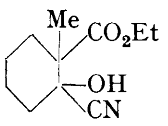
114. *Fused Carbon Rings. Part IX. The Synthesis of Stereoisomeric 1-Methyl*cyclo*hexane-1 : 2-dicarboxylic Acids and of Various Methyl*cyclo*hexanecarboxylicacetic Acids. The Influence of the Angular Methyl Group on the Stability of their Anhydrides.*

By R. P. LINSTEAD and A. F. MILLIDGE.

THE experiments now described were carried out with a view to the preparation of reference substances for the determination of the structure of the dicyclic compounds mentioned in the previous papers. The study of these substances throws some light on the effect of a 1-methyl group on the stability of the *cis*- and the *trans*-forms of cyclic 1 : 2-acids and their anhydrides. The following acids have been prepared :

Acid.	M. p.
cis-1-Methyl*cyclo*hexane-1 : 2-dicarboxylic	160°
trans- ,, ,,	210
cis- ,, -1-carboxylic-2-acetic	175
trans- ,, ,,	164
? *cis*- ,, -2-carboxylic-1-acetic	172
? *trans*- ,, ,,	132
,, ,, -3-acetic (2 forms)	165 and 140

1-Methyl*cyclo*hexane-1 : 2-dicarboxylic acid, closely related in structure to deoxycantharidinic acid, has been synthesised in both forms by a method resembling the Küster synthesis of hæmatinic acid. 2-Methyl*cyclo*hexanone-2-carboxylic ester was converted into the *cyanohydrin* (I), which was unusually stable, in harmony with Lapworth 'and Manske's views on the effect of α-alkylation (J., 1930, 1976). The corresponding *hydroxy-acid* could not be smoothly dehydrated, but Darzens dehydration of the cyanohydrin readily yielded *ethyl* 2-*cyano*-1-*methyl*-Δ^2-cyclo*hexene*-1-*carboxylate* (II). Hydrolysis of this gave 1-*methyl*-Δ^2-cyclo*hexene*-1 : 2-*dicarboxylic acid* (III), the two carboxyl groups of which differed in the expected way. Fischer–Speier esterification yielded the 2-*carbomethoxy*-compound (IV), and partial hydrolysis of the *dimethyl* ester, obtained through the silver salt, the 1-*carbomethoxy*-compound (V).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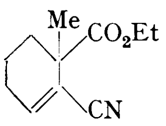
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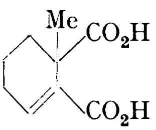
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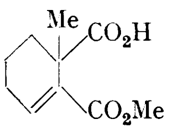
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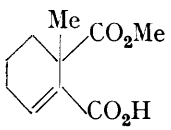
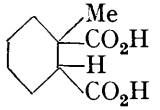
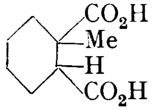

(V.)

The unsaturated cyano-ester (II) was not reduced by aluminium amalgam, but the dimethyl ester of (III) could be reduced catalytically to a mixture of the *cis*- and the *trans*-form of the corresponding saturated ester. Hydrolysis of this yielded a mixture of the acids (VI) and (VII). This was heated with hydrochloric acid at 180°, and fractional crystallisation then yielded the α-acid, m. p. 160°.

Treatment of the mixture of methyl esters with potassium (Hückel and Goth, *Ber.*, 1925, **58**, 447) yielded an ester, which was hydrolysed to an acid, m. p. 200°. Fractional crystallisation of this gave the pure β-acid, m. p. 210°.

(VI.)





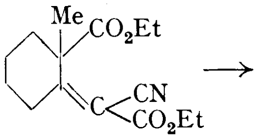
(VII.)

Optical methods cannot be used for the orientation of these acids, which are both racemates. Their configurations are therefore based on analogy and are probable but not certain. The α-form (m. p. 160°) is considered to be the *cis*-acid for the following reasons : (i) There is a general resemblance in properties between the α- and the β-acid and *cis*- and *trans*-hexahydrophthalic acid (m. p.'s 190° and 220°) respectively. The *anhydride* of the α-acid is amorphous and low-melting like that of *cis*-hexahydrophthalic acid, whereas the anhydrides of the β-acid and of *trans*-hexahydrophthalic acid are crystalline and melt at 80° and 140° respectively. (ii) When the anhydride of the α-acid is heated at 240°, it yields 21% of the isomeric anhydride. A similar mixture (30% β-) is obtained by the action of acetic anhydride on the original mixture of acids. By analogy with hexahydrophthalic acid, the acid with the more stable anhydride is the *cis*-form.

The mixture of acids obtained through the equilibration of the esters with potassium contains only 60% of the *trans*-compound, and in comparison with the results of Hückel and Goth (*loc. cit.*) the methyl group has to some extent stabilised the *cis*-form. The action of hydrochloric acid is anomalous : this process usually yields *trans*-acids, but in the present case gives a mixture containing 85% of the *cis*-acid. Ingold (J., 1925, **127**, 398) observed that the conversion of the similarly substituted *cis*-1-methyl*cyclo*propane-1 : 2-dicarboxylic acid into the *trans*-form by hydrochloric acid was only partial. We take the evidence of configuration from the anhydride equilibrium to be more reliable than that from the relative stabilities to hydrochloric acid.

Both forms of 1-methyl*cyclo*hexane-1-carboxylic-2-acetic acid have been synthesised from 2-methyl*cyclo*hexanone-2-carboxylic ester. Owing to the inhibiting effect of the two α-substituents the reactivity of the ketone group is lowered, and it fails to condense with cyanoacetic ester under the usual conditions (Barrett, Cook, and Linstead, J., 1935, 1065). In the course of an investigation which one of us is carrying out with Drs. Newitt and Sapiro of this College, it has been found that this condensation can be effected at very high pressures. An account of this work will follow later. The product of the reaction was of the usual type (VIII) and on reduction with aluminium amalgam and hydrolysis yielded *cis*-1-methyl*cyclo*hexane-1-carboxylic-2-acetic acid (IX), m. p. 174—175°. The *cis*-configuration is assigned to this acid by analogy with previous results; for example, the unsaturated cyano-esters obtained from *cyclo*pentanone-2-acetic ester and *cyclo*hexanone-2-β-propionic ester yield mainly compounds of the *cis*-series by similar treatment (Linstead and Meade, J., 1934, 935; Barrett, Cook, and Linstead, *loc. cit.*). The present acid was identical with that obtained by the oxidation of 8-methyl-2-hydrindanone (preceding papers).

While this work was in progress Chuang, Tien, and Huang (*Ber.*, 1935, **68**, 864) described a 1-methyl*cyclo*hexane-1-carboxylic-2-acetic acid, m. p. 163—164°, obtained from the same keto-ester by the Reformatsky condensation with bromoacetic ester, dehydration of the product to the unsaturated ester (X, or an isomeride), reduction, and hydrolysis. We have confirmed this result. The acid is isomeric and not identical with that of m. p. 174—175°, and is identical with that obtained by Hibbit and Linstead in small quantity by the oxidation of 8-methyl-2-hydrindanone (Part VII). The *trans*-configuration (XI), which follows by exclusion, falls into line with the orientation of *cyclo*pentane-1 : 2-diacetic acid. When this is made from *cyclo*pentanone-2-acetic ester by the Reformatsky route, the product may contain a considerable proportion of *trans*-material (Linstead and Meade, *loc. cit.*; Hückel, Goth, and Demmler, *Ber.*, 1934, **67**, 2102).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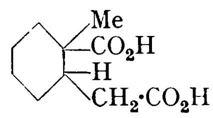
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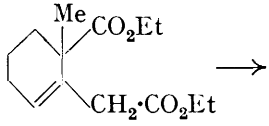
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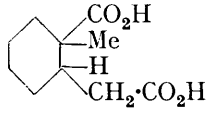
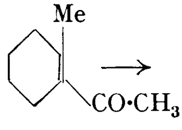

(XI.)

The acids (IX) and (XI) do not appear to be interconvertible by the usual methods, in agreement with the absence of a $>CH{\cdot}CO_2H$ group in the ring.

To consolidate the whole position we have prepared the *cis*- and the *trans*-form of 1-methyl*cyclo*hexane-2-carboxylic-1-acetic acid and two of the four forms of 1-methyl*cyclo*hexane-2-carboxylic-3-acetic acid. While the work was in progress the preparation of one form of the first of these acids was reported by Clemo and Dickenson (J., 1935, 735), who used the method of Ruzicka, Koolhaas, and Wind (*Helv. Chim. Acta*, 1931, **14**, 1161).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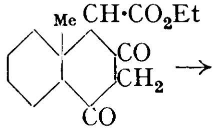
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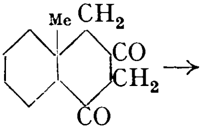
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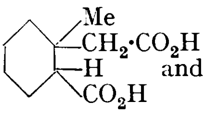
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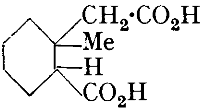
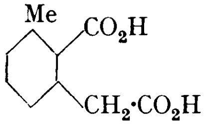

(XVI.)

We found that hypobromite oxidation of the mixture of 9-methyldecalin-2 : 4-diones (XIV), obtained by the hydrolysis of (XIII), yielded a mixture of two acids (XV, XVI), melting at 171—172° and 131—132°, the former of which was isolated by Clemo and Dickenson. These acids are interconvertible and are therefore related as *cis*- and *trans*-isomerides. Clemo and Dickenson rightly point out that Ruzicka's work does not exclude the possibility that in the condensation of acetylmethyl*cyclo*hexene (XII) with sodiomalonic ester a migration of the double bond might precede addition; in which case the diketodecalin derivatives would contain an 8- instead of a 9-methyl group and the acid(s) obtained on oxidation would have formula (XVII). Their experiments on the dehydrogenation of the hydrocarbon derived from (XIV), however, favour the 9-methyl arrangement.

We have confirmed Ruzicka's interpretation of the addition (XII ⟶ XIII) by the synthesis of the higher-melting form of 1-methyl*cyclo*hexane-2-carboxylic-1-acetic acid from its lower homologue by a process corresponding to Haller's synthesis of homocamphoric acid. *cis*-1-Methyl*cyclo*hexane-1 : 2-dicarboxylic acid anhydride was reduced to the corresponding lactone, probably a mixture of (XVIII) and (XIX), by means of sodium and alcohol. The lactone was heated with potassium cyanide, and the acidic product hydrolysed with hydrochloric acid to 1-methyl*cyclo*hexane-2-carboxylic-1-acetic acid, m. p. 172°, identical with that prepared from 9-methyldecalindione.



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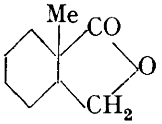

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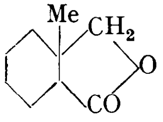

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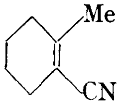

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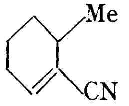

(XXI.)

The fact that the product was a 1-acetic acid (XV or XVI) and not a 2-acetic acid (IX or XI) shows that the lactone which reacted was the form (XIX). Camphoric anhydride yields mainly α-campholide (corresponding to XVIII) on reduction. In view of this it seems probable that our lactone was a mixture of (XVIII) and (XIX), the latter being more reactive towards potassium cyanide. From the work of Hückel *et al.* (*Annalen*, 1934, **514**, 240) the lactones are the *cis*-modifications.

The configurations of the 1-methyl*cyclo*hexane-2-carboxylic-1-acetic acids are uncertain. Clemo and Dickenson (*loc. cit.*) take the 172°-acid to be the *cis*-form, presumably by analogy with the reported oxidation of decalin-1 : 3-dione to *cis*-*cyclo*hexane-1-carboxylic-2-acetic acid (Kon and Qudrat-i-Khuda, J., 1926, 3071). It has been shown, however, that this oxidation actually yields the *trans*-acid (Barrett, Cook, and Linstead, *loc. cit.**). It is known that Ruzicka, Koolhaas, and Wind's diketone (XIV) gave a 9-methyldecalin on Clemmensen reduction, from which the *trans*-isomeride was isolated by fractionation. Our preparations of this diketone yielded on oxidation the 172°- and the 132°-acid in the proportion of about 7 : 3 (the actual ratio was probably nearer equality than this, because the lower-melting acid is harder to isolate). The evidence from this source is thus indecisive, but perhaps favours the *trans*-configuration for the 172°-acid. Other considerations, however, lead to the opposite view. The 172°-acid has been prepared from a *cis*-lactone (although this evidence is rendered less decisive by the high temperature—280°—required for the fission of the lactone ring). When the 172°-acid is heated with hydrochloric acid at 200°, it changes to the extent of 92% into the 132°-acid. Chuang, Ma, and Tien (*Ber.*, 1935, **68**, 1946) have examined the corresponding derivatives of *cyclo*pentane. By the oxidation of an 8-methylhydrindandione (which on general stereochemical grounds should be *cis*-) they obtained a *cis*-1-methyl*cyclo*pentane-2-carboxylic-1-acetic acid, with a stable anhydride. This was converted almost completely into the *trans*-isomeride by hydrochloric acid at 200°. In spite of the anomalous behaviour of 1-methyl*cyclo*hexane-1 : 2-dicarboxylic acid, it is reasonable to suppose that the *cyclo*pentane and the *cyclo*hexane series would behave similarly in this reaction; in which case the 172°-acid would be *cis*-. On the whole we regard this as the more probable configuration.

Both forms of the acid gave anhydrides. When the anhydride of the 172°-acid was heated to 250°, it yielded a mixture containing 55% of its isomeride, which was separated

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* A recent paper by Chuang and Tien (*Ber.*, 1936, **69**, 25) describes the oxidation of pure *trans*-decalin-1 : 3-dione to *trans*-*cyclo*hexane-1-carboxylic-2-acetic acid, but makes no reference to the prior work of Barrett, Cook, and Linstead. Chuang and Tien's experiments indicate that at least a considerable proportion of the primary product in reactions such as (XII ⟶ XIII) has a *cis*-locking of the 6-membered rings. This *cis*-material may subsequently change to *trans*- during hot alkaline hydrolysis (as of XIII ⟶ XIV). This is surprising in view of the fact that the additions are carried out in the presence of sodium ethoxide, which would be expected to yield the stable *trans*-α-decalone system.

into the acids of m. p. 172° and 132°. When the *cis*-acid was heated to 350° with baryta, it yielded anhydride but no ketone, showing that the usual rules hold.

Two forms of 1-*methyl*cyclo*hexane*-2-*carboxylic*-3-*acetic acids* (XVII) were synthesised by the addition of sodiomalonic ester to the unsaturated nitrile obtained by dehydration of 2-methyl*cyclo*hexanone cyanohydrin. This was presumably a mixture of the Δ^1- and the Δ^6-form (XX and XXI), but only the latter reacted and the yield of additive product was small. The reaction is analogous to that studied by Perkin (J., 1896, **69**, 1460), who found that αββ-trimethylacrylic ester did not condense with ethyl sodiomalonate, whereas the isomeric α-*iso*propylacrylic ester reacted. The mixture obtained by hydrolysing the condensation product was separated into two isomeric forms of (XVII). One of these, m. p. 165°, yielded the other, m. p. 140°, when heated with hydrochloric acid at 190°. These acids probably contain the carboxyl group respectively in the *cis*- and the *trans*-position to the acetic acid group, the orientation of the latter to the methyl group being unknown.

As far as can be seen at present, the angular methyl group tends to stabilise the *cis*-forms of *o*-dicyclic systems. This is shown by the following figures :

Acids.	% *cis*-Anhydride at equilibrium.	Reference.
{ *cyclo*Hexane-2-carboxylic-1-acetic	25	Windaus, Hückel, and Reverey, *Ber.*, 1923, **56**, 91.
{ 1-Methyl ,, ,,	*ca.* 50 *	This paper.
{ *cyclo*Pentane-2-carboxylic-1-acetic	86	Cook and Linstead, J., 1934, 956.
{ 1-Methyl ,, ,,	*ca.* 100	Chuang, Ma, and Tien, *loc. cit.*

* Independent of which configuration is finally established.

This also appears in the tendency for the *cis*-form of 9-methyldecalindione (XIV) to persist after alkaline hydrolysis of the keto-ester (XV). The stabilisation of the *cis*-form is in agreement with Hückel's theoretical views (" Fortschritte," 1927, **19**, Heft 4, 61). It is uncertain whether the anhydride equilibrium of the 1-methyl*cyclo*hexane-1 : 2-dicarboxylic acids constitutes an exception to this.

Attempts at the preparation of methyl*cyclo*hexanecarboxylicacetic acids by the addition of butadiene to derivatives of α- and β-methylglutaconic acids were fruitless. The preparation of α-methylglutaconic acid has been improved.

EXPERIMENTAL.

1-*Methyl*cyclo*hexane*-1 : 2-*dicarboxylic Acids*.—Ethyl 2-methyl*cyclo*hexanone-2-carboxylate was prepared in 90—95% yield by the action of methyl iodide on sodio*cyclo*hexanone-2-carboxylic ester in boiling benzene. Hydrogen cyanide from 50 g. of potassium cyanide (Wade and Panting, J., 1898, **73**, 256), cooled in a freezing mixture, was treated with a few drops of potassium cyanide solution and then with 50 g. of the methylated keto-ester in drops. The mixture was kept in ice over-night, the alkali neutralised with sulphuric acid, and the excess of hydrogen cyanide removed by suction. *Ethyl* 1-*cyano*-2-*methyl*cyclo*hexanol*-2-*carboxylate* (I) distilled at 148—149°/12 mm. as a colourless viscous liquid; yield, 90—95% (Found : C, 63·0; H, 8·3. $C_{11}H_{17}O_3N$ requires C, 62·6; H, 8·2%). It suffers very little decomposition on distillation or on standing in glass vessels at room temperature for a few days.

10 G. were shaken in the cold for 3 days with 60 c.c. of concentrated hydrochloric acid. The mixture was then boiled for 24 hours and evaporated to dryness under reduced pressure. The residue was freed from neutral matter by dissolution in aqueous sodium carbonate and extraction with ether, and was then acidified and extracted thoroughly with ether. 2-*Methyl*cyclo*hexanol*-1 : 2-*dicarboxylic acid* was isolated from the extract in 60% yield, m. p. 166—167° after crystallisation from acetone and light petroleum [Found : C, 53·5; H, 6·9; equiv., 102. $C_9H_{14}O_5$ requires C, 53·4; H, 7·0% ; equiv. (dibasic), 101]. The acid slowly decolourises alkaline permanganate. If the preliminary shaking with hydrochloric acid is omitted in the hydrolysis of the cyanohydrin, there is much fission to 2-methyl*cyclo*hexanone and the yield falls to 30%. When the acid was boiled with acetic anhydride, it yielded the anhydride of the acetoxy-acid (m. p. 86—87° ; from light petroleum) which by the action of water or dilute alkali (followed by acidification) yielded 2-*acetoxy*-1-*methyl*cyclo*hexane*-1 : 2-*dicarboxylic acid*. This, crystallised from ethyl acetate and light petroleum, had m. p. 168°, depressed by admixture with the hydroxy-acid [Found : C, 54·4; H, 6·6; equiv., 122·5. $C_{11}H_{16}O_6$ requires C, 54·1; H, 6·6% ; equiv. (dibasic), 122].

To an ice-cold mixture of 42 g. (0·2 mol.) of the cyanohydrin of 2-methyl*cyclo*hexanonecarboxylic ester and 32 g. (0·4 mol.) of dry pyridine, 48 g. (0·4 mol.) of thionyl chloride were slowly added with shaking. White pyridine salts separated and the mixture turned brown. It was heated on the steam-bath for an hour, cooled, treated with ice and hydrochloric acid, and extracted with ether. The extract was filtered, shaken with caustic soda solution and then with water, and dried over sodium sulphate. The residue from the ether yielded a low fraction containing dissolved sulphur, and *ethyl 2-cyano-1-methyl-*Δ^2-cyclo*hexene-1-carboxylate* (II), b. p. 140—141°/9 mm.; yield, 90—95% (Found: C, 68·1; H, 7·7. $C_{11}H_{15}O_2N$ requires C, 68·3; H, 7·8%). This was hydrolysed by boiling with an excess of concentrated hydrochloric acid. The acid (III) separated even while hot and was filtered off after the mixture had been cooled and diluted. Yield, 85—90%.

1-*Methyl-*Δ^2-cyclo*hexene-1 : 2-dicarboxylic acid* (III) is soluble in cold water to about 0·2% and crystallised from water or, better, acetic acid in rhombic prisms, m. p. 229—230° (efferv.) (Found: C, 58·5; H, 6·3. $C_9H_{12}O_4$ requires C, 58·7; H, 6·5%). The *anhydride* was obtained by boiling the acid with acetic anhydride for 2 hours and removing the excess with the aid of the pump. The solid residue formed plates, m. p. 67—68°, from ether–light petroleum (Found: C, 65·2; H, 6·0. $C_9H_{10}O_3$ requires C, 65·0; H, 6·1%). The acid has a tendency to form an acid silver salt and the *disilver* salt was best prepared by slowly adding a neutral solution of the ammonium salt to a stirred excess of silver nitrate solution and continuing the stirring overnight. Even so the salt was somewhat deficient in silver (Found: Ag, 50·8. $C_9H_{10}O_4Ag_2$ requires Ag, 53·8%). The *dimethyl* ester, b. p. 140°/11 mm., was obtained by boiling the silver salt with methyl iodide in ether for 24 hours. It was isolated in the usual manner and freed from a little monoester with sodium carbonate. It could also be prepared by Fischer–Speier esterification for 10 days on the water-bath (Found: C, 62·1; H, 7·5. $C_{11}H_{16}O_4$ requires C, 62·2; H, 7·6%). When the acid (2 g.) was boiled for 3 hours with 50 c.c. of 5% methyl-alcoholic sulphuric acid, it yielded *2-carbomethoxy-1-methyl-*Δ^2-cyclo*hexene-1-carboxylic acid* (IV), isolated by means of ether in the usual manner. This solidified fairly rapidly and formed small plates, m. p. 112—114°, from acetone–light petroleum [Found: C, 60·2; H, 6·9; equiv., 196. $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1%; equiv. (monobasic), 198]. 1·5 G. of the dimethyl ester were refluxed for 3 hours with 0·4 g. of caustic potash in 10 c.c. of aqueous methyl alcohol. The alcohol was removed, water added, and any unchanged di-ester removed with ether. The solution was then acidified and extracted thoroughly with ether. The extract was dried over sodium sulphate, and the solvent removed. The residue of *1-carbomethoxy-1-methyl-*Δ^2-cyclo*hexene-2-carboxylic acid* (V) solidified rapidly and formed a microcrystalline powder, m. p. 119—120°, from acetone–light petroleum (Found: C, 60·3; H, 6·9%; equiv., 197). A mixture of the two isomeric monomethyl esters melted below 100°.

40 G. of the dimethyl ester were hydrogenated in alcoholic solution with 0·3 g. of Adams's catalyst, the theoretical quantity of hydrogen being absorbed in 6 days. The solution was filtered, the solvent removed, and the mixture of saturated esters isolated in almost theoretical yield as a fraction of b. p. 122—129°/9 mm. When this was boiled for 15 hours with concentrated hydrochloric acid, white crystals separated in the hot, and were filtered off from the cooled solution. Yield, almost theoretical; m. p. indefinite, about 170°. 3 G. of the mixture of saturated dimethyl esters were added to 0·5 g. of " molecular " potassium, suspended in 15 c.c. of dry ether. The mixture was refluxed for 10 hours (which appeared to be necessary for the complete formation of the potassio-compound), cooled, and treated with water and dilute acid. The ethereal solution left 1·5 g. of an ester, b. p. 124—126°/10 mm., and there was a considerable high fraction. Hydrolysis of the ester with hydrochloric acid as before gave an acid, m. p. 200°, which by thermal analysis contained 40% of *cis*-acid (see below). This was the richest source of *trans*-material available and after crystallisation from aqueous acetone to constant m. p. gave the pure trans-*acid* (VII) as clusters of small rhombic prisms, m. p. 210°, or 213° if placed in a bath at 150° (Found: C, 57·8; H, 7·5. $C_9H_{14}O_4$ requires C, 58·0; H, 7·6%). The pure acid is practically insoluble in cold water, but is more soluble in the presence of the *cis*-form.

2 G. of the mixture of acids (m. p. *ca.* 170°) were heated at 190° for 15 hours with 10 c.c. of concentrated hydrochloric acid. There was hardly any charring. The separated acid had m. p. 164° and contained 85% of *cis*-acid. (A similar experiment at 180° scarcely affected the mixture.) Fractional crystallisation of the product from water to constant m. p. yielded the cis-*acid* (VI) as clusters of very small, irregular prisms, m. p. 160° * (Found: C, 57·9; H, 7·4%), very slightly soluble in cold water, soluble in hot. Measured volumes of standard solutions of

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* This m. p. is rather indefinite; the acid may still contain some of the *trans*-isomeride.

the two acids were mixed and evaporated to dryness. The m. p.'s of the well-ground solid residues were as follows :

% *cis*-Acid ...	100	90	80	70	60	50	40	30	20	10	0
M. p.	160°	161·5°	165°	189°	195°	198°	200°	203°	205°	207·5°	210°

The m. p. of the lower-melting acid is *not* depressed by admixture with its isomeride. This was also observed with *cis*- and *trans*-*cyclo*pentane-1 : 2-diacetic acid (Barrett and Linstead, J., 1935, 441). The composition of mixtures was determined by comparison.

The pure *trans*-acid was dissolved in an excess of warm acetyl chloride, the excess of reagent removed over caustic potash in a vacuum, and the residual solid trans-*anhydride* crystallised from ether and light petroleum; m. p. 80° (Found : C, 64·0; H, 7·1. $C_9H_{12}O_3$ requires C, 64·2; H, 7·2%). Treatment with dilute alkali, followed by acidification, regenerated the pure *trans*-acid, m. p. and mixed m. p. 210°. The pure *cis*-acid was warmed for an hour with acetic anhydride, the excess of reagent removed, and the product distilled at 144—146°/19 mm. It solidified to an amorphous mass, m. p. 60—65°, and yielded an acid, m. p. 166°, on hydration. Hence this procedure gives an anhydride containing about 80% of the *cis*-form. The anhydride obtained in this way was heated at 240° for an hour, cooled, and treated with aqueous sodium bicarbonate. The solution was decolourised with charcoal, acidified, and evaporated to dryness. The residue was rubbed with water to remove sodium salts, and dried. The acid had m. p. 166—167°, *i.e.*, contained 79% of the *cis*-form. The original mixture of acids (m. p. *ca.* 170°) was similarly treated with acetic anhydride. The product distilled at 132—135°/8 mm., melted at 25—30°, and yielded an acid, m. p. 190° (*ca.* 70% *cis*-), on hydration.

1-*Methyl*cyclo*hexane*-1-*carboxylic*-2-*acetic Acids.*—A mixture of 150 g. of ethyl 2-methyl*cyclo*hexanone-2-carboxylate, 100 g. of cyanoacetic ester, and 10 g. of piperidine gave no condensation product after 4 months at room temperature (cf. Chuang, Tien, and Huang, *loc. cit.*). The *diethyl 2-methyl*cyclo*hexylidene*-1-*cyanoacetate*-2-*carboxylate* (VIII) obtained by the condensation of a similar mixture under high pressure had b. p. 160—165°/1 mm. (Found : C, 64·3; H, 7·3. $C_{15}H_{21}O_4N$ requires C, 64·4; H, 7·6%). It deposited a small amount of solid, forming long needles from aqueous alcohol, m. p. 85—86°. 2·3 G. of the unsaturated ester were reduced for 24 hours with 4 g. of aluminium amalgam in 100 c.c. of moist ether. The product, isolated in the usual way, was hydrolysed, without purification, with boiling hydrochloric acid for 24 hours. The solution, after decoloration with charcoal, deposited *cis*-1-methyl*cyclo*hexane-1-carboxylic-2-acetic acid (IX), which crystallised from very dilute acetic acid in clusters of small rhombic prisms, m. p. 174—175° (Found : C, 60·2; H, 8·1. Calc. for $C_{10}H_{16}O_4$: C, 60·0; H, 8·1%). The acid was insoluble in cold, and only moderately soluble in boiling water.*

The diethyl ester of 1-methyl-Δ^2-*cyclo*hexene-1-carboxylic-2-acetic acid (X) was prepared essentially by Chuang, Tien, and Huang's process (*loc. cit.*) except that magnesium was used in place of zinc in the initial condensation. The corresponding saturated ester, obtained by catalytic hydrogenation in methyl alcohol, had b. p. 120—121°/1 mm., and yielded *trans*-1-methyl*cyclo*hexane-1-carboxylic-2-acetic acid on hydrolysis with boiling concentrated hydrochloric acid; m. p. (crude) 160—161°, 163—164° after recrystallisation from dilute acetic acid, in agreement with the Chinese workers. The acid gave a considerable depression of m. p. when mixed with the isomeride of m. p. 174—175°.

1-*Methyl*cyclo*hexane*-2-*carboxylic*-1-*acetic Acids.*—In the preparation of 1-carbethoxy-9-methyldecalin-2 : 4-dione (XIII) following Ruzicka, Koolhaas, and Wind (*loc. cit.*), most of the unreacted acetylmethyl*cyclo*hexene could be recovered and used for a further condensation. The diketo-ester was isolated as a solid, m. p. 130—131° (cf. Clemo and Dickenson, *loc. cit.*) (Found : C, 66·3; H, 7·8. Calc. for $C_{14}H_{20}O_4$: C, 66·7; H, 8·0%). 20 G. of this were boiled for 24 hours with 75 g. of baryta in 700 c.c. of water. The solution was cooled, acidified, and extracted with ether. The diketone (XIV) was obtained as a glassy resin in 75% yield. To a solution of 10 g. of the diketone in 40 c.c. of 10% aqueous caustic soda, cooled in ice, was added a sodium hypobromite solution made from 25 g. of bromine and 500 c.c. of ice-cold 10% aqueous caustic soda. After an hour at 0°, neutral products were removed by extraction with ether and

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* An attempt was made to prepare this acid from the lactone of 1-methyl*cyclo*hexanol-2-acetic acid by treatment with potassium cyanide, followed by hydrolysis. Ethyl *cyclo*hexanone-2-acetate (Chuang and Ma, *Ber.*, 1935, **68**, 872) yielded the lactone when treated with methylmagnesium iodide in 70% yield (b. p. 140—141°/15 mm.; equiv., 156, calc., 154), but the action of cyanide yielded only tarry material.

the solution was saturated with sulphur dioxide and acidified with dilute sulphuric acid. The excess of sulphur dioxide was removed by warming, and the cooled solution extracted continuously with ether for 48 hours. The extract left a semi-solid product, which was boiled with water (charcoal). On evaporation this solution deposited large crystals, which were recrystallised from water to a constant m. p. of 171·5°, in agreement with Clemo and Dickenson (*loc. cit.*). Yield, 4·4 g. 1-Methyl*cyclo*hexane-2-carboxylic-1-acetic acid (?*cis*-, XV) formed prisms, almost insoluble in cold water, sparingly soluble in hot, but more soluble in the presence of the isomeride described below [Found: C, 60·3; H, 8·3; equiv., 100. Calc. for $C_{10}H_{16}O_4$: C, 60·0; H, 8·1%; equiv. (dibasic), 100]. The mother-liquors from this acid were evaporated to dryness, and the sticky residue boiled with water (charcoal). The filtered solution was cooled and scratched, which caused a white crystalline powder to separate, m. p. 129—130°; yield, 1·95 g. After several crystallisations from water, *1-methyl*cyclo*hexane-2-carboxylic-1-acetic acid* (?*trans*-, XVI) was obtained as a microcrystalline powder, m. p. 131—132° (Found: C, 60·2; H, 7·9%; equiv., 99). The melting points of mixtures of these two acids were as follows:

% *cis*-	100	90	80	70	60	50	40	30	20	10	0
M. p.	171·5°	168·5°	166·5°	165°	160°	157°	153°	150°	147°	142°	131°

By treatment with acetic anhydride and distillation the acids yielded the corresponding anhydrides, from which the unchanged acids could be regenerated. The anhydride from the "*trans*"-acid was a sticky liquid, b. p. 163—165°/19 mm., that from the "*cis*"-, an amorphous solid, m. p. 50°, b. p. 152—154°/19 mm. The anhydride from the "*cis*"-acid was heated at 240—250° for 2 hours, and the acid recovered in the usual way. It had m. p. 154°, corresponding to about 45% of "*cis*"-form. By fractional crystallisation from water it was separated into the original acid and the "*trans*"-acid, m. p. and mixed m. p. 131°. This proves that the acids are stereoisomerides. The "*trans*"-acid was almost unchanged by hydrochloric acid at 190—200° (15 hours), but the "*cis*"-acid yielded an acid, m. p. 140°, containing over 90% of the "*trans*"-form. When the "*cis*"-acid was heated to 350° with 20% of baryta, the "*cis*"-anhydride distilled.

Synthesis from the Lower Homologue (cf. Haller, *Compt. rend.*, 1896, **122**, 146).—A current of hydrogen was bubbled through *cis*-1-methyl*cyclo*hexane-1 : 2-dicarboxylic anhydride maintained at 270°, and thence through a tube containing a nickel catalyst (Rupe *et al.*, *Helv. Chim. Acta*, 1918, **1**, 452; 1920, **3**, 654) at 220—240°. The only product was a hydrocarbon, b. p. 130—140°, probably 1 : 2-dimethyl*cyclo*hexane. A solution of 19 g. of the anhydride in 250 c.c. of alcohol (calcium-dried) was dropped on 30 g. of sodium at such a rate as to keep the alcohol refluxing gently. The mixture was finally heated on the steam-bath until all the sodium had dissolved, 100 c.c. more alcohol being added. The cooled solution was diluted with water, acidified with hydrochloric acid, and extracted with ether. The extract was washed with sodium bicarbonate solution and water and dried, the solvent removed, and the residue distilled; yield, 7·1 g. (40%) of *lactone* (XVIII and XIX), b. p. 129—132°/12 mm. (Found: C, 69·6; H, 9·2; equiv., 152. $C_9H_{14}O_2$ requires C, 70·0; H, 9·1%; equiv., 154). 1·5 G. of the lactone and 2 g. of powdered potassium cyanide (95% single salt) were heated in a sealed tube at 280—290° for 12 hours. The product was dissolved in water, acidified, and extracted with ether. The residue from the ether was purified in the usual manner through sodium bicarbonate solution, and the cyano-acid hydrolysed with 20 c.c. of boiling concentrated hydrochloric acid for 24 hours. The residue was boiled with water (charcoal), filtered, and allowed to crystallise. The crude acid obtained had m. p. 170°, 172° after crystallisation from water, not depressed by admixture with the acid (m. p. 171·5°) prepared from decalindione (Found: equiv., 100·5. Calc., 100).

*1-Methyl*cyclo*hexane-2-carboxylic-3-acetic Acids* (XVII).—The cyanohydrin of 2-methyl*cyclo*hexanone was prepared in the same way as the corresponding derivative of methyl*cyclo*hexanonecarboxylic ester (above). It was obtained as a semi-solid mixture of stereoisomerides, b. p. 122—123°/10 mm. (yield, 80—90%), and was dehydrated by thionyl chloride and pyridine by the method already described but without a solvent; yield of tetrahydro-*o*-toluonitrile (XX and XXI) 80%, b. p. 85—86°/10 mm. When benzene was used as a solvent, the dehydration was far from complete. To a cold solution of 15 g. of sodium in 220 c.c. of alcohol were added 50 g. of ethyl malonate, followed by 40 g. of this nitrile. After 4 days at room temperature the mixture was worked up in the usual way. Distillation yielded much unchanged nitrile and 4·5 g. of *diethyl 2-cyano-1-methyl*cyclo*hexane-3-malonate*, b. p. 180—188°/11 mm. (Found: C, 63·7; H, 8·7. $C_{15}H_{23}O_4N$ requires C, 64·0; H, 8·3%). Hydrolysis with boiling hydrochloric acid for 24 hours in the usual manner yielded a mixture of acids, m. p. 140—150°, with the correct equivalent. After several crystallisations from water this was separated into "*cis*"-1-*methyl*cyclo*hexane-2-carboxylic-3-acetic acid*, plates, m. p. 164—165° (Found: C, 59·8; H, 7·7; equiv., 99·5. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·1%; equiv., 100), and the more soluble "trans"-*isomeride*, a fine crystalline powder, m. p. 138—140° (Found: C, 59·9; H, 7·9%; equiv., 99·2). The barium salt of the "*cis*"-acid was fairly soluble, that of the "*trans*"-acid insoluble, in alcohol. When the acid of m. p. 164—165° was heated with hydrochloric acid at 200° for 12 hours, it yielded the acid of m. p. 138—140°.

Four of the isomeric carboxyacetic acids derived from methyl*cyclo*hexane have similar m. p.'s. These are the *cis*-1-carboxylic-2-acetic (175°), *trans*-1-carboxylic-2-acetic (164°), ?*cis*-2-carboxylic-1-acetic (172°), and ?*cis*-2-carboxylic-3-acetic (165°) acids. These acids depress each other's m. p.'s, which confirms their individuality. The same is true of the ?*trans*-2-carboxylic-1-acetic (132°) and ?*trans*-2-carboxylic-3-acetic (140°) acids.

Attempted Diene Condensations with Derivatives of Methylglutaconic Acids.—The following method for the preparation of α-methylglutaconic acid, based on the work of Thole and Thorpe (J., 1911, **99**, 2196), gave much more satisfactory results than those in the literature. Ethyl αγ-dicarbethoxy-α-methylglutaconate (Thole and Thorpe, *loc. cit.*) was hydrolysed and decarboxylated in two stages. A solution of 86 g. (0·25 mol.) of the ester in 65 c.c. of alcohol was added to sodium ethoxide prepared from 6 g. of sodium and 75 c.c. of alcohol. After an hour at room temperature, the product was poured into a solution of 85 g. (1·5 mols.) of caustic potash in 90 c.c. of alcohol and 30 c.c. of water. The mixture was rapidly cooled to take up the heat of reaction, and was left for 10 days at room temperature. The semi-solid mass was dissolved in water, alcohol was removed by suction, and unchanged ester by ether extraction. The solution was then cooled in ice and made strongly acid, carbon dioxide being evolved. The solution was extracted thoroughly with ether, the extract dried with sodium sulphate, and the solvent removed. The residue, a rather sticky solid, when rubbed with dry ether gave the pure high-melting form of α-methylglutaconic acid as a crystalline powder, m. p. 144—145° (cf. Feist and Pomme, *Annalen*, 1909, **370**, 61; Thole and Thorpe, *loc. cit.*). Yield, 19·5 g. (56%). A further small quantity was recovered from the ethereal washings. The *dimethyl* ester was obtained by the action of 10% methyl-alcoholic sulphuric acid at room temperature for 3 days; b. p. 117°/13 mm. (Found: C, 55·7; H, 6·8. $C_8H_{12}O_4$ requires C, 55·8; H, 7·0%).

β-Methylglutaconic acid was obtained from ethyl *iso*dehydracetate by hot alkaline hydrolysis (Feist, *Annalen*, 1906, **345**, 69; Goss, Ingold, and Thorpe, J., 1923, **123**, 348) in 90% yield; m. p. 114—115°. The *dimethyl* ester was prepared through the silver salt or by cold esterification with 10% methyl-alcoholic sulphuric acid; b. p. 109—110°/12 mm. (Found: C, 56·0; H, 6·9%). The enolic anhydride (Bland and Thorpe, J., 1912, **101**, 865) had m. p. 90°.

Butadiene was isolated from "railway hydrocarbon" by the method of Birch (*J. Ind. Eng. Chem.*, 1928, **20**, 474) as the tetrabromide and was regenerated by Thiele's method (*Annalen*, 1899, **308**, 337). A special apparatus was used in which the tetrabromide was continuously extracted by hot alcohol and the extract boiled with zinc dust. The butadiene was freed from alcohol by a water condenser and calcium chloride tube and was condensed in the reaction vessel. The diene from 20 g. of tetrabromide, 4·5 g. of β-methylglutaconic anhydride, and 7 c.c. of benzene were heated at 150° for 3 days. The anhydride was recovered unchanged. Similar experiments with the dimethyl esters of α- and β-methylglutaconic acids gave an amount of condensation product insufficient for examination. The bulk of the ester was recovered and some rubber-like substance was produced.

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