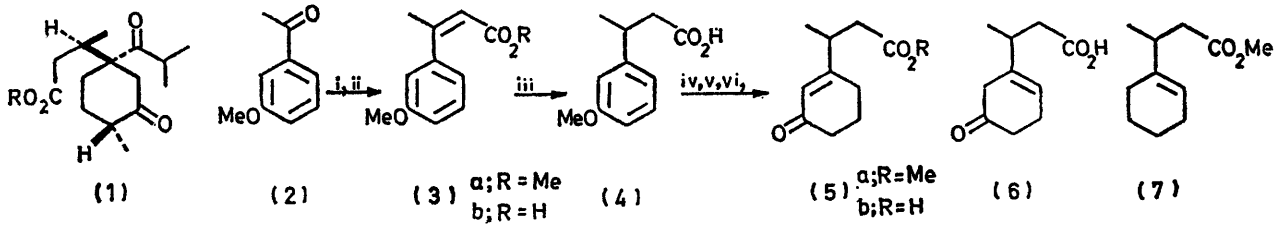
A Total Synthesis of (±)-Ethyl Acorate {(±)-Ethyl (3*RS*)-3-[(1*SR*,4*SR*)-1-Isobutyryl-4-methyl-3-oxocyclohexyl]butyrate} and (±)-Epiacoric Acid. An Application of the Generation and Alkylation of a Specific Enolate

By A. J. Birch,* J. E. T. Corrie, P. L. Macdonald, and G. Subba Rao, Research School of Chemistry, Australian National University, P.O. Box 4, Canberra ACT 2600, Australia

After the failure of appropriate conjugate additions to the model ketone methyl 3-(3-oxocyclohex-1-enyl)butyrate (5a), a mixture of (±)-ethyl acorate (1; R = Et) (see title) and (±)-ethyl epiacorate (20) (the 3-epimer) was obtained by manipulation of the addition product (13b) of a *cis–trans* mixture of but-2-enonitrile and the enolate anion generated by lithium–ammonia reduction of 1-isobutyryl-4-methylcyclohex-3-enyl acetate (12). Similar reductions of α-acetoxy-ketones may represent another general method for the production of specific enolate salts.

Acoric acid (1; R = H) [3-(1-isobutyryl-4-methyl-3-oxocyclohexyl)butyric acid] occurs in the roots of *Acorus calamus* L., a crude extract of which has been reported [1] to show antiepileptic activity. The disposition of functional groups, which results in some ready cyclisation reactions,[1] and the presence of the quaternary centre combine to make acoric acid a difficult exercise in total synthesis.

We initially envisaged the establishment of the quaternary centre by the conjugate addition of a suitable group to an appropriately substituted cyclohexenone, prepared by sequential metal–ammonia reduction and hydrolysis of an appropriate anisole derivative. The reactions leading to the required cyclohexenone derivative (5) are shown in Scheme 1.



Reagents: i, $(EtO)_2P^+(O^-)-CH_2\cdot CO_2Et$–NaH; ii, NaOH–$H_2O$; iii, Na–$NH_3$; iv, Li–$NH_3$–Bu^{t}OH; v, $(CO_2H)_2$–H_2O; vi, HCl–MeOH–H_2O

Scheme 1

The product from this reaction varied according to the hydrochloric acid concentration. Use of more concentrated acid led mostly to the ester (5a), whereas more dilute reagent gave the acid (5b). The product contained a small proportion of another compound, which from its i.r. and mass spectra appeared to be the ester (7). This material presumably arises by further reduction in the metal–ammonia solution.

Cyanation of αβ-unsaturated ketones is particularly useful for the generation of quaternary centres, since the introduced cyano-group can be converted into a variety of other substituents.[3] Reaction of an ethanolic solution of the ester (5a) with potassium cyanide at 25° led after 3 h to a single product, which was identified by its spectral properties as the corresponding ethyl ester. Thus cyanide ion appears to be an effective transesterification catalyst and may be of use with compounds which are sensitive to the strongly acidic or basic conditions normally employed. The reaction presumably occurs through an acyl cyanide intermediate, which reacts with the large excess of ethanol present.

$$RCO_2Me \rightleftharpoons RCO\cdot CN \rightleftharpoons RCO_2Et$$

When the methyl ester and potassium cyanide were heated under reflux in methanol, a high yield was obtained of a crystalline product, $C_{11}H_{13}NO_2$, $\nu_{max.}$ 3300—2500, 2230, 1690, and 1635 cm^{-1}, $\lambda_{max.}$ 271 nm (ε 8200), shifted to 303 nm (ε 17,700) by basification.

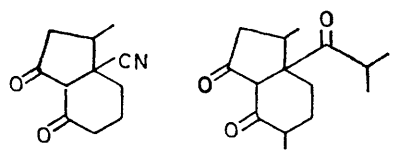
The acid (4) is known [2] but was prepared in the present work by the modified method shown. When it was reduced by the usual technique of addition of the alkali metal to a solution of the substrate and alcohol in liquid ammonia, a complex reaction occurred including reduction of the carboxy-group; the results are still being examined. However, it was possible to avoid most of the side-reactions by addition of a solution of the substrate in t-butyl alcohol to a solution of lithium in liquid ammonia. Treatment of the reduction product with aqueous oxalic acid yielded the βγ-unsaturated ketone (6) which, without purification, was treated with aqueous methanolic hydrochloric acid.

[1] A. J. Birch, F. A. Hochstein, J. A. K. Quartey, and J. P. Turnbull, *J. Chem. Soc.*, 1964, 2923.

[2] Z. Horii, Y. Tamura, H. Kugita, and K. Okumura, *J. Pharm. Soc. Japan*, 1954, **74**, 150; R. Granger, M. Corbier, J. Vinas, and P. Mau, *Bull. Soc. chim. France*, 1957, 815.

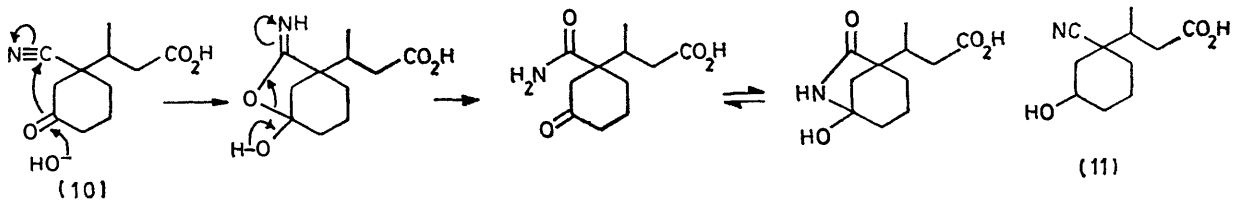
[3] W. Nagata, S. Hirai, H. Itazaki, and K. Takeda, *J. Org. Chem.*, 1961, **26**, 2413; W. Nagata, M. Yoshioka, and S. Hirai, *Tetrahedron Letters*, 1962, 461; W. Nagata, S. Hirai, H. Itazaki, and K. Takeda, *Annalen*, 1961, **641**, 184, 196.

These properties clearly indicate the presence of an enolised β-diketone grouping and this conclusion was supported by the formation of an intense violet colouration with iron(III) chloride solution. Apparently the initial cyanation product had undergone an internal Claisen condensation to give the bicyclic dione (8), which is analogous to the product (9) (both shown in the keto-form) that was obtained [1] from methyl acorate by treatment with sodium methoxide in refluxing methanol.



(8) (9)

In an attempt to avoid the development of basic conditions during cyanation reactions, Nagata [3] has carried out the reaction in aqueous dimethylformamide with added ammonium chloride to act as a buffer and with the reaction mixture kept at 100° to drive off ammonia as it was generated. When these conditions were applied to the acid (5b), cyanation was accompanied by extensive hydrolysis of the introduced cyano-group, but a low yield of the desired nitrile (10) could be isolated by virtue of its relatively low solubility. It has been suggested [4] that the ready hydrolysis of such 3-keto-nitriles occurs because of participation by the keto-group (Scheme 2).



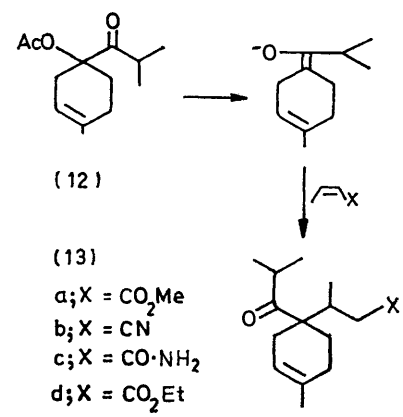
(10) (11)

SCHEME 2

Sodium borohydride reduction of the nitrile (10) proceeded smoothly to give an alcohol (11). However, all attempts to cause the cyano-group of (11) to react with an isopropyl Grignard reagent led to the recovery of unchanged starting material. This result may be rationalised in terms of steric factors: models reveal severe steric resistance to an approach of a nucleophile to the nitrile.

Attempted additions of some other nucleophiles did not yield useful products, and another approach was based on reasoning related to two known reactions: the reductive alkylation of αβ-unsaturated ketones [5] through a structurally uniform enolate anion, and the deacetoxylation of α-acetoxy-ketones by dissolving metals.[6,7] As with the reduction of αβ-unsaturated ketones, the generation of a specific enolate might be expected when an α-acetoxy-ketone is treated with a solution of lithium in ammonia. In the presence only of the weakly acidic liquid ammonia, this enolate should be stable and therefore able to react with alkylating agents. Unactivated ketones are known to function as Michael donors under basic conditions,[8,9] so that specific enolates generated in the foregoing manner should react with a suitable Michael acceptor, and a simple construction of the complete carbon skeleton of acoric acid could be envisaged. The acetoxy-ketone (12) should be convertible as shown into structure (13a or b) which on further manipulation should yield acoric acid (Scheme 3).

4-Methylcyclohex-3-enone (14) is readily prepared by Birch reduction of 4-methylanisole [10] followed by mild acidic hydrolysis of the enol ether function. It might be expected that the lithium salt of 2-isopropyl-1,3-dithian [11] would react with 4-methylcyclohex-3-enone to yield, after hydrolysis of the protecting group, 1-isobutyryl-4-methylcyclohex-3-enol (15). No such product was however obtained, presumably for steric reasons, and the only observable change was a slow shift of the double bond into conjugation with the carbonyl group.



(12)

(13)

a; X = CO_2Me

b; X = CN

c; X = $CO{\cdot}NH_2$

d; X = CO_2Et

SCHEME 3

[4] W. L. Meyer and N. G. Schrantz, *J. Org. Chem.*, 1962, **27**, 2011.

[5] G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Amer. Chem. Soc.*, 1965, **87**, 275.

[6] J. H. Chapman, J. Elks, G. H. Phillips, and L. J. Wyman, *J. Chem. Soc.*, 1956, 4344.

[7] J. S. Mills, H. J. Ringold, and C. Djerassi, *J. Amer. Chem. Soc.*, 1958, **80**, 6118.

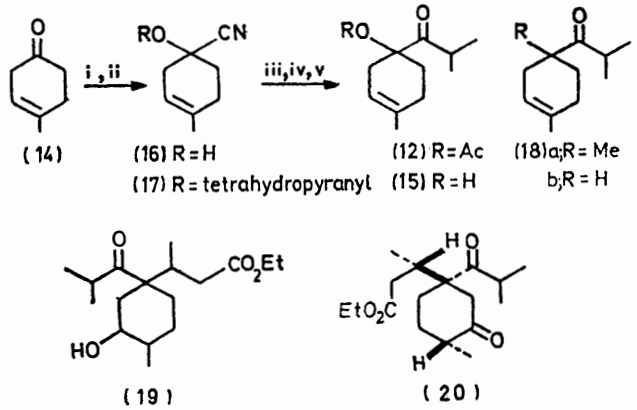
[8] H. A. Bruson, *Org. Reactions*, 1949, **5**, 79.

[9] E. D. Burgmann, D. Ginsburg, and R. Pappo, *Org. Reactions*, 1959, **10**, 179.

[10] A. J. Birch, *J. Chem. Soc.*, 1946, 593; E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, *J. Amer. Chem. Soc.*, 1968, **90**, 5618.

[11] E. J. Corey and D. Seebach, *Angew. Chem. Internat. Edn.*, 1968, **7**, 619.

An alternative approach to structure (12) is to introduce into (14) a C_1 unit such as CN which can be modified to produce the required ketol (15). Although a few cases are known in which cyanohydrins have been converted into ketones by a Grignard reagent, the yields reported have usually been low and the products frequently noted to contain material resulting from attack of the reagent on the ketone from which the cyanohydrin is derived.[12] Better results have been obtained by prior protection of the cyanohydrin as its ethoxyethyl [13] or tetrahydropyranyl [14] ether.



Reagents: i, $Me_2C(OH)\cdot CN$–H_2CO_3; ii, dihydropyran–HCl; iii, $Me_2CHMgBr$; iv, HCl–H_2O–MeOH; v, Ac_2O–*p*-$MeC_6H_4\cdot SO_3H$

SCHEME 4

In the preparation of the cyanohydrin (16), it was found to be essential to distil the acetone cyanohydrin [15] immediately before use, as the reagent appeared to deteriorate rapidly, and the use of aged material led to tars. Conversion [14] into the ether (17) proceeded readily only when undiluted reagents were used, since admixture with ether led to incomplete reaction. On treatment with isopropylmagnesium bromide, the cyano-ether (17) gave the ketol (15) in high yield, although it was necessary to employ more vigorous acidic conditions for hydrolysis of the intermediate imino-ether than those in the literature.[14] The ketol was then readily converted [16] into the required acetoxy-ketone (12).

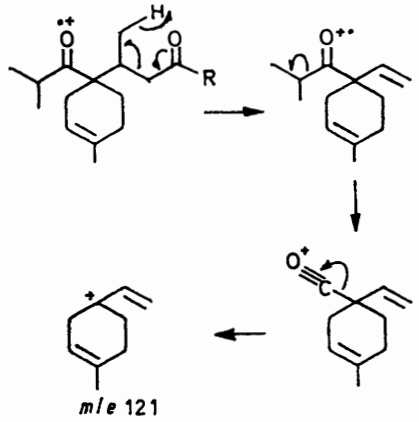
To assess whether the specifically orientated enolate anion was retained or had equilibrated with other enols, the acetoxy-ketone (12) was treated with lithium in ammonia, and the solvent was replaced by tetrahydrofuran. G.l.c. analysis of the material obtained by further treatment with methyl iodide showed one major product, which was isolated by preparative g.l.c. and shown by its spectral properties to be the expected ketone (18a); a minor product was the deacetoxylated ketone (18b).

[12] K. Kaji, *Yakugaku Zasshi*, 1957, 77, 851, 855, 858 (*Chem. Abs.*, 1958, 1949).
[13] H. J. Sims, H. B. Parseghian, and P. L. De Benneville, *J. Org. Chem.*, 1958, **23**, 724.
[14] I. Elphinoff-Felkin, *Bull. Soc. chim. France*, 1955, 784.
[15] A. A. Akhrem and A. V. Kamernitskii, *Zhur. obshchei Khim.*, 1955, **25**, 1345 (*Chem. Abs.*, 1956, **50**, 4950).

Treatment of the lithium enolate with methyl but-2-enoate gave no useful product, but a commercially available *cis–trans* mixture of but-2-enonitrile did react, preferably in liquid ammonia, and the product, apart from polymeric material, was a mixture of the ketone (18) and the desired keto-nitrile (13b), which could be separated by efficient distillation. The complexity of the methyl resonances in the ^1H n.m.r. spectrum of the nitrile clearly showed that it was a mixture of diastereoisomers.

Neither acidic nor alkaline hydrolysis of the nitrile (13b) gave satisfactory results, but treatment with alkaline hydrogen peroxide [17] gave the amide (13c). A possible side-reaction was not observed: there was no detectable epoxidation of the double bond, although peroxyimidic acids are known to effect this reaction in other systems.[18] Dreiding models indicate that an intramolecular epoxidation is unlikely, and the relatively high dilution and the bulk of the quaternary centre in the intermediate would tend to depress the rate of an intermolecular reaction. Treatment of the amide with triethyloxonium fluoroborate,[19] followed by brief acidic hydrolysis, gave the ethyl ester (13d).

The mass spectra of compounds (13b, c, and d) all showed an abundant fragment ion at *m/e* 121, which further confirmed their structures and hence the regiospecificity of the alkylation step. A possible scheme for its formation is shown (Scheme 5).



SCHEME 5

The methylcyclohexene ring was converted into methylcyclohexanone in two ways, both of which led to diastereoisomeric mixtures of racemic ethyl acorate and ethyl epiacorate. The first involved hydroxylation of the double bond with osmium tetroxide,[20] followed by treatment of the glycol with hot formic–sulphuric acid, but the overall yield was low and it was difficult to purify the product. A better method consisted of

[16] R. B. Turner, *J. Amer. Chem. Soc.*, 1953, **75**, 3489.
[17] D. H. R. Barton, E. F. Lier, and J. F. McGhie, *J. Chem. Soc.* (*C*), 1968, 1031.
[18] G. B. Payne, P. H. Deming, and P. H. Williams, *J. Org. Chem.*, 1961, **26**, 659; G. B. Payne, *Tetrahedron*, 1962, **18**, 763.
[19] L. A. Paquette, *J. Amer. Chem. Soc.*, 1964, **86**, 4096.
[20] D. H. R. Barton and D. Elad, *J. Chem. Soc.*, 1956, 2085.

hydroboration of the double bond and oxidation of the borane with hydrogen peroxide and sodium acetate to give the alcohol (19) in nearly quantitative yield. The failure of diborane to reduce the side-chain carbonyl group must be due to steric effects. The corresponding carbonyl group in methyl acorate was not reduced by potassium borohydride.[1] The alcohol (19) was readily oxidised by a modified Collins' procedure [21] to the corresponding ketone, which was a mixture of diastereoisomers similar to that obtained by the previous method. We could not resolve the mixture by g.l.c., but comparison of its ^{1}H n.m.r. spectrum with that of authentic ethyl acorate clearly indicated that it contains the latter mixed with a stereoisomer in the ratio 4 : 5.

Through the kindness of Dr. Schudel and Dr. Hrivnac (Givaudan-Esrolko AG, Dübendorf) the mixture of esters was examined on a capillary g.l.c. column (22 m × 0·3 mm) at 180° in helium, which permitted resolution of the isomers. Co-injection of authentic ethyl acorate showed that its retention time was identical with that of one of the two components of the mixture. Owing to some decomposition on the column, mostly of the natural stereoisomer and also observed with authentic material, the ratio of products could not be determined with accuracy by this method, although it appears that ethyl acorate is less abundant than ethyl epiacorate, in accord with the ^{1}H n.m.r. conclusions.

Even mild alkaline hydrolysis of the mixture gave a number of products, and the only crystalline acid isolated was not (±)-acoric acid. Re-esterification of this acid with diazoethane gave a single substance, the ^{1}H n.m.r. spectrum of which showed its identity with the major component of the previous mixture of esters. Since the experimental conditions would certainly establish the stable equatorial configuration of the ring methyl adjacent to carbonyl, as in acoric acid, the product must be the 3-epimer (20). The other products of alkaline reaction are probably the result of intramolecular processes, to which acoric acid and its derivatives are particularly prone;[1] attempted alkaline hydrolysis of authentic ethyl acorate also gave no acoric acid. Acidic hydrolysis or attempted demethylation with boron trichloride of the synthetic mixture failed to yield any crystalline acoric acid.

The ^{1}H n.m.r. spectra of the diastereoisomers show marked differences. Examination of models suggests that the configuration of the side-chain methyl group may have a considerable influence on the conformation of the isobutyryl side-chain, with the result that this would tend to lie over different portions of the ring in the two isomers. In this event the protons affected by the anisotropic effect of the isobutyryl carbonyl group would show different chemical shifts in the isomers, as was observed. Such conformational differences could explain the differing stabilities to alkali of the epimeric esters.

[21] R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, 1970, **35**, 4000.

The reduction of α-acetoxy- and similar ketones promises to be another general method for the generation of specific enolate anions. Since this work was completed, a similar type of process has been reported [22] in the reduction of an α-epoxy-ketone.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were determined for solutions in carbon tetrachloride, unless otherwise stated, on a Perkin-Elmer 257 instrument, and u.v. spectra were recorded for solutions in ethanol on a Unicam SP 800 spectrophotometer. ^{1}H N.m.r. spectra were recorded for solutions in deuteriochloroform on a Varian HA-100 spectrometer, with tetramethylsilane as standard. Mass spectra were taken on an A.E.I. MS902 instrument; in general only those signals of greater than 10% relative intensity are reported. Analytical g.l.c. was carried out on a Perkin-Elmer 881 gas chromatograph with glass columns (6 ft × ⅛ in) packed with 1·5% XE60 or 5% Carbowax 20M on Chromosorb W (80—100 mesh) and nitrogen carrier gas at a flow rate of 30 ml min^{-1}. Small scale preparative g.l.c. was performed on a Varian Aerograph 202-1C gas chromatograph with a stainless steel column (5 ft × 0·25 in) packed with 20% Carbowax 20M on Chromosorb W (60—80 mesh) and helium carrier gas at a flow rate of 60 ml min^{-1}. Preparative t.l.c. was carried out on plates (20 × 20 × 0·1 cm) coated with Merck KGF_{254} adsorbent.

Ethyl 3-(3-*Methoxyphenyl*)*but*-2-*enoate* (3a).—Ethyl diethoxyphosphinylacetate (74·7 g) was added during 45 min under nitrogen to a stirred suspension of sodium hydride (8 g) in dry benzene (100 ml) at 30—35°. The mixture was stirred for a further 1 h at room temperature, after which a solution of 3′-methoxyacetophenone (50 g) in dry benzene (50 ml) was added during 40 min while the temperature was maintained at 20—22°. The mixture was heated at 65° for 15 min, cooled, diluted with water, and extracted with benzene. The extract was washed with water and brine, dried, and evaporated, and the residue was distilled to afford the ester (3a) (55 g, 77%), b.p. 115—117° at 0·35 mmHg (lit.,[2] 150—152° at 5 mmHg); δ 6·7—7·4 (4H, m, aromatic), 6·10 [1H, q, *J* 1·5 Hz, C(2)H], 4·19 (2H, q, *J* 7 Hz, O·CH_2), 3·78 (3H, s, OMe), 2·53 (3H, d, allylic Me), and 1·30 p.p.m. (3H, t, CH_2·CH_3).

3-(3-*Methoxyphenyl*)*but*-2-*enoic Acid* (3b).—The ester (3a) was hydrolysed according to the method of Granger *et al.*[2] to afford the acid (3b), m.p. 100—101° (lit.,[2] 101—102°), δ 6·8—7·5 (4H, m, aromatic), 6·20 [1H, q, *J* 1 Hz, C(2)H], 3·86 (3H, s, OMe), and 2·61 p.p.m. (3H, d, allylic Me).

3-(3-*Methoxyphenyl*)*butanoic Acid* (4).—To a stirred solution of the acid (3b) (15 g) in liquid ammonia (700 ml), sodium (15 g) was added, and the solution was stirred for 2 h. Ammonium chloride was added to destroy excess of sodium and the ammonia was allowed to evaporate. The residue was diluted with water, washed with ether, and acidified with concentrated hydrochloric acid. The material recovered with ethyl acetate was distilled to give the acid (4) (14 g), b.p. 140—143° at 0·2 mmHg (lit.,[2] 149—152° at 1·5 mmHg); δ 6·6—7·3 (4H, m, aromatic), 3·77 (3H, s, OMe), 3·25 [1H, m, C(3)H], 2·60 [2H, m, $C(2)H_2$], and 1·31 p.p.m. (3H, d, *J* 6 Hz, CH_3·CH).

[22] J. D. McChesney and A. F. Wycpalek, *Chem. Comm.*, 1971, **542**.

Methyl 3-(3-*Oxocyclohex*-1-*enyl*)*butanoate* (5a).—A solution of the acid (4) (28 g) in anhydrous t-butyl alcohol (250 ml) was added during 15 min to a stirred solution of lithium (6 g) in liquid ammonia (2·5 l). After a further 2 h, ammonium chloride was added to destroy the excess of lithium and the ammonia was allowed to evaporate. The residue was diluted with water, washed with ether, and acidified with oxalic acid. The solution was saturated with ammonium sulphate and extracted with ether to yield the crude βγ-unsaturated ketone (6) as an oil (25·2 g), $\nu_{max.}$ 3700—2400, 1720, and 1710 cm^{-1}. This material was left in methanol (80 ml) and M-hydrochloric acid (220 ml) for 2 h; the solution was then concentrated under reduced pressure and extracted with ether. The extract was washed with sodium hydrogen carbonate solution, dried, and evaporated to yield the crude *keto-ester* (5a) (4·7 g). After preparative t.l.c. (light petroleum–esther, 1 : 3) followed by short-path distillation the product had t_R 4·4 min (XE60; 150°) (Found: C, 67·3; H, 8·1%; M^+, 196. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·3%; M, 196); $\lambda_{max.}$ 234 nm (ε 14,700); $\nu_{max.}$ 1738, 1670, and 1625 cm^{-1}; δ 5·86 (1H, s, –CH=), 3·65 (3H, s, OMe), 2·20—2·95 [7H, m, C(2)H_2, C(3)H, ring C(4)H_2, and ring C(6)H_2], 1·83—2·16 [2H, m, ring C(5)H_2], and 1·17 p.p.m. (3H, d, J 6·5 Hz, CH_3·CH).

The sodium hydrogen carbonate extract was acidified with concentrated hydrochloric acid, saturated with ammonium sulphate, and extracted with ether to afford the crude *acid* (5b), $\nu_{max.}$ 3700—2400, 1710, and 1670 cm^{-1}. Treatment of this material with ethereal diazomethane, followed by preparative g.l.c. (20% Carbowax 20M; 120° then 1° min^{-1}) afforded, as well as a small proportion (*ca.* 10%) of the ester (7), the ester (5a) (Found: M^+, 182. $C_{11}H_{18}O_2$ requires M, 182); $\nu_{max.}$ 1740 cm^{-1}.

Ethyl 3-(3-*Oxocyclohex*-1-*enyl*)*butanoate*.—A solution of the methyl ester (5a) (0·25 g) and potassium cyanide (0·25 g) in 95% ethanol (12 ml) was stirred at room temperature for 3 h; t.l.c. then showed the absence of starting material. The solution was concentrated, diluted with water, and extracted with ether to give the crude ethyl ester of the acid (5b) (0·26 g). After preparative t.l.c. (light petroleum–ether, 3 : 7), the product had $\lambda_{max.}$ 234 nm; $\nu_{max.}$ 1735, 1670, and 1625 cm^{-1}; *m/e* 210.

9-*Methyl*-5,7-*dioxobicyclo*[4,3,0]*nonane*-1-*carbonitrile* (8).—A solution of the methyl ester (5a) (2·7 g) and potassium cyanide (2 g) in methanol (28 ml) and water (2 ml) was refluxed for 2 h, concentrated, diluted with water, and washed with ether. The aqueous solution was acidified with concentrated hydrochloric acid, saturated with ammonium sulphate, and extracted with ether to yield the *diketone* (8), m.p. 121—122° (from ethyl acetate–cyclohexane) (Found: C, 69·6; H, 7·0; N, 7·1%; M^+, 191. $C_{11}H_{13}NO_2$ requires C, 69·1; H, 6·9; N, 7·3%; M, 191); δ 10·2br (1H, s, OH), 1·8—2·8 (9H, m, aliphatic CH), and 1·35 p.p.m. (3H, d, Me).

3-(1-*Cyano*-3-*oxocyclohexyl*)*butanoic Acid* (10).—A solution of the acid (5b) (13 g), potassium cyanide (9 g), and ammonium chloride (5·5 g) in dimethylformamide (560 ml) and water (70 ml) was stirred at 97° for 12 h, then evaporated to dryness. The residue was taken up in saturated ammonium sulphate solution and acidified with concentrated hydrochloric acid. Extraction with ethyl acetate gave a brown gum (11·8 g) which deposited the *cyano-acid* (10) (2·5 g) when left at 0° in a small volume of ethyl acetate. Recrystallisation from ethyl acetate–cyclohexane gave a sample of m.p. 144—147° (Found: C, 63·1; H, 7·2; N, 6·7%; M^+, 209. $C_{11}H_{15}NO_3$ requires C, 63·1; H, 7·2; N, 6·7%; M, 209); $\nu_{max.}$ (Nujol) 3700—2400, 2240, 1728, and 1695 cm^{-1}; δ [$(CD_3)_2SO$] 12·1br (1H, s, CO_2H), 1·4—2·8 (11H, m, aliphatic CH), and 1·02 and 1·04 p.p.m. (total 3H, 2 × d, J 6·0 Hz, CH·CH_3 of diastereoisomers); *m/e* 41(39%), 42(22), 43(22), 45(12), 53(14), 55(25), 67(37), 68(15), 69(28), 87(11), 94(20), 95(24), 121(16), 122(100), 123(48), and 191(12).

3-(1-*Cyano*-3-*hydroxycyclohexyl*)*butanoic Acid* (11).—A solution of the cyano-acid (10) (0·69 g) and sodium borohydride (0·40 g) in ethanol (30 ml) was kept at 4° for 16 h, concentrated under reduced pressure, and diluted with saturated ammonium sulphate solution. The mixture was extracted with ethyl acetate to afford the alcohol (11) as a gum (0·64 g), $\nu_{max.}$ 3700—2300, 2240, and 1710 cm^{-1}. Esterification with ethereal diazomethane gave the corresponding *methyl ester*, t_R 7·5 min (XE60; 180°) (Found: M^+, 225·1363. $C_{12}H_{19}NO_3$ requires M, 225·1365); $\nu_{max.}$ 3400, 2240, and 1740 cm^{-1}; δ 4·05 [1H, envelope, ring C(3)H], 3·68 (3H, s, OMe), 1·2—2·9 (12H, m, aliphatic CH and OH), and 1·11 p.p.m. (3H, d, CH·CH_3).

Attempted Grignard Reactions.—A solution of the nitrile (11) (0·5 g) in ether (10 ml) was added to isopropylmagnesium bromide [from isopropyl bromide (2 g), magnesium (0·5 g), and ether (30 ml)] and the mixture was refluxed under nitrogen for 2 days, cooled, and diluted with saturated ammonium sulphate solution. The mixture was extracted with ethyl acetate and the extracts washed with water and brine, dried, and evaporated to afford only starting material (0·45 g), identified by its i.r. spectrum and, after esterification with diazomethane, by its g.l.c. retention time. Similar results were obtained with isopropylmagnesium iodide and when tetrahydrofuran was used as the solvent.

4-*Methylcyclohex*-3-*enone* (14).—Reduction of 4-methylanisole with lithium–t-pentyl alcohol–liquid ammonia gave 1-methoxy-4-methylcyclohexa-1,4-diene,[10] t_R 5·2 min (5% Carbowax 20M; 70°) contaminated with *ca.* 5% of 1-methoxy-4-methylcyclohexene, t_R 1·7 min. Hydrolysis of the mixture with cold 25% sulphuric acid yielded 4-methylcyclohex-3-enone, b.p. 74° at 22 mmHg (lit.,[10] 74° at 17 mmHg); $\nu_{max.}$ 1715 cm^{-1}; δ 5·43br (1H, s, –CH=), 2·82br (2H, s, =CH·CH_2·CO), 2·25—2·65 (4H, m, CH_2·CH), and 1·78br p.p.m. (3H, s, Me). A small broadened doublet at δ 6·87 (–CH=C·CO–) revealed the presence of *ca.* 5% of 4-methylcyclohex-2-enone.

2-*Isopropyl*-1,3-*dithian*.—This was prepared by the general method of Seebach and Steinmuller;[23] b.p. 111—113° at 15 mmHg (lit.,[24] 134° at 35 mmHg).

Attenpted Condensation of 2-*Isopropyl*-1,3-*dithian with the Ketone* (14).—Butyl-lithium (2·5M-solution in hexane; 22 ml) was added dropwise under nitrogen to a stirred solution of 2-isopropyl-1,3-dithian (8·1 g) in anhydrous tetrahydrofuran (150 ml), cooled to −30°. The solution was stirred at −30° for 2 h, after which a solution of 4-methylcyclohex-3-enone (5·5 g) in tetrahydrofuran (20 ml) was added slowly. This solution was kept at 5° for for 18 h, then concentrated under reduced pressure. The residue was shaken with water and ether, and the ether extracts were washed with brine, dried, and evaporated.

[23] D. Seebach and D. Steinmuller, *Angew. Chem. Internat. Edn.*, 1968, **7**, 619.

[24] S. Oae, *N.* Tagaki, and A. Ohno, *Tetrahedron*, 1964, **20**, 427.

The i.r. spectrum of the residue gave little indication of any reaction. When the mixture was kept at 5° for 80 h, then at 25° for 18 h, and worked up as before, the only significant change in the i.r. spectrum was the appearance of some conjugated ketone absorption.

4-*Methyl*-1-(*tetrahydropyran*-2-*yloxy*)*cyclohex*-3-*enecarbonitrile* (17).—A mixture of 4-methylcyclohex-3-enone (36 g) and freshly distilled acetone cyanohydrin (80 ml) was stirred under nitrogen, treated with aqueous 50% potassium carbonate (0·6 ml), and then stirred for 12 h at 25°. Toluene-*p*-sulphonic acid monohydrate (2 g) was added and after 10 min the mixture was diluted with ether and washed several times with slightly acidified water and brine, dried, and evaporated. The residue was fractionally distilled from a few crystals of toluene-*p*-sulphonic acid. After a forerun of unchanged acetone cyanohydrin, the required 1-*hydroxy*-4-*methylcyclohex*-3-*enecarbonitrile* (16) passed over as an oil (34 g, 76%), b.p. 96—98° at 0·6 mmHg, $\nu_{max.}$ 3420, 2250, and 1095 cm^{-1}. The cyanohydrin (34 g) was mixed with dihydropyran (67 ml) and a saturated solution of hydrogen chloride in ether (10 drops), and the mixture was stirred at room temperature for 36 h. After treatment with anhydrous potassium carbonate (2 g) it was diluted with ether, washed with sodium hydrogen carbonate and brine, dried (K_2CO_3), and evaporated. The residue was distilled from a little anhydrous potassium carbonate to afford the *cyano-ether* (17) as a sweet-smelling liquid (51 g, 90%), b.p. 103—104° and 0·6 mmHg (Found: C, 70·9; H, 8·5; N, 6·3%; M^+, 221. $C_{13}H_{19}NO_2$ requires C, 70·6; H, 8·6; N, 6·3%; *M*, 221); $\nu_{max.}$ 2245, 1125, 1080, and 1043 cm^{-1}; δ 5·25 (1H, m, –CH=), 5·08 (1H, m, O·CH·O), 3·40—3·70 and 3·72—4·10 (2H, 2 × m, CH_2·O), and 1·71br (3H, s, Me) superimposed on 1·4—2·8 p.p.m. (12H, envelope, aliphatic CH).

1-*Isobutyryl*-4-*methylcyclohex*-3-*enol* (15).—Isopropylmagnesium bromide was prepared under nitrogen from magnesium turnings (11·6 g) and isopropyl bromide (45·2 ml) in ether (300 ml). The solution was cooled below 5° and treated dropwise with a solution of the cyano-ether (17) (51 g) in ether (170 ml). The mixture was then stirred at 25° for 1 h and poured on a mixture of crushed ice and ammonium chloride. The ether layer was separated and the aqueous phase extracted with more ether. The combined extracts were washed with water and brine, dried, and evaporated. The residue was dissolved in methanol (400 ml) and 2M-hydrochloric acid (130 ml) and the solution was refluxed for 2 h, then cooled, diluted with water, and worked up in the usual way. The residue was distilled to yield the *ketol* (15) (38·8 g, 92%) as a liquid, b.p. 77—80° at 0·4 mmHg (Found: C, 72·9; H, 10·0%; M^+, 182. $C_{11}H_{18}O_2$ requires C, 72·5; H, 10·0%; *M*, 182); $\nu_{max.}$ 3600, 3480, 1705, 1385, and 1103 cm^{-1}; δ 5·28—5·46 (1H, envelope, =CH–), 3·64 (1H, s, OH), 3·14 (1H, septet, *J* 6·8 Hz, Me_2CH), 1·73br (3H, s, MeC=) superimposed on 1·3—2·8 (6H, m, aliphatic CH), and 1·11 p.p.m. [6H, d, $(CH_3)_2CH$].

1-*Isobutyryl*-4-*methylcyclohex*-3-*enyl Acetate* (12).—The ketol (15) (10·5 g) in acetic acid (100 ml) was added to a solution of toluene-*p*-sulphonic acid (21 g) in acetic anhydride (20 ml); the solution was kept overnight at 25°, then poured over crushed ice and extracted with ether. The extracts were washed with water, sodium carbonate, water, and brine, dried, and evaporated. The residue was distilled to give the *acetoxy-ketone* (12) (9·5 g, 73%) as a liquid, b.p. 92—96° at 0·7 mmHg (Found: C, 69·6; H, 9·3. $C_{13}H_{20}O_3$ requires C, 69·6; H, 9·0%); $\nu_{max.}$ 1740, 1720, and 1238 cm^{-1}; δ 5·29 (1H, envelope, =CH–), 3·00 (1H, septet, *J* 6·8 Hz, Me_2CH), 2·09 (3H, s, $MeCO_2$) and 1·71br (3H, s, MeC=) superimposed on 1·5—2·7 (6H, m, aliphatic CH), and 1·10 p.p.m. [6H, d, $(CH_3)_2CH$]; *m/e* 41(15%), 43(100), 71(27,) 77(14), 91(14), 93(49), 111(82), 113(22), 121(88), 149(15), and 164(23).

1,4-*Dimethylcyclohex*-3-*enyl Isopropyl Ketone* (18a).—A solution of the acetoxy-ketone (12) (0·5 g) in dry tetrahydrofuran (7 ml) was added dropwise under nitrogen to a stirred solution of lithium (40 mg) in anhydrous ammonia (20 ml). The solution was stirred for 10 min, diluted with tetrahydrofuran (20 ml), and refluxed briefly with nitrogen flow to drive off the ammonia. The solution was cooled to 5°, treated with methyl iodide (3 g), then refluxed for 1 h and left overnight at 25°. It was then diluted with water and worked up in the usual way. The residue was purified by short-path distillation at 0·5 mmHg (bath temp. 100—110°) to afford an oil (0·28 g). After preparative g.l.c., the *ketone* (18a) showed t_R 3·0 min (5% Carbowax 20M; 130°) (Found: M^+, 180. $C_{12}H_{20}O$ requires *M*, 180); $\nu_{max.}$ 1702 cm^{-1}; δ 5·34 (1H, envelope, CH), 3·20 (1H, septet, *J* 6·8 Hz, Me_2CH), 1·64br (3H, s, allylic Me) superimposed on 1·5—2·7 (6H, m, aliphatic CH), 1·14 (3H, s, CMe), and 1·02 and 1·06 p.p.m. [6H, 2 × d, $(CH_3)_2CH$] *m/e* 41(17%), 43(31), 55(10), 67(39), 71(10), 81(10), 93(11), 108(13), 109(100), and 137(37).

3-(1-*Isobutyryl*-4-*methylcyclohex*-3-*enyl*)*butyronitrile* (13b).—A solution of the acetoxy-ketone (12) (34·5 g) in dry tetrahydrofuran (450 ml) was added under nitrogen to a stirred solution of lithium (2·60 g) in anhydrous ammonia (650 ml). The solution was then stirred for 10 min, and a few crystals of hydrated iron(III) nitrate were added to destroy excess of lithium. When the blue colour had disappeared (*ca.* 5 min) a solution of crotononitrile (120 ml) in dry tetrahydrofuran (450 ml) was added and the mixture was kept at 0—5° for 12 h, then diluted with water and extracted with ether. The extracts were washed with dilute sulphuric acid, water, and brine, dried, and evaporated. To a solution of the residue in chloroform (140 ml) was added pentane (700 ml). After 1 h, the solvent was decanted from the precipitated gum and evaporated. The residue was distilled to give fraction A, b.p. 63—70° at 0·8 mmHg, and fraction B, b.p. 80—145° at 0·8 mmHg.

Fraction A was redistilled to afford the *ketone* (18b) (6 g), b.p. 56—58° at 0·4 mmHg (Found: C, 79·2; H, 10·9%; M^+, 166. $C_{11}H_{18}O$ requires C, 79·5; H, 10·9%; *M*, 166); $\nu_{max.}$ 1706 cm^{-1}; δ 5·39 (1H, envelope, –CH=), 2·78 (1H, septet, *J* 6·8 Hz, Me_2CH) superimposed on 2·5—2·9 (1H, envelope, CO·CH), 1·66br (3H, s, allylic Me) superimposed on 1·5—2·4 (6H, m, aliphatic CH), and 1·10 p.p.m. [6H, d, $(CH_3)_2CH$]; *m/e* 41(15%), 43(47), 55(11), 67(22), 71(22), 79(10), 95(80), 123(100), and 166(15).

Fraction B was fractionally distilled through a Nester-Faust spinning-band column. After a forerun, the *nitrile* (13b) was obtained as a viscous liquid (9·2 g), b.p. 111—113° at 0·3 mmHg (Found: C, 77·1; H, 10·0; N, 6·3%; M^+, 233. $C_{15}H_{23}NO$ requires C, 77·2; H, 9·9; N, 6·0%; *M*, 233); $\nu_{max.}$ 2259 and 1692 cm^{-1}; δ 5·38 (1H, envelope, =CH–), 3·07 (1H, septet, *J* 6·6 Hz, Me_2CH), 1·62br (3H, s, allylic Me) superimposed on 1·5—2·7 (9H, m, aliphatic CH), and 0·90—1·12 p.p.m. (9H, m, 3 × CH·CH_3); *m/e* 41(25%), 43(100), 67(10), 71(79), 77(10), 79(13), 81(14), 91(10), 93(21), 119(22), 121(49), 162(56), 165(42), and 190(17).

3-(1-*Isobutyryl*-4-*methylcyclohex*-3-*enyl*)*butyramide* (13c). —To a stirred solution of the keto-nitrile (13b) (1 g) in acetone (35 ml) was added 2M-sodium hydroxide (1 ml), followed by hydrogen peroxide (30%; 6·6 ml). After 0·5 h further sodium hydroxide solution (0·73 ml) and hydrogen peroxide (4·8 ml) were added and the solution was stirred for 12 h at 25°, diluted with water, and extracted with ether. The extracts were washed with water to remove excess of peroxide then with brine, dried, and evaporated. The residue was triturated with carbon tetrachloride to give crystals of the *keto-amide* (13c) (0·7 g, 65%), m.p. 134—137° (unchanged by recrystallisation from carbon tetrachloride–hexane) (Found: C, 72·0; H, 10·4; N, 5·7%; M^+, 251. $C_{15}H_{25}NO_2$ requires C, 71·7; H, 10·0; N, 5·6%; *M*, 251); $\nu_{max.}$ ($CHCl_3$) 3520, 3400, 1687, 1675, and 1590 cm.$^{-1}$; δ 5·56—6·10 (2H, envelope, $CO{\cdot}NH_2$, exchanged with D_2O–NaOD), 5·37 (1H, envelope, =CH–), 3·16 (1H, septet, *J* 6·6 Hz, Me_2CH), 1·60br (3H, s, allylic Me) superimposed on 1·4—2·6 (9H, m, aliphatic CH), and 0·8—1·1 p.p.m. (9H, m, 3 × $CH{\cdot}CH_3$).

Ethyl 3-(1-*Isobutyryl*-4-*methylcyclohex*-3-*enyl*)*butyrate* (13d).—1-Chloro-2,3-epoxypropane (7·52 ml) was added under nitrogen to a stirred solution of freshly distilled boron trifluoride–ether complex (16 ml) in dry ether (60 ml) at such a rate that a gentle reflux was maintained. The mixture was stirred for a further 2 h, then left to settle, and the solvent was decanted. The residue was washed well with ether and dissolved in dry methylene chloride (40 ml). The solution was cooled to 15° and a solution of the keto-amide (13c) (4 g) in methylene chloride (80 ml) was added slowly. The solution was stirred under nitrogen for 18 h at 25°, then concentrated under reduced pressure, and the residue was refluxed for 0·5 h with 0·5M-sulphuric acid (80 ml). The solution was cooled and extracted with ether and the extracts were washed with water and brine, dried, and evaporated. The residue was chromatographed in chloroform–hexane (1 : 5) over silica gel (250 g). Elution with chloroform–hexane (2 : 1) gave an oil which upon distillation gave a very volatile forerun, followed by the *keto-ester* (13d) (2·1 g) as a viscous liquid, b.p. 152—154° at 1·7 mmHg (Found: C, 72·6; H, 9·9%; M^+, 280. $C_{17}H_{28}O_3$ requires C, 72·8; H, 10·1%; *M*, 280), $\nu_{max.}$ 1733, 1697, and 1182 cm^{-1}; δ 5·36 (1H, envelope, $-CH=$), 4·12 (2H, q, *J* 7·2 Hz, $O{\cdot}CH_2$), 3·13 (1H, septet, *J* 6·6 Hz, $Me_2(CH)$, 1·60br (3H, s, allylic Me) superimposed on 1·4—2·6 (9H, m, aliphatic CH), 1·26 (3H, t, $CH_2{\cdot}CH_3$), and 0·8—1·2 p.p.m. (9H, m, 3 × $CH{\cdot}CH_3$); *m/e* 41(29%), 43(73), 53(10), 55(14), 67(13), 69(17), 71(32), 77(14), 79(19), 81(26), 91(14), 93(26), 95(12), 105(17), 107(15), 119(23), 120(10), 121(81), 122(16), 123(18), 135(18), 147(10), 163(23), 164(12), 165(100), 166(16), 191(19), 209(16), 211(16), 237(15), and 280(14).

Ethyl Acorate {*Ethyl* (3RS)-3-[(1SR, 4SR)-1-*Isobutyryl*-4-*methyl*-3-*oxocyclohexyl*]*butyrate*} (1; R = Et).—An ethereal solution of acoric acid was treated with excess of ethereal diazoethane (prepared from *N*-ethyl-*N*-nitrosourea) and the solvent was removed under reduced pressure. Preparative t.l.c. on silica gel in ethyl acetate–chloroform (15 : 85) followed by short-path distillation at 150° and 0·1 mmHg gave *ethyl acorate* as a viscous liquid (Found: C, 68·8; H, 9·5%; M^+, 296. $C_{17}H_{28}O_4$ requires C, 68·9; H, 9·5%; *M*, 296); $\nu_{max.}$ 1734, 1718, 1703, and 1180 cm^{-1}; δ 4·10 (2H, q, *J* 7·2 Hz, $O{\cdot}CH_2$), 3·15 (1H, septet, *J* 6·5 Hz. $MeCH$), 1·3—2·9 (10H, m, aliphatic CH), 1·25 (3H, t, $CH_2{\cdot}CH_3$), and 0·9—1·15 p.p.m. (9H, m, 3 × $CH{\cdot}CH_3$); *m/e* 41(30%), 43(95), 44(11), 55(15), 67(14), 69(27), 71(100), 81(15), 109(32), 111(45), 119(12), 123(14), 137(14), 138(94), 139(13), 151(44), 179(43), 181(13), 208(47), 225(44), 226(11), and 251(10).

Ethyl 3-(1-*Isobutyryl*-4-*methyl*-3-*oxocyclohexyl*)*butyrate*.—(i) To a solution of the keto-ester (13d) (0·5 g) in dry dioxan (50 ml) was added osmium tetroxide (0·55 g), and the solution was stirred in the dark for 96 h at 25° and saturated with hydrogen sulphide. The precipitate was removed by centrifugation, the supernatant solution was evaporated under reduced pressure, and the residue was subjected to preparative t.l.c. on silica gel (two plates; 40 × 20 × 0·1 cm) in ethyl acetate–chloroform (9 : 1) to give the diol as an oil (0·39 g), $\nu_{max.}$ 3620, 2570, 1732, and 1696 cm^{-1}. This material was dissolved in a mixture of anhydrous formic acid and concentrated sulphuric acid (100 : 1; 3 ml) and the solution was heated on a steam-bath for 1 h, cooled, diluted with water, and extracted with ether. The extract was washed with sodium hydrogen carbonate solution and brine, dried, and evaporated, and the residue was subjected to preparative t.l.c. on silica gel (40 × 20 × 0·1 cm) in ethyl acetate–chloroform (15 : 85) to afford a pale pink oil (0·16 g). This was short-path distilled at 150° and 0·1 mmHg to give the *diketo-ester* as a viscous liquid (0·105 g) (Found: M^+ 296. $C_{17}H_{18}O_4$ requires *M*, 296); $\nu_{max.}$ 1734, 1718, and 1703 cm^{-1}; the n.m.r. spectrum was a combination of the spectra of ethyl acorate and ethyl epiacorate, which were clearly distinguishable by slight differences (about 2 Hz) of chemical shifts, especially in the regions δ 4·1 and 2·0, and the Me resonances at δ 0·8—1·3; *m/e* 41(23%), 43(69), 55(12), 67(11), 69(19), 71(83), 81(10), 109(22), 111(35), 119(14), 123(10), 137(12), 138(74), 151(30), 179(100), 180(17), 181(11), 208(39), 225(31), and 251(10).

(ii) To a stirred solution of diborane in tetrahydrofuran (0·85M; 1·17 ml) cooled to 0° under nitrogen was added a solution of the keto-ester (13d) (0·56 g) in dry tetrahydrofuran (4 ml). The solution was stirred for 2·5 h at 0°, then treated with water (1 ml), 3M-sodium acetate (1·2 ml) and 30% hydrogen peroxide (1·2 ml), with occasional cooling to keep the temperature below 40°. The mixture was stirred for 1 h, then diluted with brine, and extracted with ether. The extract was washed with water and brine, dried, and evaporated to leave the crude alcohol (0·59 g), $\nu_{max.}$ 3620, 1731, and 1695 cm.$^{-1}$. A solution of the alcohol in dry methylene chloride (5 ml) was added to a solution prepared by stirring pyridine (1·90 g) and chromium trioxide (1·20 g) in dry methylene chloride for 15 min. The mixture was stirred for a further 15 min, then decanted, and the tarry residue was washed with ether (40 ml). The combined organic solutions were washed with 5% sodium hydroxide, 5% hydrochloric acid, 5% sodium hydrogen carbonate, and brine, dried, and evaporated, and the residue was purified by preparative t.l.c. as before to give the diketo-ester (0·32 g.), identical with the sample obtained in (i).

(±)-*Epiacoric Acid* {(3SR)-3-[(1SR, 4SR)-1-*Isobutyryl*-4-*methyl*-3-*oxocyclohexyl*]*butyric Acid*}.—A solution of the foregoing diketoester (0·1 g) in ethanol (5 ml) was cooled to 5° and treated with potassium hydroxide (30 mg) in water (0·5 ml). The solution was kept at 5° for 14 h, then diluted with sodium hydrogen carbonate solution extracted with ether. The extract was discarded and the aqueous solution was acidified with concentrated hydrochloric acid and extracted with ether. This extract was washed with brine,

dried, and evaporated and the residue was recrystallised twice from ether–pentane to produce needles of (±)-*epiacoric acid* (6 mg), m.p. 143—145° (Found: C, 67·2; H, 9·0%; M^+, 268. $C_{15}H_{24}O_4$ requires C, 67·1; H, 9·0%; M, 268); $\nu_{max.}$ ($CHCl_3$) 3500, 3300—2400, 1705, and 1695sh cm^{-1}; 10·14br (1H, s, CO_2H), 3·15 (1H, septet, J 6·6 Hz, Me_2CH), 1·2—2·9 (10H, m, aliphatic CH), and 0·9—1·2 p.p.m. (9H, m, 3 × $CH{\cdot}CH_3$); *m/e* 41(27%), 43(98), 55(14), 67(13), 69(11), 71(100), 81(12), 109(22), 111(58), 137(10), 138(76), 151(26), 179(27), 180(52), 181(18), 197(36), 198(10), and 208(14).

(±)-*Ethyl Epiacorate*.—An ethereal solution of (±)-epiacoric acid was treated with excess of ethereal diazoethane (prepared from *N*-ethyl-*N*-nitrosourea) and the solvent was evaporated off. The residue was filtered in ether solution through a small bed of Celite and the solvent was evaporated off. The n.m.r. spectrum of the residue showed δ 4·15 (2H, q, J 7·2 Hz, $O{\cdot}CH_2$), 3·16 (1H, septet, J 6·5 Hz, Me_2CH), 1·3—2·9 (10H, m, aliphatic CH), 1·28 (3H, t, $CH_2{\cdot}CH_3$), and 0·8—1·2 p.p.m. (9H, m, 3 × $CH{\cdot}CH_3$).

We thank the Commonwealth Scientific and Industrial Research Organisation for financial assistance (to J. E. T. C.).

[1/2353 *Received*, 8*th December*, 1971]