497. *Synthetical Studies on Terpenoids. Part X.*[1] * *Stereospecific Syntheses of (±)-Clovan-9-one and (±)-Clovane*

By Anil Kumar Kundu, Nitya Gopal Kundu, and
Phanindra Chandra Dutta

Stereospecific syntheses of (±)-clovan-9-one and (±)-clovane have been described and their structural and stereochemical identity has been established with the corresponding products from natural sources by infrared studies.

Caryophyllene and isocaryophyllene, because of the presence of an interesting ring-system in their molecular framework, undergo under acidic conditions varied types of rearrangements, characteristic of medium-sized rings. Caryophyllene under mild acid treatment[2] affords caryolan-1-ol (I) and clovene (II), whereas under vigorous acid treatment[3] isoclovene (III) and ψ-clovene (IV) are formed. The tendency to undergo molecular rearrangement is not confined to hydrocarbons but is found also in their derivatives. Thus, caryophyllene monoxide, on acid treatment, affords clovan-2β,9α-diol (V) and this has been converted into the ketone (VI).[2b] On Wolff–Kishner reduction of the diketone corresponding to the diol, clovane (VII) was obtained and shown to be identical with the hydrocarbon available from catalytic reduction of clovene.[2] Recently, two additional carbonyl compounds (VIII) and (IX) along with the glycol (V) have been isolated[4] from the reaction mixture and the salient structural features of these two interesting compounds have been fully established.

Synthetical studies have of late been undertaken in this field with remarkable success, resulting in the total syntheses[5] of caryophyllenes. In addition, Raphael has disclosed the total synthesis[6] of clovene. Experiments were also initiated in this laboratory for the synthesis of the ring system present in clovene and a preliminary Communication[7] covering some aspects of this attempt has already appeared.

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* Presented by one of us (P. C. D.) in seminars, held on July 7—10, 1964, at Ecole Polytechnique, Paris, France.

[1] Part IX, S. L. Mukherjee and P. C. Dutta, *J.*, 1964, 3554.

[2] (*a*) An excellent review of recent investigations on caryophyllenes is included in J. Simonsen's "The Terpenes," 2nd edn., Cambridge University Press, 1951, vol. III, p. 39; 1957, vol. V, p. 517; (*b*) A. Aebi, D. H. R. Barton, and A. S. Lindsey, *J.*, 1953, 3124.

[3] T. G. Halsall and D. W. Theobald, *Quart. Rev.*, 1962, **16**, 101.

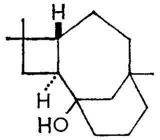
[4] E. W. Warnhoff, Abstract: International Symposium on the Chemistry of Natural Products, Kyoto, Japan, 1964, p. 16.

[5] E. J. Corey, R. B. Mitra, and H. Uda, *J. Amer. Chem. Soc.*, 1964, **86**, 485.

[6] P. Doyle, I. R. Maclean, W. Parker, and R. A. Raphael, *Proc. Chem. Soc.*, 1963, 239.

[7] N. G. Kundu, S. L. Mukherjee, and P. C. Dutta, *Tetrahedron Letters*, 1962, 627.

Two approaches to the building up of the tricarbocyclic ring-system present in clovene can be envisaged. First the bridged structure comprising A and C may be developed followed by attachment of ring B. This approach has been successfully utilised by Raphael (*loc. cit.*). Alternatively, the hydrindane system with appropriate functional groups may be constructed and the bridged structure may subsequently be added. The former approach was at first undertaken and, with that end in view, diethyl 1-methyl-4-oxocyclohexane-1,3-dicarboxylate (X)[8] was treated with ethyl acrylate according to Michael's procedure, affording ethyl β-(1,5-diethoxycarbonyl-5-methyl-2-oxocyclohexyl)propionate (XI) in excellent yield. This was next converted into the ethylenedioxy-compound (XII) and the resulting material was subjected to Dieckmann cyclisation. A crystalline material, m. p. 167°, was isolated along with a liquid product, the latter affording a strong bluish-violet coloration with ferric chloride. The products could not be definitely characterised and the scheme was not pursued further.



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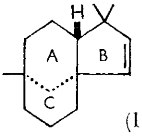

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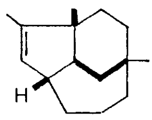

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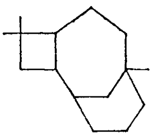

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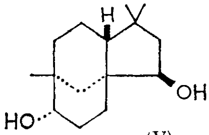

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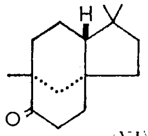

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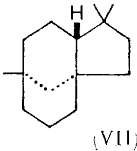

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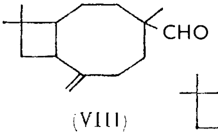

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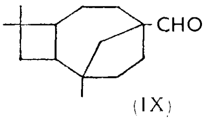

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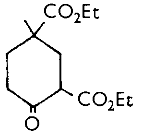
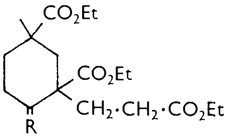


(X)



(XI : R = O)

(XII : R = $-O\cdot C_2H_4\cdot O-$)

In an alternative approach, 1-methyl-3-oxocyclohexyl cyanide[9] (XIII) was condensed with ethyl cyanoacetate according to Cope; the resulting unsaturated cyano-ester (XIV) took up elements of hydrogen cyanide readily with the concomitant elimination[10] of the ester group, affording the trinitrile (XV). This was hydrolysed by heating under reflux with hydrochloric acid to the corresponding tricarboxylic acid (XVa) which, in turn, was esterified with ethereal diazomethane to afford the trimethyl ester (XVb). The trimethyl ester was partially hydrolysed to the monobasic acid (XVc) which, on treatment with oxalyl chloride, afforded the corresponding acid chloride. This was treated with ethereal diazomethane in the cold. The resulting crystalline diazo-ketone (XVd) on Arndt–Eistert homologation afforded methyl β-(1,3-dimethoxycarbonyl-3-methylcyclohexyl)-propionate (XVe). The compound was heated under reflux with potassium t-butoxide in benzene, and a low boiling product was isolated along with a high boiling one. The former, on hydrolysis, afforded an acid, m. p. 155°, which from elemental analyses appeared to be methylcyclohexane-1,3-dicarboxylic acid, whereas the latter gave rise to an acid, m. p. 232—233°, which was not definitely characterised. It is quite evident that the propionic acid chain in compound (XVe) is not in *cis*-relationship with the 1-methoxycarbonyl group and compound (XVI) is produced by the reverse Michael addition.

In order to substantiate further the proposed stereochemistry of compound (XV), the

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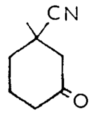
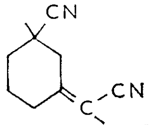
[8] M. Rubin and H. Wishinsky, *J. Amer. Chem. Soc.*, 1946, **68**, 338.

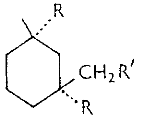
[9] N. K. Chakravarty and D. K. Banerjee, *J. Indian Chem. Soc.*, 1946, **23**, 377.

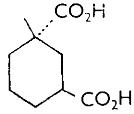
[10] J. Harley-Mason and A. H. Jackson, *J.*, 1954, 3651.

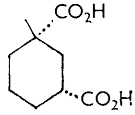
silver salt of the acid (XVc) was refluxed with bromine in carbon tetrachloride[11] to afford dimethyl 1-bromomethyl-3-methylcyclohexane-1,3-dicarboxylate (XVII) from which bromine was removed with zinc dust in acetic acid. Dimethyl 1,3-dimethylcyclohexane-1,3-dicarboxylate (XVIIa) was hydrolysed to 1,3-dimethylcyclohexane-1,3-dicarboxylic acid (XVIII), shown to be a *cis*-dicarboxylic acid by its ready conversion into the anhydride (XIX) by heating with acetic anhydride. This definitely proves that, during the addition of hydrogen cyanide to compound (XIV), the incoming cyano-radical approaches the molecule from the side of the existing cyano-group resulting in a *cis*-relationship of the methyl and acetonitrile chain in (XV). The complete stereospecificity in the cyanide addition is probably governed by the much smaller volume of the *sp*-hybridised cyano-group occupying an axial conformation in comparison with that of *sp*^{3}-methyl. This is also evident from their " A " values.[12] Moreover, from stereoelectronic considerations, the cyanide ion should attack the double bond from a direction perpendicular to the plane of the conjugated system and from the sterically less-hindered side, as this process is closely akin to Michael addition.[13]

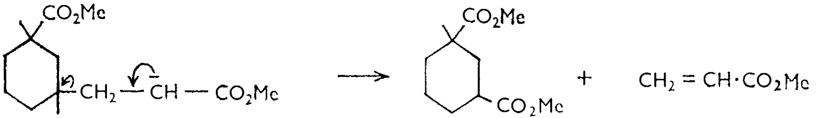

(XIII)


(XIV)

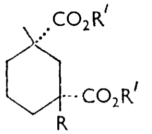

(XV; R = R = CN)
(XVa; R = R' = CO_2H)
(XVb: R = R' = CO_2Me)
(XVc; R = CO_2Me, R' = CO_2H)
(XVd; R = CO_2Me, R' = $COCHN_2$)
(XVe; R = CO_2Me, R' = CH_2CO_2Me)

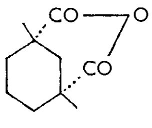

(XVIa)


(XVIb)


(XVI)

(XVII : R = CH_2Br, R' = Me)
(XVIIa : R = R' = Me)
(XVIII : R = Me, R' = H)




(XIX)

In view of the unpromising results so far obtained in connection with the development of the bridged-ring moiety present in clovene, the synthesis of the tricarbocyclic ring-system was attempted from a bicyclic system, the alternative approach suggested earlier. This appeared to be more encouraging in view of the successful results already achieved in related systems in this laboratory.[14] The bicyclic ketone (XXIII) seemed to be a promising intermediate for this purpose and this was successfully synthesised as follows. Ethyl α-cyano-β-*p*-methoxyphenylcrotonate (XX) was obtained in good yield (see Experimental section) although for obvious reasons no attempt was made to separate the two isomers, probably geometric, in crystalline forms.[15] The conjugate addition of methylmagnesium iodide[16] was effected in the presence of cuprous iodide and the resulting product (XXI) on

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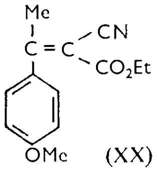
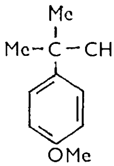
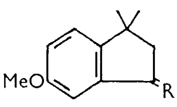
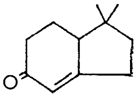
[11] H. Hunsdiecker and C. Hunsdiecker, *Ber.*, 1942, **75B**, 291; R. G. Johnson and R. K. Ingham, *Chem. Rev.*, 1956, **56**, 219.
[12] N. L. Allinger and W. Szkrybalo, *J. Org. Chem.*, 1962, **27**, 4601.
[13] H. O. House and H. W. Thompson, *J. Org. Chem.*, 1963, **28**, 360.
[14] N. G. Kundu and P. C. Dutta, *J.*, 1962, 533.
[15] W. Baker, J. F. W. McOmie, and A. S. Weaving, *J.*, 1956, 2018.
[16] A. J. Birch and R. Robinson, *J.*, 1943, 501; W. Parker and R. A. Raphael, *J.*, 1955, 1723.

subsequent purification with a solution of potassium cyanide did not show any ultraviolet absorption in the 320—322 mμ region. This, on mild hydrolysis followed by decarboxylation, afforded the nitrile (XXIa) whereas alkaline hydrolysis under drastic conditions and subsequent decarboxylation resulted in the formation of β-methyl-β-*p*-methoxyphenylbutyric acid (XXIb). This was cyclised with polyphosphoric acid[17] to the indanone (XXII). The reduction of the ketone to the corresponding hydrocarbon in good yield, along with a high-boiling residue, was effected by hydrogenation[18] in the presence of a catalytic amount of perchloric acid. The aromatic ring of the indane (XXIIa) was again reduced with sodium in liquid ammonia[19] and the resulting product was hydrolysed with dilute sulphuric acid, whereupon the αβ-unsaturated ketone (XXIII) having characteristic spectral properties was obtained in a satisfactory yield.


(XX)


(XXI: R = CN, R′ = CO_2Et)
(XXIa: R = CN, R′ = H)
(XXIb: R = CO_2H, R′ = H)


(XXII: R = O)
(XXIIa: R = H_2)


(XXIII)

Conjugate addition of hydrogen cyanide under acidic conditions completely failed in the case of the αβ-unsaturated ketone (XXIII) though excellent results[14] were obtained with $\Delta^{1,9}$-octahydronaphthalen-2-one (XXIV) under identical conditions. However, when compound (XXIII) was refluxed with an aqueous ethanolic solution of potassium cyanide and subsequently hydrolysed with alkali, an acidic material was isolated in satisfactory yield. On esterification with ethereal diazomethane, this afforded a liquid which analysed well for compound (XXV). Evidently, conjugate addition of hydrogen cyanide followed by 1,2-addition at the carbonyl function had taken place. Structure (XXV) was further confirmed by converting it into the chloro-compound (XXVa) and finally into compound (XXVb) by boiling with zinc dust in acetic acid. Addition of two molecules of hydrogen cyanide was also observed with the $\Delta^{1,9}$-one (XXIV) and with 3-methylcyclohex-2-enone (XXVI). The $\Delta^{1,9}$-one, under identical conditions, afforded a mixture of the lactone (XXVII) and the hydroxydicarboxylic ester (XXVIII) as revealed by infrared studies and elemental analyses. The mixture was subsequently converted into compound (XXVIIIa) by treatment with phosphorus oxychloride in pyridine followed by refluxing with zinc dust in acetic acid. The slightly low analytical values for carbon and hydrogen can be attributed to the presence of traces of the lactone (XXVII). 3-Methylcyclohex-2-enone (XXVI) predominantly gave the hydroxydicarboxylic ester (XXIX) together with a small percentage of the corresponding lactonic ester, as is evident from elemental analyses and from infrared studies. It was next converted into the unsaturated diester (XXIXa) by treatment with phosphorus oxychloride in pyridine. On catalytic hydrogenation, the saturated diester (XXIXb) was obtained. It was subsequently hydrolysed to the dicarboxylic acid (XVIb), m. p. 200—201°, by heating under reflux with potassium hydroxide in diethylene glycol. The acid, m. p. 200—201°, belongs to the *cis*-series as is evident from its ready conversion into the anhydride on being heated with acetic anhydride. The acid is regenerated when the anhydride is warmed with dilute sodium hydroxide solution and then acidified with dilute hydrochloric acid. Evidently, the acid (XVIa) melting at 155°, described earlier, should be the *trans*-isomer. To substantiate this point the dimethyl ester corresponding to the acid of m. p. 200—201°, was equilibrated by being heated under reflux with sodium methoxide in methanol for a prolonged period. Subsequent alkaline hydrolysis afforded

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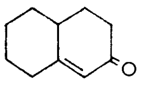
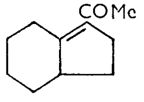
[17] S. Dev, *J. Indian Chem. Soc.*, 1955, **32**, 255.

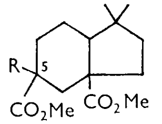
[18] K. W. Rosenmund and E. Karg, *Ber.*, 1942, **75**, 1850; W. S. Johnson, R. G. Christiansen, and R. E. Ireland, *J. Amer. Chem. Soc.*, 1957, **79**, 1995.

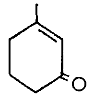
[19] A. J. Birch, *Quart. Rev.*, 1950, **4**, 69.

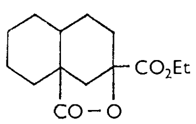
the acid (XVIa), m. p. 153—155° alone or mixed with the sample described earlier. After repeated crystallisation of the same acid, the melting point rose to 200—201° and showed no depression in mixed melting point with the original *cis*-acid, m. p. 200—201°. From the mother-liquor, a few crystals of the acid, m. p. 155°, could be isolated and this was found to exert considerable depression in mixed melting point with the acid, m. p. 200—201°. From the above experiments it is clear that equilibration gives a mixture of *cis*- and *trans*-acids and the higher-melting one is the pure *cis*-isomer (XVIb). The lower melting one may be the pure *trans*-acid (XVIa) or a eutectic mixture containing an unknown proportion of the *cis*-acid.

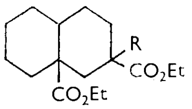

(XXIV)

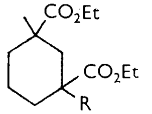

(XXIVa)

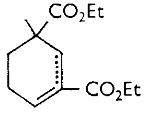

(XXV : R = OH)
(XXVa : R = Cl)
(XXVb : R = H)


(XXVI)

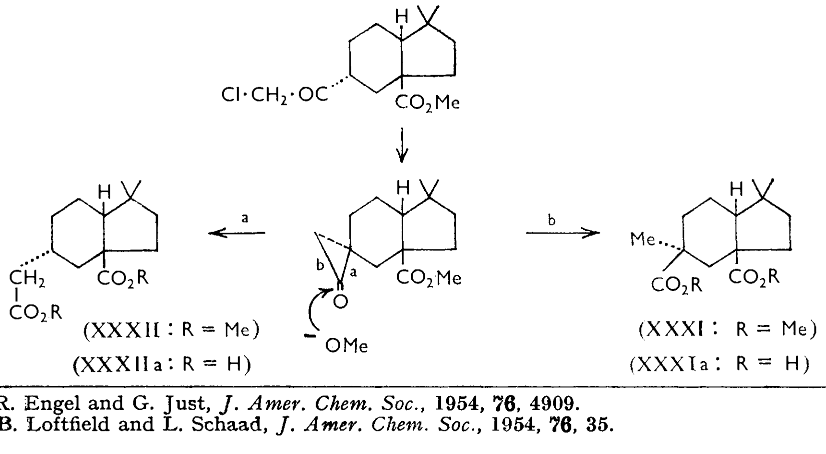

(XXVII)


(XXVIII : R = OH)
(XXVIIIa : R = H)


(XXIX : R = OH)
(XXIXb : R = H)


(XXIXa)

Returning to the bicyclic system an attempt was next made to introduce the methyl group at the 5-position in compound (XXVb). This was hydrolysed to the acid ester (XXX) and this was further characterised through the anilide. This was converted into the acid chloride (XXXa), then into the diazo-ketone (XXXb) with an excess of diazomethane, and finally into the chloro-ketone (XXXc) with dry hydrogen chloride.[20] This was subjected to Favorskii rearrangement [21] in the presence of sodium methoxide in methanol and the desired diester (XXXI) isolated in extremely poor yield, the major product being the isomeric diester (XXXII). The diacid (XXXIa), obtained on drastic alkaline hydrolysis of (XXXI), was treated with acetic anhydride. Formation of the anhydride (XXXV) having infrared absorption at 5·56 and 5·68 μ, characteristic of the glutaric anhydride system, showed that the two carboxyl groups are *cis*-oriented. Failure to isolate any other isomeric diacid strongly points to the validity of the arguments advanced above. Attempts to cyclise the isomeric diester (XXXII), according to the Dieckmann procedure did not succeed and revealed that the acetic acid chain is in *trans*-orientation with respect to the angular ester group. The formation of the above two isomeric diesters and their stereochemical assignment can be explained by the following Scheme: [21]


(XXXII : R = Me)
(XXXIIa : R = H)
(XXXI : R = Me)
(XXXIa : R = H)

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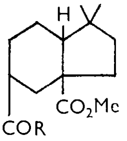
[20] C. R. Engel and G. Just, *J. Amer. Chem. Soc.*, 1954, **76**, 4909.
[21] R. B. Loftfield and L. Schaad, *J. Amer. Chem. Soc.*, 1954, **76**, 35.

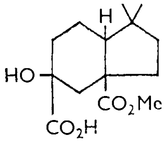
The formation of desired product (XXXI) in only about 5% yield evidently through fission of bond b, and of compound (XXXII) in about 35% yield from rupture of a, arises from the presence of powerful 1 : 3-diaxial interaction in compound (XXXI), although with chloromethyl cyclohexyl ketone, formation of a compound analogous to (XXXII) has not been observed.[21]

As all the asymmetric centres of the clovene molecule are present in compound (XXXI), it is now pertinent to discuss the stereochemistry of the ring-junction. It will necessarily be *cis* because of the presence of the hydrindane system,[22] although the presence of a *trans*-system to an appreciable extent has recently been established.[23] In the present case, the ring-junction has been developed through conjugate addition of hydrocyanic acid evidently under reversible conditions, in contrast to the similar addition process in the case of the compound (XXIVa) according to the kinetically controlled mechanism, leading to the formation of all four isomers in different amounts.[24]

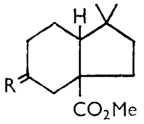
Various attempts were made to obtain the compound in better yield, with the methyl group in the hydrindane system at the proper position, and with desired stereochemistry. In the course of one of the attempts, the chloro-ketone (XXXc) was converted into the methyl ketone (XXXd) by treatment with zinc and acetic acid. The reactive methyl group of (XXXd) was blocked with n-hexanethiol through its formyl derivative [25] and the resulting compound, on treatment with potassium t-butoxide and methyl iodide, afforded no useful product. In another unsuccessful attempt the hydroxy-diester (XXV) was converted into the hydroxy-acid ester (XXXIII), followed by oxidation with lead tetra-acetate [26] to the keto-ester (XXXIV). Condensation of the keto-ester with ethyl cyanoacetate, according to Cope, afforded the corresponding unsaturated cyano-ester (XXXIVa). The conjugate addition of methylmagnesium iodide in the presence of cuprous iodide [16] completely failed, apparently owing to steric reasons.[13,27] An attempt to methylate the diester (XXVb) directly with potassium t-butoxide in benzene and methyl iodide was also unsuccessful. However, a very elegant preparation of compound (XXXI) in an excellent yield was finally developed, *i.e.*, methylation of compound (XXVb) with triphenylmethylsodium [28] and methyl iodide. The identity of the product was established by hydrolysis to the diacid (XXXIa), m. p. 172—173°. The approach of the methyl group during methylation of compound (XXVb) evidently took place from the sterically favoured equatorial position, resulting in the desired stereochemistry in compound (XXXI).



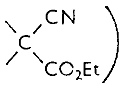
(XXX : R = OH)
(XXXa : R = Cl)
(XXXb : R = CHN$_2$)
(XXXc : R = CH$_2$Cl)
(XXXd : R = Me)



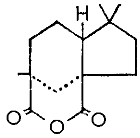
(XXXIII)



(XXXIV : R = O)



(XXXIVa : R = $>C(CN)CO_2Et$)

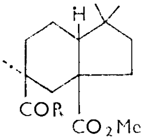


(XXXV)

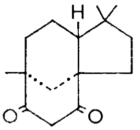
Ring c could now be built up along well-trodden paths successfully exploited by Stork in the synthesis of cedrol.[29] The methylated diester (XXXI), on partial saponification afforded the acid ester (XXXVI), characterised further through the anilide. Although both

[22] W. Hückel, M. Sachs, I. Yantschulewitsch, and F. Nerdel, *Annalen*, 1935, **518**, 155.
[23] H. O. House and G. H. Rasmusson, *J. Org. Chem.*, 1963, **28**, 31.
[24] W. L. Meyer and J. F. Wolfe, *J. Org. Chem.*, 1964, **29**, 170.
[25] R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, 1962, **27**, 1615.
[26] J. F. Grove and B. J. Riley, *J.*, 1961, 1105.
[27] U. R. Ghatak, N. N. Saha, and P. C. Dutta, *J. Amer. Chem. Soc.*, 1957, **79**, 4487; J. Klein, *Tetrahedron*, 1964, **20**, 465.
[28] B. E. Hudson and C. R. Hauser, *J. Amer. Chem. Soc.*, 1940, **62**, 2457.
[29] G. Stork and F. H. Clarke, jun., *J. Amer. Chem. Soc.*, 1961, **83**, 3114.

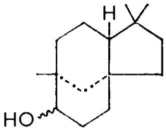
the ester groups are tertiary in nature, the one situated at the ring-junction should be more sterically hindered than the other one at C-5; hence, the rate of hydrolysis of these two ester groups should be appreciably different. The structure (XXXVI) for the half-acid ester is reasonably justified. The free carboxyl group of compound (XXXVI) was then transformed into a methyl ketone by the following route. The acid chloride, prepared from (XXXVI) with thionyl chloride and pyridine, was transformed into the diazo-ketone, then into the chloro-ketone, and finally into the methyl ketone (XXXVIa). The yield was only 10%, but by the same procedure the methyl ketone (XXXd) was obtained in 80% yield from the corresponding acid ester (XXX). In another method, the anhydride (XXXV) was treated with dimethylcadmium [30] in benzene affording thereby also a methyl ketone in extremely poor yield. Although the analytical values for hydrogen and carbon of this ketone and its semicarbazone tallied with those of the expected compounds, the melting point (178°) of this semicarbazone was different from the melting point (195°) of the derivative from the methyl ketone (XXXVIa) obtained previously, and there was no depression in mixed melting point of these two semicarbazones. However, an excellent yield of the methyl ketone (XXXVIa) was obtained by conversion of the acid ester (XXXVI) into the acid chloride with oxalyl chloride, followed by condensation with ethyl ethoxymagnesium malonate [31] and subsequent hydrolysis under standard conditions. The semicarbazone of this methyl ketone was identical in all respects with the semicarbazone of the ketone obtained by the diazo-ketone–chloro-ketone method. The methyl ketone (XXVIa) was subjected to ring closure with potassium t-butoxide in boiling benzene when the desired β-diketone (XXXVII) was obtained as a solid. Reduction [32] of the β-diketone with lithium aluminium hydride led to the formation of a mixture of the saturated (XXXVIII) and unsaturated alcohols (XXXIX). Oxidation of a part of the alcohol mixture with chromic acid afforded the corresponding ketones, the ultraviolet spectra of which indicated the presence of the αβ-unsaturated carbonyl compound to the extent of about 30%. The latter is evidently represented by structure (XL). Catalytic hydrogenation of the major portion of the alcohol mixture, obtained directly from lithium aluminium hydride reduction, afforded an oil which after chromatographic purification gave a waxy solid, m. p. 40—41°. The unsaturated alcohol (XXXIX) was also isolated from the crude mixture of alcohols by chromatography, again as a waxy material, m. p. 70—71°. Oxidation of the saturated alcohol with chromic acid in acetone furnished the corresponding saturated ketone as an oil. It afforded a yellow 2,4-dinitrophenylhydrazone, m. p. 171°, which on admixture with the sample from the ketone (VI) showed no depression. Incidentally, the ketone (VI), previously [26] described as an oil, has been obtained as a crystalline solid, m. p. 45—46°. Infrared spectra of these two ketones are superimposable. This unequivocally establishes the structure and stereochemistry of the synthetic tricarbocyclic ketone. Incidentally, it lends additional support to the mechanism of reduction of unsymmetrical β-diketones with lithium aluminium hydride originally suggested by Stork,[33]



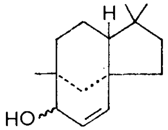
(XXXVI : R = OH)
(XXXVIa : R = Me)



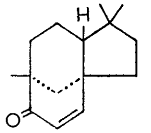
(XXXVII)



(XXXVIII)



(XXXIX)



(XL)

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[30] J. W. Wilson, C. L. Zirkle, E. L. Anderson, J. J. Stehle, and G. L. Ullyot, *J. Org. Chem.*, 1951, **16**, 792.

[31] W. G. Walker and C. R. Hauser, *J. Amer. Chem. Soc.*, 1946, **68**, 1386.

[32] A. S. Dreiding and J. A. Hartman, *J. Amer. Chem. Soc.*, 1953, **75**, 3723.

[33] Ref. 29, footnote, p. 3120.

and the thermodynamically controlled process of addition of hydrocyanic acid in (XXIII) as suggested earlier. The synthetic ketone, on modified Wolff–Kishner reduction,[34] afforded the desired hydrocarbon, clovane (VII), the identity of which was again established by infrared-spectroscopic comparison with the hydrocarbon prepared in this laboratory according to the method of Lutz [2] from the diol (V), through the corresponding diketone.

EXPERIMENTAL

Ultraviolet spectra were measured for ethanol solutions. Light petroleum had b. p. 40—60°. All the compounds described herein and containing asymmetric carbon atoms are the racemic forms.

Ethyl β-(1,5-*Diethoxycarbonyl*-5-*methyl*-2-*oxocyclohexyl*)*propionate* (XI).—To a solution of potassium t-butoxide in t-butyl alcohol [from potassium (0·1 g.) and t-butyl alcohol (25 c.c.)] was added diethyl 1-methyl-4-oxocyclohexane-1,3-dicarboxylate (X) (17 g.) at room temperature. The mixture was stirred for 45 min. and freshly distilled ethyl acrylate (10 g.) in t-butyl alcohol (20 c.c.) was added dropwise, the temperature being maintained constant. The solution was stirred for 24 hr. The product was decomposed with glacial acetic acid (2 c.c.), diluted with water, and extracted with benzene. On distillation it afforded the *ester* as a viscous liquid (16·2 g.), b. p. 171—178°/0·2 mm. (Found: C, 61·1; H, 8·0. $C_{18}H_{28}O_7$ requires C, 60·7; H, 7·9%).

Ethyl β-(1,5-*Diethoxycarbonyl*-2,2-*ethylenedioxy*-5-*methylcyclohexyl*)*propionate* (XII).—A mixture of the foregoing ketone (15 g.), freshly distilled ethylene glycol (3 g.), and toluene-*p*-sulphonic acid (400 mg.) in dry thiophen-free benzene (100 c.c.) was refluxed in a constant water separator for 40 hr. The mixture was worked up and the *product* isolated on distillation as a colourless viscous liquid (6 g.), b. p. 185—190°/0·2 mm. (Found: C, 59·9; H, 8·1. $C_{20}H_{32}O_8$ requires C, 60·0; H, 8·1%) along with a forerun (5 g.), b. p. 170—185°/0·2 mm., which was not further investigated.

Ethyl 3-*Cyano*-3-*methylcyclohexylidenecyanoacetate* (XIV).—A mixture of 3-cyano-3-methylcyclohexanone (XIII) (24 g.), ethyl cyanoacetate (25 g.), glacial acetic acid (8·5 g.), ammonium acetate (2 g.), and benzene (100 c.c.) was heated under reflux and the water formed during the reaction was separated in a Dean–Stark apparatus. Ammonium acetate (1 g.) was added at intervals of 4 hr. until the total amount added was 7 g. The solution was refluxed for a total of 35 hr. It was washed repeatedly with water and the solvent removed. On distillation the residue afforded the desired *product* (34·4 g.), b. p. 165—170°/0·2 mm., $\lambda_{max.}$ 234 mμ (log ε 4·1) (Found: C, 67·1; H, 6·9. $C_{13}H_{16}N_2O_2$ requires C, 67·2; H, 6·9%).

1,3-*Dicyano*-3-*methylcyclohexaneacetonitrile* (XV).—A mixture of the foregoing cyano-ester (11·6 g.) in rectified spirit (40 c.c.) and potassium cyanide (6·5 g.) dissolved in water (15 c.c.) was heated under reflux for 2 hr. Ethanol was removed under reduced pressure and the residue acidified with dilute hydrochloric acid in the cold. The solid was filtered and washed several times with water. It was crystallised from ethanol, giving colourless *needles* (8·1 g.), m. p. 198—199° (Found: C, 69·9; H, 7·1. $C_{11}H_{13}N_3$ requires C, 70·6; H, 7·1%).

3-*Methyl*-1,3-*dicarboxycyclohexaneacetic Acid* (XVa).—The above trinitrile (XV) (45 g.) was heated under reflux with concentrated hydrochloric acid (500 c.c.) for 50 hr. It was cooled and the solid which separated was filtered. The solid was further hydrolysed by being heated under reflux with potassium hydroxide (30 g.) dissolved in water (150 c.c.) for 10 hr. The solution was boiled with charcoal and filtered. The filtrate was cooled and acidified with dilute hydrochloric acid, whereupon a crystalline solid (30 g.) was obtained. It crystallised as *needles*, m. p. 206° (from ethanol) (Found: C, 54·1; H, 6·7. $C_{11}H_{16}O_6$ requires C, 54·1; H, 6·6%).

Methyl 1,3-*Dimethoxycarboxyl*-3-*methylcyclohexaneacetate* (XVb).—The above acid (XVa) (30 g.) was heated under reflux with methanol (300 c.c.) and concentrated sulphuric acid (30 c.c.) for 30 hr. The product was diluted with water and extracted with ether. On removal of the solvent, a gummy mass was obtained. This was dissolved in ether (100 c.c.) and the solution treated with excess of an ethereal solution of diazomethane. It afforded, on distillation, a

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[34] G. R. Pettit, P. Hofer, W. J. Bowyer, T. R. Kasturi, R. C. Bansal, R. E. Kadunce, and B. Green, *Tetrahedron*, 1963, **19**, 1143.

colourless liquid (23 g.), b. p. 140—145°/0·4 mm. This solidified on standing, and was crystallised from light petroleum as *plates*, m. p. 44° (Found: C, 58·8; H, 7·9. $C_{14}H_{22}O_6$ requires C, 58·7; H, 7·8%).

1,3-*Dimethoxycarbonyl*-3-*methylcyclohexaneacetic Acid* (XVc).—The above triester (XVb) (10·9 g.) was added to a solution of potassium hydroxide (2·7 g.) in water (3 c.c.) and methanol (20 c.c.), set aside at room temperature for 2 hr., and refluxed for 1 hr. The mixture was diluted with water and extracted with ether to remove the neutral fraction. Acidification of the aqueous alkaline solution with dilute hydrochloric acid and subsequent extraction with ether gave the desired *acid* (10 g.), m. p. 140° (from ethyl acetate) (Found: C, 57·1; H, 7·4. $C_{13}H_{20}O_6$ requires C, 57·3; H, 7·4%).

Methyl β-(1,3-*Dimethoxycarbonyl*-3-*methylcyclohexyl*)*propionate* (XVe).—To a benzene (50 c.c.) suspension of the dry sodium salt of the acid (XVc) [from the acid (9·7 g.) and sodium (0·77 g.)] in methanol (20 c.c.), was added a solution of oxalyl chloride (9 c.c.) in benzene (30 c.c.) containing a few drops of pyridine at 0°. The mixture was set aside at 5° overnight. Benzene and excess of oxalyl chloride were removed under reduced pressure at room temperature and the last traces of oxalyl chloride by repeated addition and evaporation of benzene. The acid chloride was taken up in benzene and filtered from the solid materials. The clear solution was slowly added at 0° to an ethereal solution of diazomethane, prepared from nitrosomethylurea (30 g.) and dried over potassium hydroxide for 6 hr. Excess of diazomethane and ether were removed under reduced pressure at room temperature. The residue was dissolved in methanol (150 c.c.), warmed (60°), and a methanolic suspension of silver oxide [from silver nitrate (20 g.)], was added to it in portions during 1 hr. Heating at 60° was continued for 30 min. and the solution was next heated under reflux for 1 hr. It was finally heated with charcoal, filtered, and methanol removed. The residue on distillation afforded a colourless liquid (7 g.), b. p. 144—150°/0·4 mm. This solidified on standing, to yield *plates*, m. p. 57° (from light petroleum) (Found: C, 59·7; H, 8·3. $C_{15}H_{24}O_6$ requires C, 60·0; H, 8·1%).

Methylcyclohexane-trans(?)-1,3-*dicarboxylic Acid* (XVIa).—To potassium t-butoxide [from potassium (4 g.) and heated at 100° *in vacuo* to remove the solvent] was added benzene (250 c.c.). To the boiling suspension was added dropwise compound (XVe) (3 g.) dissolved in benzene (300 c.c.) in 2 hr., benzene (*ca.* 100 c.c.) being simultaneously distilled off. The mixture was heated for 3 hr. during dropwise addition and simultaneous distillation of benzene (250 c.c.), cooled under nitrogen, and decomposed with ice and hydrochloric acid. The organic layer was separated and the aqueous layer (brine) extracted with benzene. On distillation, the residue afforded two fractions: (*a*) a mobile colourless liquid (1·1 g.), b. p. 115—120°/0·2 mm., no coloration with ethanolic ferric chloride solution; and (*b*) a viscous liquid (1 g.), b. p. 170—220°/0·2 mm. This gave a strong bluish-violet coloration with ethanolic ferric chloride solution.

The low-boiling fraction (300 mg.) was added to a solution of potassium hydroxide (500 mg.) in rectified spirit (12 c.c.) and heated under reflux for 40 hr. It was worked up to afford the *acid* (200 mg.), star-shaped crystals, m. p. 155° (from ethyl acetate–light petroleum) (Found: C, 57·7; H, 8·0. $C_9H_{14}O_4$ requires C, 58·1; H, 7·6%).

Dimethyl 1,3-*Dimethylcyclohexane*-1,3-*dicarboxylate* (XVIIa).—The acid (XVc) (10 g.) was dissolved in methanol (30 c.c.) and neutralised with N-sodium hydroxide solution (phenolphthalein). A solution of silver nitrate (6 g.) in distilled water (25 c.c.) was added dropwise and the precipitated silver salt filtered and dried *in vacuo* at 90°. To a vigorously stirred boiling suspension of the dry silver salt in dry carbon tetrachloride (100 c.c.) was added bromine (2 c.c.) in carbon tetrachloride (50 c.c.) in 20 min. Refluxing was continued for 3 hr. with stirring. The mixture was cooled and the precipitated silver bromide removed by filtration. The carbon tetrachloride solution was washed with 10% sodium hydroxide solution and water and dried. The neutral residue (4 g.) obtained on removal of the solvent was dissolved in glacial acetic acid (100 c.c.) and treated with zinc dust (15 g.) during 1 hr. It was then refluxed for 10 hr. Acetic acid was removed under reduced pressure and the product extracted with ether. On distillation it afforded a liquid (1·8 g.), b. p. 90—93°/0·6 mm. which solidified on standing, giving *plates*, m. p. 57° (from light petroleum) (Found: C, 63·2; H, 8·9. $C_{12}H_{20}O_4$ requires C, 63·1; H, 8·8%). From the alkaline extract the unreacted acid ester was recovered on acidification.

1,3-*Dimethylcyclohexane*-1,3-*dicarboxylic Acid* (XVIII).—The above diester (XVIIIa) (1·6 g.) was heated under reflux with a solution of potassium hydroxide (2·5 g.) in rectified spirit (25 c.c.) for 40 hr. Ethanol was removed and the residue dissolved in water. On removal of the neutral matter, the *acid* (1·2 g.) was isolated from the alkaline solution as small plates, m. p. 216° (from light petroleum) (Found: C, 59·6; H, 7·8. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·1%). The corresponding anhydride (XIX) was prepared by heating under reflux the acid (1 g.) with acetic anhydride (20 c.c.) for 8 hr. The *anhydride* sublimed at 110—120°/0·4 mm., yielding long needles, m. p. 108° (from ethyl acetate–light petroleum) (Found: C, 65·5; H, 7·7. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·7%).

Ethyl α-*Cyano*-β-(p-*methoxyphenyl*)-β-*methylbutyrate* (XXI).—A mixture of *p*-methoxyacetophenone (190 g.), ethyl cyanoacetate (210 g.), glacial acetic acid (122 g.), benzene (1000 c.c.), and ammonium acetate (12 g.) was refluxed under the usual conditions, the water formed during the reaction being separated in a modified Dean–Stark apparatus. Ammonium acetate (5 g.) was added at intervals of 4 hr. until the total amount added was 42 g. The solution was refluxed for a total of 35 hr. The product was isolated on distillation furnishing a pale yellow viscous liquid (237 g.), b. p. 172—180°/0·6 mm., $\lambda_{max.}$ 320—322 mμ (log ε 4·0). To a boiling solution of methylmagnesium iodide [from magnesium (4·4 g.) and methyl iodide (13 c.c.)] in ether (100 c.c.) was added anhydrous, finely powdered cuprous iodide (1·4 g.), and the mixture subsequently stirred for 15 min. The solution was cooled in ice and to this was added, during 45 min. and with constant stirring, the above unsaturated cyano-ester (11·5 g.) in ether (40 c.c.). The mixture was stirred for 1 hr. in the cold and then heated under reflux for 2 hr. It was cooled in a freezing mixture and decomposed carefully with ice and hydrochloric acid. The ethereal extract was washed with dilute hydrochloric acid, 5% sodium carbonate solution, and dilute sodium thiosulphate solution. The residue after removal of the solvent was dissolved in rectified spirit (15 c.c.), treated with a solution of potassium cyanide (5·5 g.) in water (15 c.c), and the solution heated with stirring for 15 min. on a steam-bath. It was cooled, acidified with hydrochloric acid, and extracted with benzene. The organic extract was washed with 5% sodium carbonate solution and water, and the solvent removed. The residue, on distillation afforded a colourless *liquid* (7 g.), b. p. 167—172°/0·6 mm. (Found: C, 69·2; H, 7·4. $C_{15}H_{19}NO_3$ requires C, 68·9; H, 7·3%).

β-(p-*Methoxyphenyl*)-β-*methylbutyronitrile* (XXIa).—Ethyl α-cyano-β-(*p*-methoxyphenyl)-β-methylbutyrate (6 g.) was heated under reflux with sodium hydroxide (6 g.) in water (60 c.c.) for 2 hr. It was cooled and the neutral matter extracted with ether. The alkaline layer was again extracted with ether after acidification. The residue after removal of the solvent was decarboxylated by being heated on an oil-bath (200—210°). It was taken up in ether and the ethereal layer washed with 5% sodium carbonate solution to remove the acidic material. The organic layer afforded, on distillation, a colourless *liquid* (4 g.), b. p. 125—130°/0·4 mm. (Found: C, 76·0; H, 8·0. $C_{12}H_{15}NO$ requires C, 76·2; H, 8·0%).

β-(p-*Methoxyphenyl*)-β-*methylbutyric Acid* (XXIb).—Ethyl α-cyano-β-(*p*-methoxyphenyl)-β-methylbutyrate (5 g.), potassium hydroxide (7 g.) in water (7 c.c.), and ethylene glycol (30 c.c.) were heated under reflux for 40 hr. On acidification with hydrochloric acid a solid separated. It was decarboxylated at 210° for 4 hr. and the acidic material (3 g.) isolated. It was crystallised from ethyl acetate, giving *needles*, m. p. 89—90° (Found: C, 69·1; H, 7·9. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%).

5-*Methoxy*-1,1-*dimethylindan*-3-*one* (XXII).—To polyphosphoric acid [prepared from phosphorus pentoxide (120 g.) and syrupy (85%) phosphoric acid (55 c.c.)] was added with stirring β-(*p*-methoxyphenyl)-β-methylbutyric acid (32 g.) in small portions at 70°. The mixture gradually turned brown and was allowed to cool down to room temperature in 50 min. with occasional stirring. It was decomposed with ice-cold water and extracted with ether. The extract was washed repeatedly with sodium carbonate solution (5%) and then with water. On removal of the solvent, the residue distilled at 138—145°/8 mm. as a colourless liquid (17 g.). It readily afforded a red 2,4-*dinitrophenylhydrazone*, needles, m. p. 266—267° (from ethyl acetate) (Found: C, 58·3; H, 5·1; N, 15·1. $C_{18}H_{18}N_4O_5$ requires C, 58·4; H, 4·9; N, 15·1%). From the sodium carbonate washings, unreacted acid (8·0 g.) was recovered on acidification.

5-*Methoxy*-1,1-*dimethylindane* (XXIIa).—(*a*) The above ketone (XXII) (13·5 g.) was hydrogenated in glacial acetic acid (30 c.c.) containing perchloric acid (0·5 c.c.) in the presence of 10% palladium–charcoal (200 mg.). After the catalyst had been filtered off the filtrate was distilled and the fraction boiling at 105—110°/10 mm. was obtained as a colourless mobile liquid (9·1 g.).

(*b*) The ketone (XXII) (8·7 g.) in redistilled diethylene glycol (85 c.c.) was heated under reflux with 85% hydrazine hydrate (5·5 c.c.) and potassium hydroxide (6 g.) at 150° for 1 hr. and then at 200° for another hour. Dilution of the product with water, acidification with dilute hydrochloric acid, and extraction with ether afforded the *methyl ether* (7·2 g.), b. p. 105—110°/10 mm. (Found: C, 81·7; H, 9·3. $C_{12}H_{16}O$ requires C, 81·8; H, 9·2%).

5,6,7,7*a*-*Tetrahydro*-1,1-*dimethylindan*-5-*one* (XXIII).—5-Methoxy-1,1-dimethylindane (9·5 g.) in dry ether (25 c.c.) was dissolved in liquid ammonia (400 c.c.) and sodium (6·2 g.), cut into small pieces, was added during 20 min. with efficient stirring. Stirring was continued for a further 20 min., followed by the dropwise addition of magnesium-dried alcohol (*ca.* 25 c.c.), until the blue colour of the solution disappeared. Ammonia was allowed to evaporate off and the residue decomposed with ice and hydrochloric acid and extracted with ether. Refluxing the crude product with 10% sulphuric acid (100 c.c.) for 6 hr., followed by the usual working-up, furnished a colourless *liquid* (8·4 g.), b. p. 120—125°/10 mm., with a camphoraceous odour, $\lambda_{max.}$ 230 mμ (log ε 3·9) (Found: C, 80·0; H, 9·7. $C_{11}H_{16}O$ requires C, 80·4; H, 9·8%). The 2,4-*dinitrophenylhydrazone* crystallised from methanol–ethyl acetate as needles, m. p. 168° (Found: C, 59·2; H, 6·0; N, 16·1. $C_{17}H_{20}N_4O_4$ requires C, 59·3; H, 5·9; N, 16·3%).

Dimethyl Perhydro-5-*hydroxy*-1,1-*dimethylindene*-3a,5-*dicarboxylate* (XXV).—To the above bicyclic ketone (XXIII) (14 g.) in ethanol (70 c.c.) was added potassium cyanide (12 g.) in water (40 c.c.) and the mixture heated under reflux for 10 hr. under nitrogen. A solution of potassium hydroxide (12 g.) in water (100 c.c.) was added and the mixture refluxed for a further 40 hr. It was acidified with dilute hydrochloric acid and extracted with ether. The ethereal solution was washed repeatedly with 5% sodium carbonate solution. The crude acidic material (12 g.), obtained on acidification of the alkaline washings and subsequent extraction with ether, was esterified with diazomethane in methanol to afford a colourless *liquid* (6·9 g.), b. p. 147—152°/0·4 mm. (Found: C, 63·5; H, 8·7. $C_{15}H_{24}O_5$ requires C, 63·4; H, 8·5%).

Dimethyl Perhydro-1,1-*dimethylindene*-3a,5-*dicarboxylate* (XXVb).—To the above hydroxy-ester (6 g.) in ether (15 c.c.) was added phosphorus pentachloride (5·3 g.) in small portions in the cold and the mixture left overnight. It was poured into ice-cold methanol (20 c.c.) and the product diluted with water (brine) and extracted with ether. The crude chloro-ester (4·5 g.) was dissolved in glacial acetic acid (45 c.c.) and to it was added zinc dust (15 g.) portionwise during 1 hr. The mixture was heated under reflux for 10 hr. and poured into water. The product was extracted with ether and on distillation it afforded a colourless *liquid* (3·5 g.), b. p. 126—128°/0·4 mm. (Found: C, 67·0; H, 8·9. $C_{15}H_{24}O_4$ requires C, 67·1; H, 9·0%).

Diethyl 2-*Hydroxydecalin*-2,8a-*dicarboxylate* (XXVIII) *and the Corresponding γ-Lactone* (XXVII).—$\Delta^{1,9}$-Octahydronaphthalen-2-one (30 g.) dissolved in rectified spirit (140 c.c.) and potassium cyanide (65 g.) in water (130 c.c.) were mixed together, set aside for 15 hr. at room temperature, and heated under reflux for 15 hr. A solution of potassium hydroxide (30 g.) in water (300 c.c.) was added and heating continued for a further 60 hr. The mixture was acidified with dilute hydrochloric acid and extracted with ether. The ethereal solution was washed repeatedly with 5% sodium carbonate solution. On acidification of the alkaline washings with dilute hydrochloric acid and subsequent extraction with ether, an acidic material (*ca.* 25 g.) was obtained. This was esterified by being heated under reflux with absolute ethanol (125 c.c.) containing concentrated sulphuric acid (20 c.c.). On the usual working-up, a colourless liquid (21 g.), b. p. 135—145°/0·1 mm., was obtained. It absorbed in the infrared at 2·85, 5·6, and 5·8 μ and a shoulder at 4·25 μ (CN) (Found: C, 65·2; H, 8·4. Calc. for $C_{16}H_{26}O_5$ (hydroxy-diester): C, 64·4; H, 8·9. Calc. for $C_{14}H_{20}O_4$ (lactonic ester): C, 66·6; H, 8·0%).

Diethyl Decalin-2,8a-*dicarboxylate* (XXVIIIa).—The above mixture of the lactonic ester and the hydroxy-diester (10 g.) was dissolved in dry pyridine (40 c.c.) and treated with phosphorus oxychloride (7 c.c.) in the cold and the mixture heated on a water-bath for 1 hr. It was cooled and poured into ice and hydrochloric acid and the product extracted with ether. The crude product (*ca.* 6 g.) was dissolved in glacial acetic acid (60 c.c.) and treated with zinc dust (20 g.) and heated under reflux for 10 hr. A colourless *liquid* (3 g.), b. p. 150—155°/0·4 mm., was finally obtained (Found: C, 67·5; H, 8·4. $C_{16}H_{26}O_4$ requires C, 68·1; H, 9·3%).

Diethyl 1-*Hydroxy*-3-*methylcyclohexane*-1,3-*dicarboxylate* (XXIX) *and the Corresponding γ-Lactone*.—3-Methylcyclohex-2-enone (28 g.) dissolved in rectified spirit (100 c.c.) and potassium cyanide (70 g.) in water (150 c.c.) were mixed together and set aside at room temperature for 12 hr. The mixture was heated under reflux for 17 hr., a solution of potassium hydroxide (42 g.) in water (180 c.c.) was added, and heating continued for a further 50 hr. It was decomposed with dilute hydrochloric acid and the acidic product (*ca.* 42 g.) was isolated on extraction with absolute ethanol (100 c.c.) containing sulphuric acid (15 c.c.) for 40 hr. After the usual working-up, a colourless liquid (38 g.), b. p. 150—155°/9 mm., was obtained. The ester absorbed in the infrared at 2·75, 5·65, and a broad band at 5·78 μ (Found: C, 61·0; H, 8·5. Calc. for $C_{13}H_{22}O_5$ (hydroxy-diester): C, 60·4; H, 8·6. Calc. for $C_{11}H_{16}O_4$ (lactonic ester): C, 62·3; H, 7·6%).

Diethyl 1-*Methylcyclohex*-2-*ene*-1,3-*dicarboxylate* (XXIXa) *and/or its Bond Isomer.*—The above product (15 g.) was dissolved in pyridine (70 c.c.) and treated with phosphorus oxychloride (10 c.c.) as described before. After working up in the usual way, a colourless *liquid* (10 g.), b. p. 150—156°/15 mm., was obtained (Found: C, 64·8; H, 8·2. $C_{13}H_{20}O_4$ requires C, 65·0; H, 8·4%).

Diethyl 1-*Methylcyclohexane*-1,3-*dicarboxylate* (XXIXb).—The above unsaturated diester (8 g.) was hydrogenated in ethanol in the presence of 10% palladium–charcoal (200 mg.). The *product* (7 g.) distilled at 148—153°/15 mm. (Found: C, 64·1; H, 8·8. $C_{13}H_{22}O_4$ requires C, 64·4; H, 9·2%).

1-*Methylcyclohexane*-cis-1,3-*dicarboxylic Acid* (XVIb).—The above diester (3 g.), potassium hydroxide (3 g.) dissolved in water (3 c.c.), and ethylene glycol (30 c.c.) were heated under reflux for 15 hr. The resulting acid (2·1 g.) melted at 198—199°. This crude acid (200 mg.) was heated with acetic anhydride (3 c.c.) for 24 hr. on a steam-bath. Excess of acetic anhydride was removed under reduced pressure. The *anhydride* was distilled at 100—110°/1 mm. to give a viscous liquid. It absorbed in the infrared at 5·56 and 5·70 μ (Found: C, 64·4; H, 7·3. $C_9H_{12}O_3$ requires C, 64·3; H, 7·2%). This was dissolved in 10% sodium hydroxide solution (1 c.c.) by warming. After cooling, the solution was acidified with dilute hydrochloric acid. The regenerated *acid* melted at 199—200° and showed no depression with the starting acid. It was crystallised from ethyl acetate–light petroleum, m. p. 200—201° (Found: C, 58·4; H, 7·7. $C_9H_{14}O_4$ requires C, 58·1; H, 7·6%).

Equilibration of 1-*Methylcyclohexane*-cis-1,3-*dicarboxylic Acid.*—The *cis*-acid (200 mg.) was esterified with diazomethane. The diester was heated under reflux for 100 hr. with sodium methoxide [from sodium (0·4 g.)] in methanol (10 c.c.). Water (1 c.c.) was next added and hydrolysis carried out by heating the mixture under reflux for 40 hr. Methanol was removed and the neutral material extracted with ether. The alkaline portion was acidified with dilute hydrochloric acid and extracted with ether. The crude solid thus obtained melted at 140—145°. After one crystallisation (light petroleum–ethyl acetate) it melted at 153—155°. After the fourth crystallisation from the same solvent it melted at 200—201°. From the more soluble portion after prolonged standing in the cold, a few crystals were obtained which melted at 155°, but depressed the melting point when mixed with the acid of m. p. 200—201°.

Perhydro-3a-*methoxycarbonyl*-1,1-*dimethylindene*-5-*carboxylic Acid* (XXX).—The diester (XXVb) (3·5 g.) was added to a solution of potassium hydroxide (1·1 g.) dissolved in the minimum quantity of water and methanol (25 c.c.). The solution was left overnight and then heated under reflux for 2 hr. The acidic product (2·9 g.) was isolated as an oil in the usual way. The *ester anilide* crystallised from light petroleum, m. p. 121° (Found: C, 72·5; H, 8·1. $C_{20}H_{27}NO_3$ requires C, 72·9; H, 8·3%).

Dimethyl Perhydro-1,1,5-*trimethylindene*-3a,5-*dicarboxylate* (XXXI).—To an ice-cold solution of the above acid ester (2·9 g.) in dry ether (20 c.c.) containing pyridine (0·9 c.c.) was added thionyl chloride (1·1 c.c.), and the mixture was kept at 0° overnight. The ethereal solution was filtered through glass wool and the solvent removed under reduced pressure at room temperature. The resultant acid chloride in benzene (5 c.c.) was added slowly at 0° to an ethereal solution of diazomethane, prepared from nitrosomethylurea (7 g.) and dried over potassium hydroxide for 6 hr. The mixture was left for 1 hr. Excess of dry hydrogen chloride was then passed for 20 min. into the mixture, cooled in ice, and the product left overnight. The solution was filtered through glass wool and evaporated under reduced pressure at room temperature, whereupon a viscous brown oil (2·8 g.) was obtained. To an ice-cold solution of sodium methoxide in methanol, prepared from sodium (0·7 g.) and magnesium-dried methanol (25 c.c.), was added a solution of the above crude chloro-ketone in dry methanol (10 c.c.), and the mixture was kept at 4° for 45 hr. The excess of the base was neutralised by the addition of acetic acid and the solution evaporated to a thick mass on a steam-bath under reduced pressure. It was diluted with water and extracted with ether. On distillation it afforded a liquid (1·5 g.), b. p. 140—147°/0·4 mm. This was added to a 5% solution of potassium hydroxide in methanol (15 c.c.), kept overnight at room temperature, and finally heated under reflux for 2 hr. The product was diluted with water and the neutral fraction extracted with ether. The resultant *diester* distilled at 130—135°/0·6 mm. giving a colourless oil (150 mg.) (Found: C, 67·7; H, 9·0. $C_{16}H_{26}O_4$ requires C, 68·0; H, 9·3%).

Methyl Perhydro-3a-*methoxycarboxyl*-1,1-*dimethylindene*-5-*acetate* (XXXII).—The aqueous alkaline solution, left after extraction of the neutral fraction described above, was acidified with dilute hydrochloric acid and the solution extracted with ether. The residue left after removal of the solvent was esterified with diazomethane. The *diester* (XXXII) (1·2 g.) distilled at 145—150°/0·4 mm. (Found: C, 68·0; H, 9·3%).

Perhydro-1,1,5-*trimethylindene*-3a,5-*dicarboxylic Acid* (XXXIa).—The diester (XXXI) (140 mg.), potassium hydroxide (300 mg.) in water (0·5 c.c.), and ethylene glycol (4 c.c.) were refluxed for 25 hr. The *acid* (100 mg.), isolated in the usual way, was crystallised from light petroleum–ethyl acetate, m. p. 172—173° (Found: C, 66·0; H, 8·7. $C_{14}H_{22}O_4$ requires C, 66·1; H, 8·7%). The *anhydride* (XXXV), obtained from the acid by heating under reflux with acetic anhydride (5 c.c.) for 5 hr., was purified by distillation and crystallised from light petroleum–ethyl acetate giving needles, m. p. 99—100° (Found: C, 71·3; H, 8·4. $C_{14}H_{20}O_3$ requires C, 71·2; H, 8·5%).

3a-*Carboxyperhydro*-1,1-*dimethylindene*-5-*acetic Acid* (XXXIIa).—The diester (XXXII) (500 mg.), potassium hydroxide (1 g.) in water (1 c.c.), and ethylene glycol (10 c.c.) were refluxed for 25 hr. The *acid*, isolated in the usual way, was crystallised from light petroleum–ethyl acetate, m. p. 180—181° (Found: C, 65·9; H, 8·8. $C_{14}H_{22}O_4$ requires C, 66·1; H, 8·7%).

Methyl 5-*Acetylperhydro*-1,1-*dimethylindene*-3a-*carboxylate* (XXXd).—The chloro-ketone (XXXc), prepared from the acid ester (XXX) (7 g.) according to the conditions described above, was dissolved in glacial acetic acid (75 c.c.), and zinc dust (15 g.) was added in a few portions with shaking during 30 min. The mixture was heated at 55—60° on a water-bath for 3 hr. and then for 2 hr. on a boiling-water-bath. After being worked up in the usual way, it afforded a colourless *liquid* (5·6 g.), b. p. 120°/0·4 mm. (Found: C, 71·3; H, 9·7. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%). The *semicarbazone* crystallised from ethanol, m. p. 192—193° (Found: C, 61·6; H, 9·0. $C_{16}H_{27}N_3O_3$ requires C, 62·1; H, 8·8%).

Methyl Perhydro-1,1-*dimethyl*-5-*oxoindene*-3a-*carboxylate* (XXXIV).—Dimethyl perhydro-5-hydroxy-1,1-dimethylindene-3a,5-dicarboxylate (6 g.) was added to a solution of potassium hydroxide (1·5 g.), dissolved in the minimum quantity of water and methanol (30 c.c.). The solution was left overnight and then heated under reflux for 2 hr. The acidic material (5 g.) was isolated as an oil. This was dissolved in a mixture of benzene (30 c.c.) and methanol (60 c.c.) and to it was added, with shaking, lead tetra-acetate (15 g.). The mixture was left overnight. Most of the solvent was removed under reduced pressure at room temperature and the residue diluted with water and extracted with ether. The *keto-ester* (3·2 g.) was isolated on distillation, b. p. 115—120°/0·4 mm. (Found: C, 69·5; H, 9·2. $C_{13}H_{20}O_3$ requires C, 69·6; H, 9·0%).

Ethyl Perhydro-3a-*methoxycarbonyl*-1,1-*dimethylindenylidene*-5-*cyanoacetate* (XXXIVa).—The above keto-ester (XXXIV) (2·8 g.), ethyl cyanoacetate (3 g.), glacial acetic acid (1 c.c.), benzene (50 c.c.), and ammonium acetate (200 mg.) were heated under reflux under the usual conditions, the water formed being separated continuously. Ammonium acetate (100 mg.) was added at intervals of 5 hr. until the total amount added was 600 mg. The total period of refluxing was 30 hr. Finally, a pale yellow viscous *liquid* (3·1 g.), b. p. 160—162°/0·3 mm., was obtained, $\lambda_{max.}$ 242 mμ (log ε 4·2) (Found: C, 68·1; H, 8·1. $C_{18}H_{25}NO_4$ requires C, 67·7; H, 7·9%).

Dimethyl 1,1,5-*Trimethylhexahydroindan*-5,9-*dicarboxylate* (XXXI).—To an ice-cold solution of the diester (XXVb) (6·6 g.) in ether (50 c.c.) was added rapidly a 0·21N-solution of triphenylmethylsodium (*ca.* 150 c.c.) in excess until a red colour of triphenylmethylsodium persisted. The reaction was carried out under pure, dry nitrogen. The mixture was set aside at room temperature with occasional shaking for 1 hr. During this period the red colour faded to pale orange. Methyl iodide (25 c.c.) was added dropwise at room temperature and the mixture left overnight. The ethereal solution was filtered to remove the precipitated sodium iodide and the solvent removed. The viscous mass was added to a solution of potassium hydroxide (1·5 g.) in methanol (45 c.c.), the solution left overnight, and finally refluxed for 2 hr. It afforded an acidic material (1·2 g.) which was rejected. The neutral fraction was added to a solution of potassium hydroxide (5 g.) in rectified spirit (50 c.c.) and heated under reflux for 30 hr. The solution was acidified with dilute hydrochloric acid and extracted with ether. The desired acid, isolated from alkaline washings of the ethereal extract, crystallised from light petroleum–ethyl acetate, m. p. 172—173°. It showed no depression in mixed melting point with the diacid (XXXIa), obtained as described previously. However, it was esterified with diazomethane; and the product distilled at 125—130°/0·2 mm.

Perhydro-3a-*methoxycarbonyl*-1,1,5-*trimethylindene*-5-*carboxylic Acid* (XXXVI).—The diester (XXXI) (8·1 g.) was added to a solution of potassium hydroxide (1·6 g.), dissolved in the minimum quantity of water and methanol (40 c.c.). The solution was set aside for 3 days and then refluxed for 2 hr. The acidic material (5·6 g.) was isolated as an oil in the usual way. The acid ester afforded the *anilide* through the corresponding acid chloride, and it crystallised as plates, m. p. 101° (from ethyl acetate–light petroleum) (Found: C, 73·2; H, 8·5. $C_{21}H_{29}NO_3$ requires C, 73·4; H, 8·5%).

Methyl 5-*Acetylperhydro*-1,1,5-*trimethylindene*-3a-*carboxylate* (XXXVIa).—(*a*) The above acid ester (XXXVI) (2·7 g.) in dry ether (20 c.c.) containing pyridine (0·8 c.c.) was treated with purified thionyl chloride (1 c.c.) at 0° and then kept overnight at 4°. Excess of thionyl chloride and ether were removed under reduced pressure at room temperature. The acid chloride in benzene (5 c.c.) was poured slowly at 0° into an ethereal solution of diazomethane, prepared from nitrosomethylurea (7 g.) and dried for 6 hr. over potassium hydroxide. After 30 min., excess of dry hydrogen chloride was passed for 20 min. into the mixture, cooled in ice. The crude chloro-ketone, obtained after removal of the solvent under reduced pressure, was treated with acetic acid (30 c.c.) and zinc dust (10 g.). It was heated for 8 hr. on a boiling-water bath and the product extracted with ether. On distillation, the *ester* formed an *oil* (350 mg.), b. p. 115—120°/0·4 mm. (Found: C, 71·5; H, 9·9. $C_{16}H_{26}O_3$ requires C, 72·1; H, 9·8%). It readily afforded the *semicarbazone*, m. p. 195° (from 90% ethanol) (Found: C, 63·1; H, 9·2. $C_{17}H_{29}N_3O_3$ requires C, 63·1; H, 9·0%).

(*b*) To a boiling solution of the Grignard reagent prepared from magnesium (0·48 g.) and methyl iodide (3 c.c.) in ether (30 c.c.), was added finely powdered, anhydrous cadmium chloride (5·5 g.) and the whole refluxed for 30 min. Ether was replaced by benzene (30 c.c.). The product was cooled in ice and the anhydride (XXXV) (2·3 g.) dissolved in benzene (10 c.c.) was added dropwise during 20 min. The mixture was refluxed for 2 hr. and decomposed with 10% sulphuric acid. The benzene layer was washed with 5% sodium carbonate solution and then water, and the solvent removed. The neutral material (1·8 g.), m. p. 96—98°, was characterised as the unreacted anhydride. The alkaline extract, on acidification with hydrochloric acid, afforded an oil which was esterified with diazomethane. The product (350 mg.) readily afforded the *semicarbazone*, m. p. 178°. It showed no depression in mixed melting point with the semicarbazone previously described and melting at 195° (Found: C, 62·9; H, 8·9%). The *ketone*, regenerated from the semicarbazone by heating under reflux with 10% oxalic acid solution for 2 hr., was distilled at 90—95°/0·4 mm. (Found: C, 72·3; H, 10·0. $C_{16}H_{26}O_3$ requires C, 72·1; H, 9·8%).

(*c*) The acid chloride, prepared from the acid ester (XXXVI) (6 g.) and oxalyl chloride (5·5 c.c. through the dry sodium salt as described above, was dissolved in benzene (25 c.c.). A solution of diethyl malonate (14 c.c.) in magnesium-dried ethanol (5·5 c.c.) was added dropwise to a stirred suspension of magnesium (2 g.) under ethanol (3 c.c.) containing carbon tetrachloride (0·2 c.c.). After the initial vigorous reaction had subsided, the mixture was heated on the boiling-water-bath for 2 hr., cooled, ether (50 c.c.) was added, and the whole was again refluxed for 2 hr. Ether and alcohol were removed under reduced pressure. Traces of ethanol were removed by adding fresh benzene (2 × 50 c.c.) and removing it under reduced pressure. The gummy residue was dissolved in benzene (50 c.c.) and a solution of the above acid chloride in benzene was dropwise added with stirring in the cold (ice-bath) during 20 min. It was stirred in the cold for an additional 30 min. and then refluxed for 4 hr., whereupon a deep violet solution resulted. It was cooled and decomposed with cold dilute hydrochloric acid. The organic layer was separated and the aqueous layer extracted with ether. The combined organic layer was washed with 2% sodium hydrogen carbonate solution and finally with water. After the low-boiling solvents had been removed a light brown oil was obtained, which gave a red coloration with an ethanolic solution of ferric chloride. The sodium hydrogen carbonate extract, on acidification, regenerated the unreacted acid (0·7 g.). The above neutral residue was mixed with acetic acid (12 c.c.), concentrated sulphuric acid (14 c.c.), and water (65 c.c.). The mixture was refluxed for 15 hr., cooled, and extracted with ether. The ethereal layer was washed with 5% sodium hydrogen carbonate solution, then with water, and dried. After removal of the solvent, the residue was distilled to afford a liquid (4 g.), b. p. 122—123°/0·6 mm. It readily afforded the semicarbazone, m. p. 195°, and showed no depression in melting point with the semicarbazone, m. p. 195°, prepared according to the method (*a*).

4,4,8-*Trimethyltricyclo*[6,3,1,$0^{1,5}$]*dodecane*-9,11-*dione* (XXXVII).—Potassium t-butoxide [from potassium (3·1 g.)] was heated at 100° *in vacuo* and the dry cake was dissolved in benzene (150 c.c.). To the boiling solution was added dropwise during 1 hr. the keto-ester (XXXVIa) (2·7 g.) dissolved in benzene (100 c.c.). Benzene (*ca.* 100 c.c.) was simultaneously distilled off during this period. The mixture was further refluxed with dropwise addition and simultaneous distillation of benzene (200 c.c.) during 2·5 hr. The mixture was cooled under nitrogen and decomposed with ice and hydrochloric acid. The light yellow benzene layer was separated and the aqueous layer (brine) extracted with benzene. On removal of the solvent, a white *solid* (2·2 g.) was obtained. It was distilled at 120—122°/0·2 mm., m. p. 157—158° (Found: C, 76·7; H, 9·4. $C_{15}H_{22}O_2$ requires C, 76·9; H, 9·5%).

4,4,8-*Trimethyltricyclo*[6,3,1,$0^{1,5}$]*dodecan*-9-*one* [(±)-*Clovan*-9-*one*] (VI).—The β-diketone (XXXVII) (1·6 g.) was added with stirring to an ice-cold suspension of lithium aluminium hydride (2 g.) in dry ether (50 c.c.). The mixture was refluxed for 17 hr. The product was cooled, and the excess of lithium aluminium hydride decomposed with saturated aqueous sodium sulphate solution. Anhydrous sodium sulphate was next added in lumps and the separated solids were filtered off and washed well with ether. Removal of the solvent gave a colourless gummy mass (1·35 g.). A fraction (0·2 g.) of this product was chromatographed on alumina (Merck). Fractions 2—6 (30 c.c. each), eluted with light petroleum afforded a scum which was rejected. Fractions 7—12 (30 c.c. each), eluted with benzene, gave the unsaturated alcohol (XXXIX) (50 mg.). This was crystallised from light petroleum as waxy solid, m. p. 70—71°. It gave a strong yellow coloration with tetranitromethane. The remaining portion of the gummy mass (1 g.) was hydrogenated in ethanol (15 c.c.) in the presence of 10% palladium–charcoal (100 mg.). This was filtered and the solvent removed *in vacuo*. The saturated alcohol thus obtained was dissolved in acetone (10 c.c.) and treated with Jones's reagent dropwise at room temperature, with shaking, until an orange colour persisted. The mixture was set aside at room temperature for 30 min., diluted with water, and the product extracted with ether (brine). The *ketone*, after removal of the solvent, was distilled at 100—105°/0·6 mm. (Found: C, 81·6; H, 11·2. $C_{15}H_{24}O$ requires C, 81·7; H, 11·0%). It afforded the 2,4-*dinitrophenylhydrazone*, needles, m. p. 171° (from methanol–ethyl acetate) (Found: C, 62·9; H, 7·0; N, 13·8. $C_{21}H_{28}N_4O_4$ requires C, 63·0; H, 7·0; N, 14·0%).

4,4,8-*Trimethyltricyclo*[6,3,1,$0^{1,5}$]*dodecane* [(±)-*Clovane*] (VII).—The ketone (300 mg.) in redistilled diethylene glycol (5 c.c.) was heated under reflux with 100% hydrazine (1 c.c.) for 2 hr. A solution of sodium (150 mg.) in diethylene glycol (3·5 c.c.) was added and the whole heated at 180° for 2 hr. and at 210° for a further 4 hr. The product was diluted with water, acidified, and extracted with ether. The *hydrocarbon* was isolated on distillation and purified by redistillation over metallic sodium, b. p. 80—85°/10 mm. (Found: C, 87·3; H, 13·0. $C_{15}H_{26}$ requires C, 87·3; H, 12·7%).

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