821. *Studies in the Synthesis of Terpenes. Part VII.* Synthesis of 9-Methyl-6-oxo-$\Delta^{4(10)}$-1-octalylacetic Acid.*

By B. R. DAVIS, S. R. GUPTA, and T. G. HALSALL.

Two methods have been devised for the synthesis of the substituted cyclohexanone (IX). This has been converted into the octalylacetic acid (XIV; R = H).

AN intermediate of interest for the synthesis of triterpenes is the bicyclic acid(I).[1,2] It had been our aim to synthesise it starting from 10-methyl-$\Delta^{1(9)}$-octal-2-one (II) by way of the decalone (III).[3] Attempts, however, to bring about alkylation at $C_{(1)}$ in the decalone all failed. Very recently Church, Ireland, and Marshall[2] have introduced a substituent in this position in a different, but very ingenious manner, by pyrolysing the compound (IV) to the aldehyde (V).

Our attention has now turned to the possibility of preparing the intermediate (I) by starting with the acid (XIV; R = H), which already contains a substituent at the position equivalent to $C_{(9)}$ in the triterpenes, and bringing about the transformations on it already accomplished with the octalone (II).[3] As a preliminary, the synthesis of the acid (XIV) has been studied.

Ethyl 2-methyl-3-oxocyclohexylacetate (IX; R = Et) has been prepared by two methods. In the first, the starting material was 2-methylcyclohexane-1,3-dione which was converted by the procedure of Eschenmoser, Schreiber, and Julia[4] into the isobutyl enol ether (VI). The ether was treated under Reformatsky conditions with zinc and ethyl bromoacetate, giving the cyclohexylideneacetate (VII) in 50% yield. Its ultraviolet absorption ($\lambda_{max.}$ 2650 Å, ε 18,000) indicated that the intermediate β-hydroxy-ester had been dehydrated and that no homoannular diene was present. The enol ether group was cleaved by dissolving the product (VII) in a small volume of methanol

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* Part VI, *J.*, 1961, 3251.

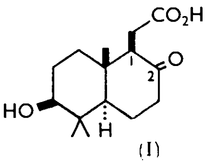
[1] Stork, Davies, and Meisels, *J. Amer. Chem. Soc.*, 1959, **81**, 5516.

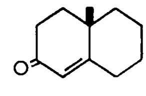
[2] Church, Ireland, and Marshall, *Tetrahedron Letters*, 1961, No. 1, 34.

[3] Halsall, Rodewald, and Willis, *J.*, 1959, 2798.

[4] Eschenmoser, Schreiber, and Julia, *Helv. Chim. Acta*, 1953, **36**, 482.

and adding a catalytic amount of hydrochloric acid. After the solution had been kept at 20° for about 15 minutes it was worked up and the cyclohexenone (VIII) was obtained in good yield: its ultraviolet and infrared spectra [$\lambda_{max.}$ 2425 Å, ε 12,250; $\nu_{max.}$ 1735 (satd. CO_2Et), and 1667 and 1616 (C=C·CO–) cm.$^{-1}$] showed that an αβ-unsaturated ketone grouping was present rather than an αβ-unsaturated ester grouping. The cyclohexenone (VIII) was finally hydrogenated over palladium–charcoal to give the ethyl ester (IX; R = Et).


(I)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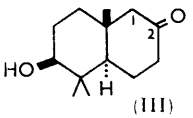
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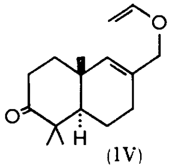
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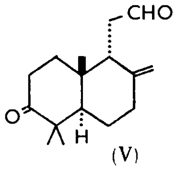
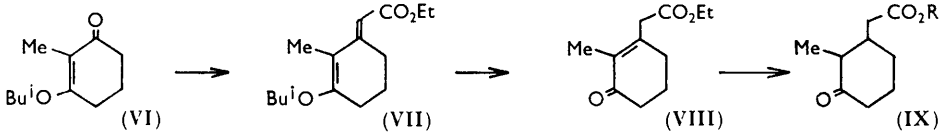
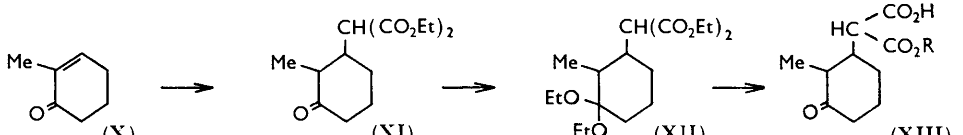
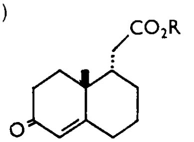

(V)

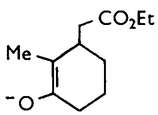
All the substances obtained are racemates.

In the second method 2-methylcyclohexanone was used as starting material. It was converted by the procedure of Warnhoff and Johnson[5] into 2-methylcyclohex-2-en-1-one (X), and this into the cyclohexylmalonate (XI) in 78% yield by Michael addition of the anion from diethylmalonate across the double bond. The keto-group in the malonate (XI) was protected by ketalisation using triethyl orthoformate, and the resulting ketal ester (XII) was partially hydrolysed with one mol. of potassium hydroxide in aqueous ethanol. After hydrolysis of the ketal the resulting acidic fraction was decarboxylated to a mixture of the cyclohexylacetic acid (IX; R = H) (17%) and its ester (IX; R = Et) (63%). The ester was identical with that prepared from 2-methylcyclohexane-1,3-dione. As it was prepared by a method which will permit the methyl group next to the carbonyl group to take up the more stable configuration it is likely that the methyl group is *trans* to the ethoxycarbonylmethyl group.





(XIV) 

 (XV)

The addition of a second ring to the keto-ester (IX; R = Et) was best brought about by condensing it with methyl vinyl ketone in benzene in the presence of " Triton B " in benzene–ethanol: the ester (XIV; R = Et) was then obtained in *ca.* 30% yield, unchanged keto-ester (IX; R = Et) being recovered in a fairly pure state. The ester (XIV; R = Et) was characterised by hydrolysis to the crystalline acid (XIV; R = H). If the addition of the methyl vinyl ketone occurs axially[6] to the enolate anion (XV) in the conformation

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[5] Warnhoff and Johnson, *J. Amer. Chem. Soc.*, 1953, **75**, 494.

[6] Cf. Howe and McQuillin, *J.*, 1958, 1194.

with the ethoxycarbonylmethyl group equatorial, then in the ester (XIV; R = Et) and the corresponding acid the side-chain will be *trans* to the angular methyl group.

EXPERIMENTAL

M. p.s were determined on a Kofler block and are corrected.

3-*Isobutoxy*-2-*methylcyclohex*-2-*enone* (VI).—This enol ether, n_D^{20} 1·5050, $\lambda_{max.}$ 2670 Å (ε 18,000), was prepared in *ca.* 90% yield by the method of Eschenmoser, Schreiber, and Julia[4] from 2-methylcyclohexane-1,3-dione.[7]

Preparation of Ethyl 3-*Isobutoxy*-2-*methylcyclohex*-2-*enylideneacetate* (VII).—Freshly activated zinc wool (3·3 g., 1·0 atom-equiv.) and a few crystals of iodine were placed in a three-necked flask. Part (~10 c.c.) of a mixture of 3-isobutoxy-2-methylcyclohex-2-enone (9·1 g., 1·0 mol.), ethyl bromoacetate (8·4 g., 1·0 mol.), and dry benzene (40 c.c.) was run on to the zinc at 100° with stirring. A vigorous reaction soon started. The rest of the mixture was added dropwise during 45 min. by which time nearly all the zinc had dissolved. After the mixture had been heated and stirred for a further 2 hr. it was cooled and 10% sulphuric acid (25 c.c.) was added. The benzene layer was separated and worked up in the usual manner, to give a yellow liquid (9·07 g.). This was distilled at 0·06—0·08 mm. to give a series of fractions (6·32 g.), b. p. 93° to 95—98°, n_D^{20} 1·5000 and a fraction, b. p. 98—125°, n_D^{20} 1·5021. The fractions with n_D^{20} 1·5000 were combined to give *ethyl* 3-*isobutoxy*-2-*methylcyclohex*-2-*enylideneacetate* (VII), $\lambda_{max.}$ 2650 Å (ε 18,000) (Found: C, 71·2; H, 9·55. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%). In subsequent experiments larger quantities of 3-isobutoxy-2-methylcyclohex-2-enone were employed without appreciable change in yield.

Ethyl 2-*Methyl*-3-*oxocyclohex*-1-*enylacetate* (VIII).—Ethyl 3-isobutoxy-2-methylcyclohex-2-enylideneacetate (7 g.) in methanol (25 c.c.) and water (5 c.c.) was treated with hydrochloric acid and kept at 20° for 20 min. The mixture was then poured into ether (1 l.), washed with 1% aqueous sodium hydroxide and water, and dried ($MgSO_4$). Distillation gave the *ester* (VIII) (4·2 g.), b. p. 78—82°/0·03 mm., n_D^{21} 1·4899, $\lambda_{max.}$ 2425 Å (ε 12,250), $\nu_{max.}$ 1735, 1667, and 1616 cm.$^{-1}$ (Found: C, 66·9; H, 8·45. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·2%). It formed a 2,4-*dinitrophenylhydrazone*, m. p. 108—110° (Found: C, 54·35; H, 5·45; N, 14·45. $C_{17}H_{20}N_4O_6$ requires C, 54·25; H, 5·35; N, 14·9%).

Ethyl 2-*Methyl*-3-*oxocyclohexylacetate* (IX).—The ester (VIII) (5 g.) in ethanol (100 c.c.) was hydrogenated over 5% palladised charcoal (500 mg.) for 45 min. After filtration, distillation gave the *ester* (IX) (4·1 g.), b. p. 72—74°/0·05 mm., n_D^{17} 1·4630, $\nu_{max.}$ 1735 and 1718 cm.$^{-1}$ (Found: C, 66·6; H, 9·05. $C_{11}H_{18}O_3$ requires C, 66·65; H, 9·15%).

2-*Methylcyclohex*-2-*enone* (X).—This was prepared by the method of Warnhoff and Johnson.[5] 2-Methylcyclohexanone with sulphuryl chloride gave 2-chloro-2-methylcyclohexanone which was dehydrochlorinated directly with collidine at 160° to give 2-methylcyclohex-2-enone, b. p. 90—91°/25 mm., n_D^{25} 1·4851, $\lambda_{max.}$ 2340 Å (ε 9090). Warnhoff and Johnson[5] give b. p. 98—101°/77 mm., n_D^{25} 1·4836, $\lambda_{max.}$ 2340 Å (ε 9660).

Diethyl 2-*Methyl*-3-*oxocyclohexylmalonate* (XI).—Sodium ethoxide (0·5 g.) in ethanol (15 c.c.) was added to a mixture of diethyl malonate (16·2 g., 0·1 mole) and 2-methylcyclohex-2-enone (5·5 g., 0·05 mol.), and the solution was kept at 60° for 5 hr. and then at 20° for 12 hr. After neutralisation with acetic acid and dilution with water, the solution was extracted with ether to give a brown oil (no band at 1685 cm.$^{-1}$). Distillation gave diethyl 2′-methyl-3′-oxocyclohexylmalonate as a viscous liquid (78% yield), b. p. 125—130°/0·1 mm., n_D^{25} 1·4520, $\nu_{max.}$ (natural film) 1754 (sh), 1730, and 1715 (sh) which was characterised as its 2,4-*dinitrophenylhydrazone*, needles (from methanol), m. p. 140—141° (Found: C, 53·1; H, 5·75; N, 12·7. $C_{20}H_{26}N_4O_8$ requires C, 53·3; H, 5·8; N, 12·4%), $\lambda_{max.}$ 3600 Å (ε 21,650).

Partial Hydrolysis of Diethyl 2-*Methyl*-3-*oxocyclohexylmalonate*.—The ester (14·0 g.) was heated under reflux with triethyl orthoformate (40 c.c.), dry ethanol (50 c.c.), and toluene-*p*-sulphonic acid (0·1 g.) for 4 hr. The pH was adjusted to 10 with sodium ethoxide, and some solvent was removed. At this stage the solute had no absorption at 1715 cm.$^{-1}$. Potassium hydroxide (2·90 g., 1 mol.) in aqueous ethanol was added and the solution stored at 20° for 12 hr. Dilution with water and extraction with ether gave a neutral fraction (3·7 g., 21%)

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[7] Stetter, Büntgen, and Coenen, *Chem. Ber.*, 1955, **88**, 77.

whose infrared spectrum was identical with that of the intermediate ketal ester. The aqueous layer was acidified and the oil which separated was extracted with ether–methylene chloride (10 : 1). The total acid fraction so obtained was heated at 170—180° for 10 min. and the product dissolved in ether. Extraction with sodium hydrogen carbonate solution yielded the crude acetic acid (IX; R = H) (1·50 g., 17%). Distillation gave *2-methyl-3-oxocyclohexylacetic acid* (IX; R = H), b. p. 140°/0·1 mm., which crystallised. Recrystallisation from ether–light petroleum afforded plates, m. p. 80—81° (Found: C, 63·5; H, 8·25. $C_9H_{14}O_3$ requires C, 63·5; H, 8·3%), $\nu_{\max.}$ 1705 cm.$^{-1}$. The *semicarbazone* had m. p. 182—190° (decomp.) (Found: C, 52·8; H, 7·5; N, 18·6. $C_{10}H_{17}N_3O_3$ requires C, 52·85; H, 7·5; N, 18·5%), $\lambda_{\max.}$ 2290 Å (ε 14,000).

The neutral residue (63%, 6·48 g.) left after decarboxylation, was distilled, to give the ester (IX; R = Et), n_D^{25} 1·4590, whose infrared spectrum was identical with that of the material prepared from 2-methylcyclohexane-1,3-dione (see above).

9β-*Methyl*-6-*oxo*-$\Delta^{5(10)}$-1α-*octalylacetic acid* (XIV; R = H).—A mixture of "Triton B" (5 c.c.), benzene (70 c.c.), and ethanol (75 c.c.) was distilled azeotropically until approximately 18—20 c.c. of liquid were left. This liquid (12 c.c.) was mixed with the ester (IX; R = Et) (11·7 g.) To this, at −20° under nitrogen, freshly distilled methyl vinyl ketone (7·2 c.c.) in benzene (15 c.c.) was added dropwise during 1 hr. with stirring. Care was taken that the temperature did not rise above −20° and that an atmosphere of nitrogen was maintained. The mixture was then kept at −10° for 9 hr. and at 20° for 8 hr. It was then poured into ether (2 l.), was washed with water, twice with 0·5N-hydrochloric acid, then with sodium hydrogen carbonate solution and with water, dried, and evaporated, affording a light yellow liquid (15·9 g.), $\lambda_{\max.}$ 2400 Å (ε 3800), n_D^{22} 1·5060, which was fractionally distilled. The first three fractions (3·9 g.), b. p. 62—71°/0·05 mm., n_D^{22} 1·4700, were mainly starting material. The next three fractions (6 g.), b. p. 72—75°/0·05 mm., were combined and redistilled at 72—75°/0·05 mm., to give four fractions (*a*—*d*). Fraction (*a*) contained starting material. Fractions (*b* and *c*) (3·4 g.) had $\lambda_{\max.}$ 2390 Å (ε 10,000). Fraction (*d*) (1·54 g.) had $\lambda_{\max.}$ 2390 Å (ε 11,600), and appeared to be the *ester* (XIV; R = Et) (Found: C, 72·15; H, 8·8. $C_{15}H_{22}O_3$ requires C, 71·95; H, 8·85%).

This ester (2·0 g.) was heated under reflux with potassium hydroxide (0·56 g.) in aqueous methanol (10 c.c.) for 1 hr. The acid fraction was chromatographed in benzene on silica gel. Elution with benzene–ether (1 : 1) gave the *acid* (XIV; R = H) as prisms (from ether and from benzene–light petroleum), m. p. 131—133° (Found: C, 70·6; H, 8·3. $C_{13}H_{18}O_3$ requires C, 70·25; H, 8·2%), $\lambda_{\max.}$ 2390 and 3150 Å (ε 17,700 and 70), $\nu_{\max.}$ 1705, 1657, and 1620 cm.$^{-1}$, τ 4·21 ($>$C:CH–) and 8·85 (singlet) ($-\overset{|}{\underset{|}{C}}-$Me) ($CHCl_3$ solution).

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