R = —$C(OCHO_2)_2Me$, R′ = Et), having a potential ethyl group, and the tertiary carbinols (XI; R = —CMe_2OH, R′ = Me and XI; R = —CMe_2OH, R′ = Et), having potential isopropyl groups. Under the mildest conditions which would oxidize the aromatic methyl groups, the dioxolane was oxidized to 2-ethoxybenzene-1,3,5-tricarboxylic acid, and this method was not pursued further. The tertiary alcohols (XI; R — CMe_2OH, R′ = Me and XI; R = CMe_2OH, R′ = Et), however, were oxidized to the acids (V; R = CMe_2OH, R′ = Me and V; R = CMe_2OH, R′ = Et), which lost both the nuclear alkoxyl and the side chain hydroxyl groups during hydrogenation over Raney nickel, yielding a mixture of stereoisomers of 5-isopropyl cyclohexane-1,3-dicarboxylic acid.

The interconversion of the acids (II, III and IV) with primary and secondary alkyl groups will now be described together. Simple crystallization of the mixtures of stereoisomers of the acids (II, III and IV) with R = methyl or isopropyl gave in each case one acid only. When heated with acetic anhydride these acids readily formed cyclic anhydrides, from which, in contrast to their 5-t-alkyl analogues, they could be recovered by mild hydrolysis, and so must be *cis* dicarboxylic acids II or IV. Since the dimethyl esters were substantially unchanged by hot methanolic sodium methoxide the acids must be II (R = Me and; R = i-Pr), and the anhydrides VII (R = Me and; R = i-Pr). We had not expected that anhydrides with the conformation (VIIa), with three axial groups on the same side of the ring, would be formed under conditions allowing epimerization, since space-filling models indicated quite severe crowding, but the boat conformation (VIIb) was ruled out by the failure of the acids (II; R = t-alkyl) to form anhydrides without epimerization. These observations were rationalized by supposing that in acetic anhydride solution the anhydrides (VII), provided they can assume the conformation (VIIa), which is possible for primary or secondary 5-alkyl groups, are substantially favoured compared with the epimerizable mixed anhydrides with acetic acid. This reasoning suggested that the formation of the anhydrides (VI) from the acids (II; R = Me or i-Pr) was simply much slower than for the 5-t-alkyl analogues to the extent that the cyclic anhydrides (VII) are favoured compared with the corresponding mixed anhydrides. In practice prolonged heating of the acid (II; R = Me) in acetic anhydride with common basic catalysts gave a liquid mixture of anhydrides (sodium acetate) or tarry products (triethylamine or quinoline, in sealed tubes), but triethylene diamine was both effective as a base and stable to acetic anhydride. The anhydrides (VII) prepared in

this way could not be completely separated from the catalyst and were hydrolysed to the corresponding acids (IV). Pure samples of the anhydrides (VI and VII) were found to be most conveniently prepared by subliming a mixture of the appropriate acid and phosphorus pentoxide. After these methods for preparing and isomerizing anhydrides had been developed for the 5-methyl and 5-isopropyl acids, they were applied to the uncrystallizable mixtures of acids obtained in the synthesis of the 5-ethyl acids described earlier, to give II (R = Et) and IV (R = Et) depending on the conditions used, but the anhydrides (VI; R = Et and VII; R = Et), unlike all the others, could not be obtained solid or free from acid. The PMR spectra of the anhydrides (VI and VII) exhibited relatively large differences. The $C_{(1)}$- and $C_{(3)}$-protons give a band at $7{\cdot}01 \pm 0{\cdot}02\tau$ in the anhydrides (VI; R = Me, i-Pr, or t-Bu) and at $7{\cdot}09\tau$ in the anhydrides (VII; R = Me, or i-Pr), while the absorption due to three protons, which have not been identified, moves from $8{\cdot}5\tau$ in VI (R = Me or i-Pr) to $7{\cdot}9\tau$ in VII (R = Me or i-Pr). These changes are probably due to a change in the conformation of the anhydride ring from chair-like in VI to boat-like in VIIa, with rotation of the carbonyl groups and consequent changes in shielding of the ring protons, in order to avoid in the latter excessively large repulsions between the singly bonded oxygen atom and the axial 5-alkyl group. Models indicate that the planar anhydride group required for maximum resonance stabilisation involves substantial angle strain, as well as oxygen-alkyl repulsions in VIIa.

The acids (II; R = Me and IV; R = Me) were converted into methyl, ethyl and isopropyl esters, only the latter being separable by gas chromatography. The isopropyl esters, but not the methyl esters, of the acids (II; R = Et and IV; R = Et), and both the methyl and the isopropyl esters of the acids (II; R = i-Pr and IV; R = i-Pr) could be separated by gas chromatography. Although the only *trans* acids (III) obtained pure were the acids (III; R = H and III; R = t-Bu), the retention times of the esters of the other *trans* acids were readily obtained by gas chromatographic analysis of the mixtures formed by epimerizing the pure *cis* stereoisomers, from which the *trans* esters were always well separated (Table I in Part II).

Certain of the acids (II and IV) were converted into amino-acids (XVI and XVII) and diamines (XVIII and XIX) by the Schmidt reaction using one or two equivalents of sodium azide respectively. The amino compounds were required for pK_a measurements for comparison with the dissociation constants of the acids (II and IV) in order to elucidate the conformational equilibria in the latter and their anions and esters. The acids (II; R = t-Bu, III; R = t-Bu and IV; R = t-Bu) were also converted into the corresponding dinitriles which were required for dipole moment studies. The dinitriles (VIII; X = Y = CN and IX; X = Y = CN) were prepared by standard methods, but the anhydride (VI; R = t-Bu) resulted from all attempts to convert the acid (IV; R = t-Bu) into an acid chloride. The anhydride (VI; R = t-Bu) reacted with ammonia to give the amidic acid (X; R = CO_2H, R = $CONH_2$) which readily cyclized to the imide (X; X + Y = —CO·NH·CO—); the latter, however, did not react with ammonia to form the diamide. By treating the mixed anhydride (X; X = $CONH_2$, Y = CO·O·CO·OEt) with ammonia, the amidic acid was converted into the diamide and, unexpectedly, the cyano-acid (X; X = CN, Y = CO_2H). The latter was probably formed via an imino-anhydride and again illustrates the very easy ring closure of derivatives of the acid (IV; R = t-Bu).

EXPERIMENTAL

T-alkylation of 2,6-dimethylphenol

2,6-Dimethylphenol (250 g, 2·05 moles), 1,1-diethylpropanol (290 g, 2·5 moles) and phosphoric acid (85%, 820 g) were stirred for 2 days at 80–90°. The mixture was cooled and extracted with light petroleum (b.p. 60–80°) from which 4-(1,1-*diethylpropyl*)2,6-*dimethylphenol* separated in massive prisms (two crops, 323 g, 72%), m.p. 66–67° (Found: C, 81·6; H, 11·0. $C_{15}H_{24}O$ requires: C, 81·8; H, 11·0%). When t-butyl alcohol was used, 2,6-dimethyl-4-t-butylphenol, m.p. 77–80° raised to 80–82° (lit.[16] m.p. 75°) by recrystallization from light petroleum, was obtained in 94% yield.

Preparation of phenolic ethers

In a typical preparation a stirred mixture of 2,6-dimethyl-4-t-butylphenol (160 g, 0·9 mole), sodium hydroxide (56 g) and water (560 ml) was cooled to 10°, treated with dimethyl sulphate (105 g, 1·13 mole) added dropwise during 1 hr, and then heated on a steam bath for 3 hr. The resulting mixture of phenol and ether was treated twice more with alkali and dimethyl sulphate to give 2,6-*dimethyl-4-t-butylphenyl methyl ether* (150 g, 87%), b.p. 104–105°/0·6 mm. (Found: C, 81·0; H, 10·5. $C_{15}H_{24}O$ requires: C, 81·2; H, 10·5%). In similar reactions the repeated treatment with alkali and dialkyl sulphate was only required for phenols containing t-alkyl groups. The other new ethers prepared were 4-(1,1-*diethylpropyl*)2,6-*dimethylphenyl methyl ether* (80%), b.p. 117–119°/2 mm (Found: C, 81·8; H, 11·2. $C_{16}H_{26}O$ requires: C, 82·0; H, 11·2%), and the corresponding *ethyl ether* (80%), b.p. 111–112°/0·8 mm (Found: C, 81·9; H, 11·4. $C_{17}H_{28}O$ requires: C, 82·2; H, 11·4%).

3,5-*Dimethyl-4-ethoxyphenyl methyl ketone*

2,6-Dimethylphenyl ethyl ether (419 g, 2·8 moles) followed by acetyl chloride (230 ml, 2·8 moles) in dry benzene were added dropwise to a stirred suspension of aluminium chloride (375 g, 2·8 moles) in dry benzene (1875 ml) at 5–7°. The mixture was stirred at room temp for 2 hr, poured on ice and conc HCl, and left overnight. The product was isolated with ether and crystallized from light petroleum at −70° to give 3,5-dimethyl-4-ethoxyphenyl methyl ketone (two crops, 437 g, 82%), m.p. 25–30°, raised to m.p. 30–31° by recrystallization. (Found: C, 74·8; H, 8·7; OEt, 23·3. $C_{13}H_{18}O_3$ requires: C, 75·0; H, 8·4; OEt, 23·4%). The *semicarbazone* separated from methanol in colourless plates, m.p. 208–210° (Found: C, 62·9; H, 7·7; N, 17·2; OEt, 18·2. $C_{14}H_{21}O_3N_3$ requires: C, 62·6; H, 7·7; N, 16·9; OEt, 18·1%). Similarly 3,5-*dimethyl-4-methoxyphenyl methyl ketone* (73%), m.p. 39–40° (Found: C, 73·9; H, 7·9; OMe, 17·7. $C_{11}H_{14}O_3$ requires: C, 74·1; H, 7·9; OMe, 17·4%) was prepared from 2,6-dimethylphenyl methyl ether. The *semicarbazone* separated from methanol in colourless plates, m.p. 210–212°. (Found: C, 61·6; H, 7·5; N, 17·7; OMe, 12·9. $C_{12}H_{17}O_3N_3$ requires: C, 61·3; H, 7·3; N, 17·9; OMe, 13·1%).

2-(3,5-*Dimethyl-4-ethoxyphenyl*)2-*methyl*-1,3-*dioxolane*

A mixture of 3,5-dimethyl-4-ethoxyphenyl methyl ketone (40 g), ethylene glycol (16 g), benzene (100 ml) and a crystal of toluene-*p*-sulphonic acid was boiled under reflux using a Dean and Stark water separator for 2 days. The cooled solution was washed ($NaHCO_3$ aq.) dried, and partly evaporated to give 2-(3,5-*dimethyl-4-ethoxyphenyl*)2-*methyl*-1,3-*dioxolane* (two crops, 89%), m.p. 48°. (Found: C, 71·4; H, 8·6. $C_{14}H_{20}O_3$ requires: C, 71·2; H, 8·5%).

2,6-*Dimethyl*-1-*ethoxy*-4-(1-*hydroxy*-1-*methylethyl*) *benzene*

3,5-Dimethyl-4-ethoxyphenyl methyl ketone (450 g, 2·3 moles) was treated with a small excess of MeMgI to give 2,6-*dimethyl*-1-*ethoxy*-4-(1-*hydroxy*-1-*methylethyl*) *benzene* (440 g, 91%), m.p. 50–55°, raised to 57–58° by sublimation at 0·2 mm. (Found: C, 75·0; H, 9·5; OEt, 21·5. $C_{14}H_{22}O_2$ requires: C, 75·0; H, 9·7; OEt, 21·6%). Similarly 3,5-dimethyl-4-methoxyphenyl methyl ketone gave the corresponding tertiary alcohol (98%) as an oil which could not be purified and which was oxidized directly.

Potassium permanganate oxidations

Potassium permanganate (1 kg, 6·3 moles) was added in portions to a *hot* vigorously stirred mixture of 1,3-dimethyl-5-t-butylbenzene (162 g, 1 mole), t-butyl alcohol (800 ml), and water (2 l.)

[16] G. Darzens and H. Rost, *C. R. Acad Sci., Paris* **152**, 607 (1911).

in a 5-l. flask with three reflux condensers, at such a rate as to keep the mixture boiling steadily; any substantial accumulation of $KMnO_4$ led to an uncontrollable reaction. After a further 1 hr boiling on a steam bath any remaining $KMnO_4$ was destroyed with ethanol and the t-butyl alcohol was distilled, without stopping the stirring. The residue was filtered, the manganese oxides were washed several times with hot water, and the filtrate and washings were acidified with conc HCl to give 5-t-butylbenzene-1,3-dicarboxylic acid (194 g, 88%, average of three reactions on this scale), m.p. 335–342°, raised to 340–342° by crystallization from ethanol. Similar oxidations of other *m*-xylene derivatives gave the corresponding acids listed in Table 1, except for the dioxolane [XI; R = $C(OCH_2)_2Me$, R′ = Et] which gave only 2-ethoxybenzene-1,3,5-tricarboxylic acid and unchanged dioxolane even when limited amounts of $KMnO_4$ were used. The t-carbinol acids (V; R = CMe_2OH, R′ = OMe and V; R = CMe_2OH, R′ = OEt) were freely soluble in water and were isolated by extraction with ether.

5-Methylbenzene-1,3-dicarboxylic acid

5-Methylcyclohexa-1,3-diene-1,3,5-tricarboxylic acid (250 g)[16] was added in portions (*c.* 10 g) to a stirred mixture of conc H_2SO_4 (500 ml) and fuming H_2SO_4 (15% SO_3, 750 ml) and stirring was continued for a further ½ hr. The solution was poured onto ice to give 5-methylbenzene-1,3-dicarboxylic acid (150 g, 75%) as a brown solid, m.p. 280–290° (lit.[15] m.p. 298°), which only required treatment with charcoal and Raney nickel before hydrogenation. In preliminary experiments it was found that the temp required for this reaction was higher, and the amount of SO_2 formed was much greater, for lower concentrations of SO_3; the use of ordinary conc H_2SO_4[15] resulted in an extremely impure product.

Catalytic hydrogenations of derivatives of isophthalic acid

A solution of isophthalic acid (460 g, 2·8 moles) and sodium hydroxide (224 g, 5·6 moles) in water (3·5 l.) was heated on a steam bath (1 day) with charcoal (2 g), filtered, treated with Raney nickel (10 g) and sodium hydroxide (20 g), again heated on a steam bath (1 day), and filtered. The resulting solution was reduced with hydrogen (200 atm.) and Raney nickel (W4,[19] freshly prepared, 50 g) for up to 4 days at 180°, filtered and acidified with conc HCl to give a mixture of *cis*- and *trans*-cyclohexane-1,3-dicarboxylic acids (444 g, 93%), m.p. 150–155°, which were separated by Skita and Rössler's method.[20] Under similar conditions 5-amino-, 2-ethoxy-, 5-methoxy-, and 5-nitro-benzene-1,3-dicarboxylic acids gave the same mixture of acids, with complete hydrogenolysis of the 2- or 5-substituent, while 5-hydroxy-benzene-1,3-dicarboxylic acid was reduced to 5-hydroxy-cyclohexane-1,3-dicarboxylic acid.

Hydrogenation of the alkyl substituted derivatives of isophthalic acid increased in difficulty with increase in the size of the alkyl group. The acid (V; R = CEt_3, R′ = OMe) was fully reduced in only three out of ten attempts, even with reaction times of 1 week or more. After one partly successful reduction the acid (V; R = CEt_3, R′ = H), characterized by conversion into the *p-bromophenacyl ester*, m.p. 156–158° (Found: C, 56·2; H, 4·6; Br, 24·4. $C_{31}H_{30}O_6Br_2$ requires: C, 56·5; H, 4·6; Br, 24·3%), was the main product, although it was not obtained pure.

In all cases crystallization of the mixture of stereoisomeric acids (II, III and IV), gave the most stable stereoisomer (II) in 50–60% yield. The residues from the crystallizations were used for the preparation of anhydrides.

Preparation of anhydrides

(a) An acid was sublimed from 2–4 times its weight of phosphorus pentoxide at *c.* 100–150°/0·05 mm, and the resulting anhydride was then sublimed from fresh phosphorus pentoxide to remove the last traces of acid. When pure *cis* dicarboxylic acids were used the anhydrides were obtained in nearly quantitative yields. The *cis* acids with small alkyl groups showed no sign of epimerization but the acid (II; R = t-Bu) gave only the anhydride (VI; R = t-Bu) even under the mildest conditions.

(b) An acid was boiled for ½ hr with about 5 times its weight of acetic anhydride and a catalytic amount of sodium acetate (0·1%), the acetic acid and excess anhydride were removed in a rotary

[19] A. A. Pavlic and H. Adkins, *J. Amer. Chem. Soc.* **66**, 1471 (1946).
[20] A. Skita and R. Rössler, *Ber. Dtsch. Chem. Ges.* **72**, 265 (1939).

TABLE 2. 5-ALKYLCYCLOHEXANE-1,3-DICARBOXYLIC ACIDS AND THEIR DERIVATIVES

Acid	Derivative	M.p. (bp/mm)	Found (%) C	H	Misc.[b,c,f,g]	Formula	Required (%) C	H	Misc.[b,c,f,g]
II; R = Me	*a*	182–183	58·2	7·6	—	$C_9H_{14}O_4$	58·0	7·6	—
	b	138	51·7	4·2	27·6[a]	$C_{25}H_{24}O_6Br_2$	51·7	4·1	27·6[a]
	c	104–107	64·3	6·9	—	$C_9H_{12}O_3$	64·3	7·2	—
	d	(150–154/15)	61·5	8·5	29·0[e]	$C_{11}H_{18}O_4$	61·7	8·5	29·0[e]
	e	(101–102/0·6)	64·1	9·0	37·0[d]	$C_{13}H_{22}O_4$	64·4	9·1	37·2[d]
	f	(106–107/0·5)	66·7	9·4	—	$C_{15}H_{26}O_4$	66·6	9·7	—
IV; R = Me	*a*	213–215	57·8	7·7	—	$C_9H_{14}O_4$	58·0	7·6	—
	b	128–130	51·9	4·1	27·5[a]	$C_{25}H_{24}O_6Br_2$	51·7	4·1	27·6[a]
	c	61–62	64·3	7·1	—	$C_9H_{12}O_3$	64·3	7·2	—
	d	—	61·7	8·3	28·7[e]	$C_{11}H_{18}O_4$	61·7	8·5	29·0[e]
	e	(99–100/0·75)	64·4	9·2	37·0[d]	$C_{13}H_{22}O_4$	64·4	9·1	37·2[d]
	f	(103–104/0·45)	66·8	9·5	—	$C_{15}H_{26}O_4$	66·6	9·7	—
II; R = Et	*a*	135–137	60·0	7·9	—	$C_{10}H_{16}O_4$	60·0	8·0	—
	b	144–145	52·6	4·4	26·9[a]	$C_{26}H_{26}O_6Br_2$	52·5	4·4	26·9[a]
	d	(104–105/0·6)	63·3	8·9	27·1[e]	$C_{12}H_{20}O_4$	63·1	8·8	27·2[d]
	f	(120–122/0·6)	67·6	10·0	—	$C_{16}H_{28}O_4$	67·6	9·9	—
IV; R = Et	*a*	156–157	60·2	7·9	—	$C_{10}H_{16}O_4$	60·0	8·0	—
	b	140–141	52·5	4·4	26·9[a]	$C_{26}H_{26}O_6Br_2$	52·5	4·4	26·9[a]
	d	(106–107/0·7)	63·0	8·7	27·2[e]	$C_{12}H_{20}O_4$	63·1	8·8	27·2[d]
	f	(110–111/0·5)	67·3	9·9	—	$C_{16}H_{28}O_4$	67·6	9·9	—
II; R = i-Pr	*a*	167–169	61·7	8·5	—	$C_{11}H_{18}O_4$	61·7	8·5	—
	b	145–146	53·2	4·7	26·4[a]	$C_{27}H_{28}O_6Br_2$	53·3	4·6	26·3[a]
	c	64–66	67·5	8·5	—	$C_{11}H_{16}O_3$	67·3	8·2	—
	d	(110–112/0·75)	64·5	9·1	25·3[e]	$C_{13}H_{22}O_4$	64·4	9·1	25·6[e]
	f	(132–134/1·0)	68·7	10·2	—	$C_{17}H_{30}O_4$	68·4	10·1	—

IV; R = i-Pr	*a*	189–191	61·5	8·5	—	$C_{11}H_{16}O_4$	61·7	8·5	—
	b	141	53·4	4·5	26·2[s]	$C_{27}H_{28}O_6Br_2$	53·3	4·6	26·3[s]
	c	54–55	67·4	8·2	—	$C_{11}H_{16}O_3$	67·3	8·2	—
	d	(105–106/0·7)	64·2	9·2	25·6[q]	$C_{13}H_{22}O_4$	64·4	9·1	25·6[q]
	f	(128–130/1·0)	68·4	10·2	—	$C_{17}H_{30}O_4$	68·4	10·1	—
II; R = t-Bu	*a*	236–238	63·2	8·5	—	$C_{12}H_{20}O_4$	63·1	8·8	—
	b	110–111	54·2	4·8	25·5[s]	$C_{28}H_{30}O_6Br_2$	54·0	4·9	25·7[s]
	d	(121–123/0·1)	65·6	9·4	24·0[q]	$C_{14}H_{24}O_4$	65·6	9·4	24·2[q]
	e	—	67·8	9·7	32·0[r]	$C_{16}H_{28}O_4$	67·6	9·9	31·7[r]
	g	257–258	63·5	9·9	12·5[p]	$C_{12}H_{22}O_2N_2$	63·7	9·8	12·4[p]
	h	96–98	75·8	9·5	14·6[p]	$C_{12}H_{18}N_2$	75·7	9·5	14·7[p]
	i	69–71	64·2	9·2	13·0[q]	$C_{13}H_{22}O_4$	64·4	9·2	12·8[q]
	j	100–102; 180	55·2	8·3	10·7[q]	$C_{13}H_{23}O_5Na$	55·3	8·2	11·0[q]
III; R = t-Bu	*a*	209–210	63·4	8·6	—	$C_{12}H_{20}O_4$	63·1	8·8	—
	b	147–149	53·8	5·0	25·7[s]	$C_{28}H_{30}O_6Br_2$	54·0	4·9	25·7[s]
	d	(112–114/1·0)	65·5	9·4	24·2[q]	$C_{14}H_{24}O_4$	65·6	9·4	24·2[q]
	e	(119–120/0·7)	67·5	9·7	31·7[r]	$C_{16}H_{28}O_4$	67·6	9·9	31·7[r]
	g	200–201	63·5	9·7	12·1[p]	$C_{12}H_{22}O_2N_2$	63·5	9·7	12·1[p]
	h	65–67	75·5	9·4	14·5[p]	$C_{12}H_{18}N_2$	75·7	9·5	14·7[p]
IX; X = CO_2H, Y = CO_2Me		113–115	64·6	9·5	12·8[q]	$C_{13}H_{22}O_4$	64·4	9·2	12·8[q]
IX; X = CO_2Me, Y = CO_2H		74–75	64·5	9·0	12·8[q]	$C_{13}H_{22}O_4$	64·4	9·2	12·8[q]
IX; X = CO_2H, Y = CO_2 t-Bu		162–165	67·8	9·9	—	$C_{16}H_{28}O_4$	67·6	9·9	—
IX; X = CO_2Me, Y = CO_2 t-Bu		—	68·7	10·0	—	$C_{17}H_{30}O_4$	68·4	10·1	—

TABLE 2 (contd)

Acid	Derivative	M.p. (bp/mm)	Found (%) C	H	Misc.[b,c,d,e,f,g,h,i,k,l,m,n,p,q,r,s]	Formula	Required (%) C	H	Misc.[b,c,d,e,f,g,h,i,k,l,m,n,p,q,r,s]
IV; R = t-Bu	*a*	172–173	63·3	9·1	—	$C_{12}H_{20}O_4$	63·1	8·8	—
	b	138–140	53·8	4·9	26·0[s]	$C_{28}H_{30}O_6Br_2$	54·0	4·9	25·7[s]
	c	123–125	68·4	8·5	—	$C_{12}H_{18}O_3$	68·5	8·6	—
	d	(90/1·0)	65·9	9·5	24·5[q]	$C_{14}H_{24}O_4$	65·6	9·4	24·2[q]
	e	(118–120/1·0)	67·9	9·8	31·5[r]	$C_{16}H_{28}O_4$	67·6	9·9	31·7[r]
	g	229–232	63·4	9·5	12·5[p]	$C_{12}H_{22}O_2N_2$	63·7	9·8	12·4[p]
	h	184–186	75·7	9·2	14·8[p]	$C_{12}H_{18}N_2$	75·7	9·5	14·7[p]
	i	93–94	64·3	9·3	12·8[q]	$C_{13}H_{22}O_4$	64·4	9·2	12·8[q]
	k	190(d)	63·1	9·4	6·2[p]	$C_{13}H_{21}O_3N$	63·4	9·3	6·2[p]
	l	67–69	65·0	9·6	5·8[p]	$C_{13}H_{23}O_2N$	64·7	9·6	5·8[p]
	m	163–164	68·9	9·2	6·7[p]	$C_{13}H_{19}O_2N$	68·9	9·2	6·7[p]
	n	206–207	68·9	9·4	6·5[p]	$C_{13}H_{19}O_2N$	68·9	9·2	6·7[p]
II; R = CMe_2Et	*a*	214–215	64·2	9·4	—	$C_{13}H_{22}O_4$	64·4	9·2	—
	b	109	54·5	5·2	25·4[s]	$C_{29}H_{32}O_6Br_2$	54·7	5·1	25·1[s]
	d	(122–123/0·5)	66·9	9·4	22·7[q]	$C_{15}H_{26}O_4$	66·6	9·7	23·0[q]
IV; R = CMe_2Et	*a*	144–146	64·4	9·3	—	$C_{13}H_{22}O_4$	64·4	9·2	—
	b	115–116	54·5	5·1	25·2[s]	$C_{29}H_{32}O_6Br_2$	54·7	5·1	25·1[s]
	c	70–71	69·3	9·2	—	$C_{13}H_{20}O_3$	69·3	9·0	—
	d	(112–114/0·6)	66·6	9·5	23·2[q]	$C_{15}H_{26}O_4$	66·6	9·7	23·0[q]
II; R = CEt_3	*a*	194–196	66·6	9·7	—	$C_{15}H_{26}O_4$	66·6	9·7	—
	b	99–103	55·9	5·3	24·0[s]	$C_{31}H_{30}O_6Br_2$	56·0	5·5	24·1[s]
IV; R = CEt_3	*a*	162–164	66·9	9·6	—	$C_{15}H_{26}O_4$	66·6	9·7	—
	b	111–112	56·3	5·4	24·1[s]	$C_{31}H_{26}O_6Br_2$	56·0	5·5	24·1[s]
	c	37–38	71·3	9·5	—	$C_{15}H_{24}O_3$	71·4	9·6	—

[a] Free acid; [b] parabromophenacyl ester; [c] anhydride; [d] dimethyl ester; [e] diehtyl ester; [f] di-isopropyl ester; [g] diamide; [h] dinitrile; [i] monomethyl ester; [j] monomethyl ester sodium salt monohydrate; [k] monoamide; [l] monoamide methyl ester; [m] mononitrile; [n] imide; [p] N; [q] OMe; [r] OEt; [s] Br.

evaporator, and the viscous residue was distilled (up to 200°/1 mm) from glass wool into a wide air condenser. The solid or glassy distillate was dissolved in dry chloroform and on adding light petroleum the anhydride crystallized. Although the yields were somewhat lower than by the previous method, this was more convenient for large scale preparations or for impure acids.

Isomerization of cis-5-*alkylcyclohexane*-1,3-*dicarboxylic acids* (II) *into the* trans-5-*alkyl isomers* (IV)

In a typical reaction *cis*-5-isopropylcyclohexane-*cis*-1,3-dicarboxylic acid (5 g), triethylene diamine (Houdry Process Corporation, 0·5 g) and acetic anhydride were boiled (1 day), the acetic acid and excess acetic anhydride were removed in a rotary evaporator, and the residue was vacuum distilled. The distillate was hydrolysed with dil. HCl (25 ml) at 100° for 1 hr to give trans-5-*isopropylcyclohexane*-cis-1,3-*dicarboxylic acid* (4·6 g, 92%), m.p. 180–190°, which crystallized from ethyl acetate in needles, m.p. 189–191°.

Esterification of 5-*alkylcyclohexane*-1,3-*dicarboxylic acids* (Table 2)

All the acids were converted into methyl esters and some into ethyl esters, using pure samples of the acids and dried, distilled ethereal solutions of the appropriate diazoalkane, and the resulting esters required no purification. Isopropyl esters and certain methyl and ethyl esters required in larger amounts were prepared by Fischer–Speier esterification and were purified by distillation.

Monoalkyl and mixed dialkyl esters of the 5-t-*butylcyclohexane*-1,3-*dicarboxylic acids* (Table 2)

(a) *Methyl hydrogen* trans-5-*t-butylcyclohexane*-cis-1,3-*dicarboxylate* (X; X = CO_2H, Y = CO_2Me). The anhydride (VI; R = t-Bu; 0·5 g) was boiled with dry methanol (20 ml) for 2 hr, the excess of methanol was evaporated *in vacuo* and the residue was crystallized from light petroleum to give the ester, m.p. 93–94°.

(b) *Esters of* 5-*t-butylcyclohexane*-trans-1,3-*dicarboxylic acid.* The anhydride (VI; R = t-Bu; 0·5 g) was added to very dry methanolic sodium methoxide (from methanol, 20 ml, and sodium, 1 g) and the resulting solution was refluxed (½ hr), cooled and then acidified with acetic acid (3 ml). Trans-3-*methoxycarbonyl-trans*-5-*t-butylcyclohexane*-1-*carboxylic acid* was isolated with ether and separated from ethyl acetate–light petroleum (b.p. 60–80°) (1:4) in needles (125 mg), m.p. 113–115°. Similarly the anhydride (VI; R = t-Bu) was converted into the *mono-t-butyl ester* (IX; X = CO_2H, Y = CO_2 t-Bu) (44%). This ester with ethereal diazomethane gave the *methyl t-butyl ester* (IX; X = CO_2Me, Y = CO_2 t-Bu) as an undistillable oil which with dry hydrogen chloride gave trans-3-*methoxycarbonyl*-cis-5-*t-butylcyclohexane*-1-*carboxylic acid* (IX; X = CO_2Me, Y = CO_2H) (87%), m.p. 74–75°.

(c) *Methyl hydrogen* cis-5-*t-butylcyclohexane*-cis-1,3-*dicarboxylate* (VIII; X = CO_2H, Y = CO_2Me). A mixture of the dimethyl ester (IIa; R = t-Bu; 12·1 g), sodium hydroxide (1·9 g), water (5 ml) and methanol (40 ml) was left at room temp for 2 months. The methanol was evaporated and on cooling and adding water (15 ml) a fibrous mass of needles (10·1 g), m.p. 90–100°, precipitated and recrystallization from methanol–ethyl acetate (1:2) gave *sodium* cis-3-*methoxycarbonyl*-cis-5-*t-butylcyclohexane*-1-*carboxylate monohydrate*, m.p. 100–102° followed by effervescence and the formation of a porous mass m.p. *c.* 180°. The water of crystallization was not completely removed at temp below which the salt disproportionated. Acidification of the salt or of the mother liquors gave the *monomethyl ester* (VIII; X = CO_2H, Y = CO_2Me), m.p. 69–71° after sublimation at 60°/0·5 mm.

(d) *Methyl ethyl esters.* The four monoethyl esters of the acids (II, III, or IV; R = t-Bu) were converted by diazoethane into the methyl ethyl esters in amounts sufficient to determine gas chromatographic retention times (following paper) but not sufficient for analyses.

Preparation of dinitriles (Table 2)

The dicarboxylic acid (II; R = t-Bu) was converted into the acid chloride with thionyl chloride, and the acid chloride dissolved in dry ether was added to a mixture of liquid ammonia and ether. After the solvents had evaporated the residue was washed with water to leave the diamide (VIII; X = Y = $CONH_2$ 70%), m.p. 240–242°, which separated from methanol–ethyl acetate (1:2) in plates, m.p. 257–258°. The diamide (IX; X = Y = $CONH_2$) was prepared similarly. The anhydride (VI; R = t-Bu; 5 g) was added in small portions with swirling to liquid ammonia (50 ml) and the ammonia was allowed to evaporate. The residual ammonium salt, kept in a vacuum desiccator until no further loss in weight occurred, lost ammonia to give the free *amidic acid* (X; X = CO_2H,

TABLE 3. AMINO-ACIDS AND DIAMINES

Compound	M.p.	Found C	Found H	Found N	Formula	Required C	Required H	Required N
Cis-1,3-diamino-cis-5-methyl-cyclohexane dipicrate monohydrate	240° (dec)	37·9	4·2	18·7	$C_{19}H_{22}O_{14}N_8 \cdot H_2O$	37·8	4·0	18·6
Cis-3-amino-trans-5-isopropylcyclo-hexane-1-carboxylic acid picrate	200–202°	46·3	5·3	13·5	$C_{16}H_{22}O_9N_4$	46·4	5·3	13·5
(VIII; X = Y = NH_2), tetrabenzoyl	205–206°	78·1	6·4	5·1	$C_{38}H_{36}O_4N_2$	77·8	6·5	4·8
(VIII; X = Y = NH_2), dipicrate	260° (dec)	42·1	4·5	18·0	$C_{22}H_{26}O_{14}N_8$	42·0	4·5	17·8
(X; X = Y = NH_2), tetrabenzoyl	206–207°	77·7	6·2	5·1	$C_{38}H_{36}O_4N_2$	77·8	6·5	4·8
(X; X = Y = NH_2), dipicrate	230° (dec)	41·8	4·6	18·0	$C_{22}H_{26}O_{14}N_8$	42·0	4·5	17·8
(VIII; X = NH_2, Y = CO_2H)	>300°	66·5	10·6	6·8	$C_{11}H_{21}O_2N$	66·3	10·6	7·0
(VIII; X = NH_2, Y = CO_2H) picrate monohydrate	98–100°	45·6	6·0	12·7	$C_{17}H_{24}O_9N_4 \cdot H_2O$	45·7	5·9	12·6
(X; X = NH_2, Y = CO_2H)	>300°	66·4	10·8	7·2	$C_{11}H_{21}O_2N$	66·3	10·6	7·0
(X; X = NH_2, Y = CO_2H) picrate	208–210°	47·5	5·7	13·2	$C_{17}H_{24}O_9N_4$	47·7	5·6	13·1

Y = $CONH_2$; 5·4 g, 100%), m.p. 190° (dec), which required no purification. The amidic acid with diazomethane formed a *methyl ester* and with hot acetic anhydride formed an *imide*, which did not react with ammonia.

Methyl chloroformate (3·9 g, 35 mmoles) was added to a solution of the amidic acid (X; X = CO_2H, Y = $CONH_2$; 4·0 g, 17·5 mmoles) and triethylamine (3·6 g, 35 mmoles) in chloroform (50 ml) at −5°, the mixture was stirred for 15 min at −5° and poured into aqueous ammonia (*d.* 0·880, 100 ml). The chloroform layer gave the *diamide* (X; X = Y = $CONH_2$; 0·5 g, 18%) and the aqueous layer gave the *cyano acid* (X; X = CN, Y = CO_2H; 1·2 g, 33%). The diamides were dehydrated with boiling thionyl chloride and the resulting dinitriles were purified by repeated vacuum sublimation.

Preparation of amino-acids and diamines (Table 3)

In a typical reaction *cis*-5-t-butylcyclohexane-*cis*-1,3-dicarboxylic acid (II; R = t-Bu; 11·4 g) was stirred at 45° with conc H_2SO_4 ("AnalaR", 25 ml) and chloroform. Sodium azide (3·6 g, 1·1 equiv.) was added in small portions during 1 hr, and stirring was continued for a further 1½ hr. The mixture was poured on ice, the chloroform was removed by extraction with ether, and the aqueous solution was treated with barium carbonate ("AnalaR", 90 g) until the solution was only slightly acid (pH = 5). The solution was filtered and evaporated to dryness under red. press., and the residue was triturated with water giving cis-3-*amino*-cis-*5-t-butyl-cyclohexane*-1-*carboxylic acid* (9·0 g, 90%), m.p. 360°. The other amino-acids were prepared by the same method in 85–90% yields. For the preparation of diamines the proportion of sodium azide was doubled and the amines were isolated from the dil H_2SO_4 by first removing the chloroform and then making the solution strongly basic and extracting with ether. The amines were in all cases stored as the hygroscopic hydrochlorides but were characterized by their dipicrates and tetrabenzoyl derivatives.

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