Reactions of Cyclohexadienes. Part VIII.[1] Stereoselective and Non-stereoselective Syntheses of (±)-Juvabione

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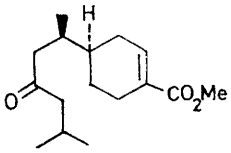
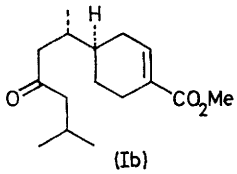
Diels–Alder adducts from readily available dihydroanisoles and several αβ-unsaturated ketones have previously been shown to undergo acid-catalysed ring-opening to yield 4-substituted cyclohexenones. As the first example of the utility of this general process in natural product synthesis, a simple and efficient synthesis of (±)-juvabione diastereoisomers has been carried out. The synthesis was extended to yield (±)-juvabione in a stereoselective manner and confirms the recently revised stereochemistry of (±)-juvabione.

THE sesquiterpene derivative (+)-juvabione (I)[2] shows juvenile hormone activity for only a limited range of insects[3] and is accordingly of considerable biological interest in connection with selective insect control. A number of structurally related compounds also have interesting biological activities,[4] and in an attempt to extend the structural range of such substances we have examined initially the synthesis of (±)-juvabione itself and then of some analogues.



(Ia)



(Ib)

The absolute stereochemistry of (+)-juvabione was originally assigned as (Ia) but recently the compound has been demonstrated by *X*-ray crystallography[5] to be correctly formulated as (Ib). Before the work was published we had completed a stereoselective synthesis of (±)-juvabione[6] which we now realize is completely in accord with structure (Ib). Had this been recognized earlier our synthesis would have been sufficient to correct the first assigned stereochemistry, since the sequence below leads in unequivocal fashion to formula (Ib) when correctly interpreted.

Syntheses of juvabione have been published, but the first type,[7,8] which is essentially an extension of the Birch and Mukherji synthesis of the curcumenes,[9] has the drawback that little possibility of stereospecificity exists, and the second type,[10] while stereoselective, is limited in the number of analogues which can be produced; also the overall yield is low.

The problem of stereospecificity in the synthesis of (Ib) is due to the situation of one asymmetric centre in a conformationally mobile side-chain, while the asymmetric centre in the ring has two substituents which are very much alike. A reasonable mechanism for stereospecific orientation of the two centres is therefore difficult to imagine, and it is unlikely that the properties of the diastereoisomeric series would differ sufficiently to enable efficient separation to be carried out readily by any sorting process other than crystallization. Fractional crystallization at a very late stage in the synthesis is the only process so far employed[7] for this separation, and the isomers are so similar in physical properties

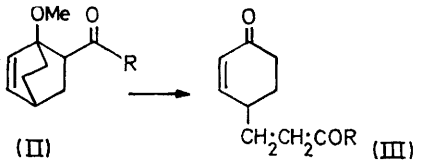
[1] Part VII, A. J. Birch and J. S. Hill, *J. Chem. Soc.* (*C*), 1967, 125.
[2] W. S. Bowers, H. M. Fales, M. J. Thompson, and E. C. Uebel, *Science*, 1966, **154**, 1020; V. Cerny, L. Dolejs, L. Labler, F. Sorm, and K. Slama, *Coll. Czech. Chem. Comm.*, 1967, **32**, 3926.
[3] K. Slama and C. M. Williams, *Proc. Nat. Acad. Sci. U.S.A.*, 1965, **54**, 411; *Biol. Bull.*, 1966, **130**, 235, 247.
[4] K. Slama, M. Suchy, and F. Sorm, *Biol. Bull.*, 1968, **134**, 154; *Science*, 1968, **162**, 582.
[5] J. F. Blount, B. A. Pawson, and G. Saucy, *Chem. Comm.*, 1969, 715.
[6] A. J. Birch, P. L. Macdonald, and V. H. Powell, *Tetrahedron Letters*, 1969, 351.
[7] K. Mori and M. Matsui, *Tetrahedron*, 1968, **24**, 3127.
[8] K. S. Ayyar and G. S. K. Rao, *Canad. J. Chem.*, 1968, **46**, 1467.
[9] A. J. Birch and S. M. Mukherji, *J. Chem. Soc.*, 1949, 2531.
[10] B. A. Pawson, H.-C. Cheung, S. Gurbaxani, and G. Saucy, *Chem. Comm.*, 1968, 1057.

that g.l.c. or other chromatographic separations were not observed.[7,8]

Stereospecificity, the production of a major proportion of one diastereoisomer, or stereoselectivity, depending on the ability to separate readily a desired diastereoisomer produced in admixture, are both best achieved in fairly rigid cyclic molecules. In the first connection the rigid steric relations of groups may lead to sterically specific reactions in a predictable manner, and in the second connection such relations may confer sufficient differences in properties to permit ready separation. In a multi-stage synthesis it is desirable to achieve stereoselectivity at an early stage since this permits the use of smaller amounts of material and means that reactions can be carried out on pure and therefore readily characterized compounds.

In the synthesis of compounds containing few or no rings, this approach of using rigid cyclic molecules impiles the availability of methods for specific ring fission. A particularly useful reaction for this purpose is the generalized αβ-fragmentation, a recent example of which can be found in the juvenile hormone series.[11] We report now an αβ-fragmentation process which has been used to generate the monocyclic skeleton of (±)-juvabione from a readily available bicyclic precursor obtained by a Diels–Alder reaction.

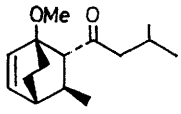
The addition of dienophiles to 1-methoxycyclohexa-1,3-dienes usually occurs readily and the products undergo an acid-catalysed αβ-fragmentation as shown in (II) ⟶ (III), first observed by Butler,[12] to give 4-substituted cyclohex-2-enones.[13] An advantage of the process is the ready availability of various 1-methoxycyclohexa-1,4-dienes from reduction of anisole derivatives with a metal–ammonia system,[14] and the fact that these can be equilibrated with a major proportion of the 1-methoxycyclohexa-1,3-dienes by a variety of methods. In fact, such equilibration can occur directly under Diels–Alder conditions, as was first shown experimentally by Rogers.[15] These *in situ* conjugations probably proceed by way of charge-



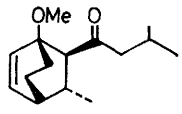
(II) (III)

transfer complexes between the unconjugated diene and the dienophile.[16] The metal–ammonia reduction products can therefore be used directly, provided that sufficiently vigorous conditions, dependent on the nature of the dienophile,[16] are employed.

But-3-en-2-one reacts readily with 1-methoxycyclohexa-1,3-diene to give mainly the *endo*-adduct as the kinetically controlled product. With *trans*-pent-3-en-2-one much more difficulty was experienced[13] with the addition; the deactivating effect of substituents in the dienophile in Diels–Alder reactions is well known.[17] However, by use of *trans*-6-methyl-2-en-4-one, homogeneous by g.l.c. and ^{1}H n.m.r. spectroscopy and produced by condensation of 4-methylpentan-2-one with acetaldehye,[18] addition to 1-methoxycyclohexa-1,4-diene could be achieved under sufficiently drastic conditions to yield a mixture of approximately equal parts of (IV) and (V) in a total yield of 80%. Owing to the rigidity of the ring system and, particularly, to the differing proximities of the carbonyl group and double bond in the two isomers, their physical properties are sufficiently different to permit separation either by g.l.c. or by spinning-band distillation. The lower-boiling adduct showed a high-field methyl n.m.r. signal [δ 0·76 p.p.m. (d, J 7 Hz)] which can only be assigned to an *endo*-methyl group, which falls within the shielding envelope of the olefinic bond.[19,20] In contrast, the higher-boiling adduct displayed a resonance [δ 1·03 p.p.m. (d, J 7 Hz)] corresponding to a methyl group which was not shielded and must therefore have the *exo*-configuration. Birch and Hill[13] have shown that in similar mixtures of adducts the methoxy-resonance always occurs slightly further upfield for the *endo*-acyl isomer than for the *exo*-acyl isomer. Since the lower-boiling adduct shows the corresponding absorption at δ 3·29 p.p.m. (*cf.* 3·24 for the higher-boiling adduct) the isomers must be (V) and (IV), respectively.



(IV)



(V)

The loss of the *endo*-acyl stereospecificity noted previously[13] with the butenone adduct is disappointing since it is this isomer (IV) which should lead to (±)-juvabione, as can be seen by examining the consequences of allocating *R*- and *S*-configurations at the asymmetric centres after ring fission, whereas the *exo*-acyl isomer (V) should give the diastereoisomer of (±)-juvabione. Although an *endo*-adduct is usually the kinetically controlled product of a Diels–Alder reaction, conducting the reaction at lower temperature (120 or 150°) merely resulted in lower yields without a significant increase in the proportion of (IV). The reaction was, however, specific to the extent of yielding only products with the acyl group adjacent to the methoxy-group and with retention

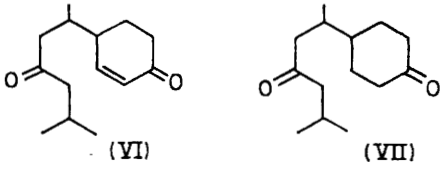
[11] R. Zurfluh, E. N. Wall, J. B. Siddall, and J. A. Edwards, *J. Amer. Chem. Soc.*, 1968, **90**, 6224.
[12] D. N. Butler, Ph.D. Thesis, University of Manchester, 1963; J. S. Meek, P. A. Monroe, and C. J. Bouboulis, *J. Org. Chem.*, 1963, **28**, 2572; A. J. Birch, D. N. Butler, and J. B. Siddall, *J. Chem. Soc.*, 1964, 2932.
[13] A. J. Birch and J. S. Hill, *J. Chem. Soc.* (*C*), 1966, 419.
[14] A. J. Birch, *Quart. Rev.*, 1950, **4**, 69.
[15] K. L. Rabone and N. A. J. Rogers, *Chem. and Ind.*, 1965, 1838.
[16] A. J. Birch and P. L. Macdonald, unpublished data.
[17] J. G. Martin and R. K. Hill, *Chem. Rev.*, 1961, **61**, 537.
[18] R. Luft, *Ann. Chim.* (*France*), 1959, **4**, 745.
[19] W. A. Ayer, C. E. McDonald, and J. B. Stothers, *Canad. J. Chem.*, 1963, **41**, 1113.
[20] R. R. Fraser, *Canad. J. Chem.*, 1962, **40**, 78.

of the *trans*-orientation of the substituents of the initial *trans*-double bond.

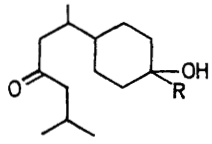
The use of the separated isomers is described later.

Nonstereoselective Synthesis.—The mixture of adducts was converted into the unsaturated dione (VI) by brief treatment under specific conditions with perchloric acid in acetic acid,[13] in essentially quantitative yield; the diastereoisomers of (VI) could not be resolved by g.l.c. Hydrogenation gave the dione (VII), which was converted by acetone cyanohydrin and base into the cyanohydrin (VIII; R = CN) with complete selectivity of reaction at the cyclohexanone carbonyl group. Whether the reaction is reversible or irreversible under these conditions has not been investigated, but in either case this is the expected result.

Dehydration of the cyanohydrin (VIII; R = CN) with phosphoryl chloride in pyridine gave the unsaturated nitrile (IX; R = CN), but it was found more convenient to convert the cyanohydrin directly into the α-hydroxy-ester (VIII; R = CO_2Me) and to dehydrate this to the unsaturated ester (IX; R = CO_2Me). The mixture of (±)-juvabione and its diastereoisomer thus obtained was indistinguishable by g.l.c. from


(VI)

(VII)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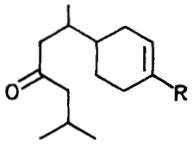
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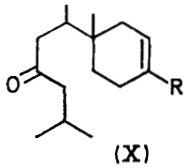
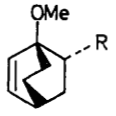

(X)

(±)-juvabione, prepared as described later, and had ^1H n.m.r., i.r., and mass spectra virtually identical with those of the racemic product. Lack of stereospecificity can only be inferred, but seems inevitable since there is no obvious mechanism whereby the direction of dehydration could be controlled by the side-chain centre and it is presumably random in both possible directions. This synthesis, with overall yield of 55% from *trans*-6-methylhept-2-en-4-one is the simplest so far reported.

The process was extended to produce the (±)-homojuvabione stereoisomers (X; R = CO_2Me), unobtainable by previous [7,8,10] procedures. Addition of *trans*-6-methylhept-2-en-4-one to 1-methoxy-4-methylcyclohexa-1,4-diene, from reduction of 1-methoxy-4-methylbenzene, gave a product which by a similar series of reactions to that already described gave (X; R = CO_2Me), presumably also as a mixture of diastereoisomers. One difference in this case was that the *exo*-acyl and *endo*-acyl adducts were formed in a ratio of *ca.* 4 : 1; a similar result was obtained by Birch and Hill[13] for the addition of *trans*-pent-3-en-2-one to 1-methoxy-4-methylcyclohexa-1,3-diene.

The (±)-norjuvabione (XIV) was synthesized by an analogous route, but a different method was used to obtain the side chain in the required adducts (XI and XII; R = $CO{\cdot}CH_2{\cdot}CHMe_2$). Addition of acrylonitrile to 1-methoxycyclohexa-1,4-diene gave the expected *endo*- (XI; R = CN) and *exo*- (XII; R = CN) adducts, which could be separated by spinning-band distillation. The lower-boiling adduct was assigned the *exo*-cyano-configuration because of the shielding of its 6-proton observed in the ^1H n.m.r. spectrum, showing [20] that this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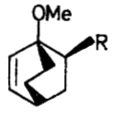
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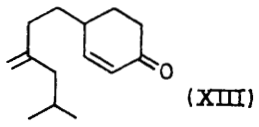
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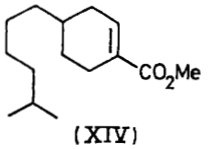
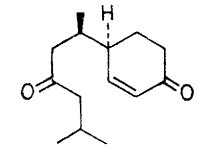

(XIV)

proton is *endo* to the double bond. These acrylonitrile adducts should be convertible into a large number of derivatives of the types (XI and XII; R = acyl) through reaction with appropriate alkyl-lithium reagents. The mixed adducts, on treatment with methyl-lithium gave an approximately 1 : 1 mixture of the ketones (XI; R = Ac) and (XII; R = Ac) which were separated by preparative g.l.c.; each one was identical with the corresponding adduct obtained by reaction of 1-methoxycyclohexa-1,3-diene with but-3-en-2-one [13] and similar separation. The mixture of ketones was treated with sodium hydride and 2-iodopropane to give a mixture of the alkylation products (XI; R = $CO{\cdot}CH_2{\cdot}CHMe_2$) and (XII; R = $CO{\cdot}CH_2{\cdot}CHMe_2$) which could be separated by preparative g.l.c. In the g.l.c. separations of (XI and XII; R = Ac) and of (XI and XII; R = $CO{\cdot}CH_2{\cdot}CHMe_2$) the *exo*-acyl adduct had the lower retention time in each case. The configurations were assigned from the chemical shifts of the bridgehead methoxy-substituents, which are known [13] to be greater for the *exo*-acyl isomers. Each adduct (XI and XII; R = $CO{\cdot}CH_2{\cdot}CHMe_2$), or the mixture, when treated with acid gave the same cyclohexenone (XIII), which was converted by a process analogous to the previous one into (±)-norjuvabione

(XIV), hydrolysis of which afforded a crystalline acid, m.p. 99—101°.

Stereoselective Synthesis.—Ring fission of the individual isomers (IV) and (V) would be expected to lead to the isomeric cyclohexenones (XV) * (XVI),* respectively (not *vice versa* as incorrectly stated in our previous communication [6]) provided that the reaction conditions did not also cause equilibrium of the products through epimerization at C-1′. As already noted, however, hydrogenation of the double bond leads to the same



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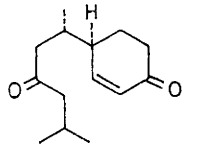

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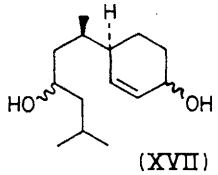
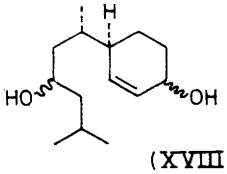


(XVII)



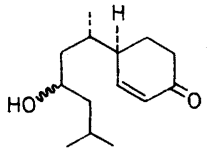
(XVIII)

product (VII) from both (XV) and (XVI), and therefore in a stereoselective synthesis the double bond, or some derivative of it, must be maintained. Wittig reactions were first examined, but their basic nature resulted in cyclization [13] rather than selective reaction of the cyclohexenone carbonyl group. Attention was therefore turned to masking the double bond reversibly.

Reduction of (XV) and of (XVI) with sodium borohydride gave the diols (XVII) and (XVIII), respectively, which were each oxidized with manganese dioxide. Under some conditions the expected specific oxidation to a cyclohexenone derivative could be detected directly, but with normally alkaline manganese dioxide the subsequent predictable ring closure occurred. Thus (XVII) yielded a mixture of the keto-ethers (XX) and (XXI) in a ratio of 5 : 1 (not necessarily respectively), apparently indicating an unexpected stereospecificity in the borohydride reduction of the side-chain carbonyl group. These ethers could be separated by column chromatography and were crystalline: the major had m.p. 59·5—60·5° and the minor m.p. 57·5—58°. The ring junction is *cis* in both cases, as shown by the low value of $J_{1,6}$ (*ca.* 3 Hz), a not unexpected result of kinetically controlled ring closure from an equatorial chain by axial nucleophilic attack of OH on the double bond. Similar oxidation of (XVIII) gave the *cis*-fused keto-ethers (XXII), as well as the rather unstable ketol (XIX), which was found to rearrange spontaneously into (XXII). Equilibration of junctions of these keto-ethers and other stereochemical questions will be discussed in a later publication.

* As with all formulae other than (Ia) and (Ib), these represent optically inactive molecules, and are used for simplicity to denote both the two possible enantiomeric structures.

Further reactions were carried out on the major isomer, (XX) or (XXI), although both could lead to (±)-juvabione. Addition of hydrogen cyanide gave the cyanohydrin (XXIII; R = CN), which was directly converted by methanolic acid into the α-hydroxy-ester (XXIII; R = CO_2Me). Dehydration of (XXIII; R = CO_2Me) with phosphoryl chloride and pyridine gave a 2 : 1 mixture of unsaturated esters, which after



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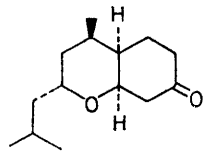

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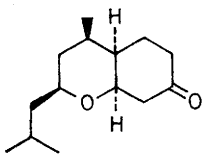
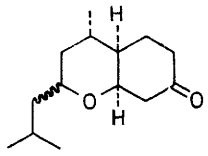


(XXI)



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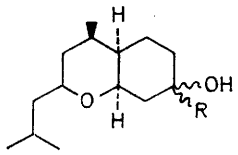

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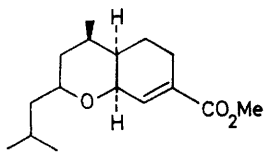

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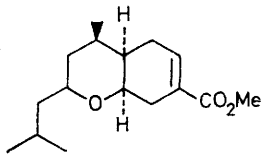

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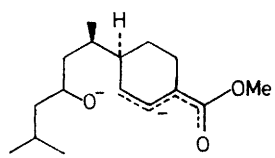

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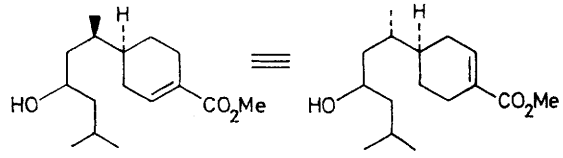

(XXVII)

chromatography on silica gel afforded (XXIV) (50%) and (XXV) (24%), the structures being confirmed by the ^1H n.m.r. spectra. In particular, the olefinic proton of (XXIV) was shown by double resonance to be coupled (J 5·5 Hz) to a proton resonating at δ 6·88, which can only be the ring-junction proton, H-1.

Reaction of (XXIV) with calcium in liquid ammonia in the absence of a proton source would be expected to cleave the ether linkage to give the intermediate anion (XXVI), which should lead to the unsaturated ester (XXVII) [or its βγ-unsaturated isomer, which can equilibrate to (XXVII)]. Reduction under these conditions gave (XXVII) (67%), the structure of which was

supported by its spectra. Oxidation of (XXVII) with chromic acid in acetone gave (±)-juvabione [(Ib) and its enantiomer], the structure of which was supported by its spectra and by hydrolysis to (±)-todomatuic acid, m.p. 66—67° (lit.,[7] 66—67°).

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. Light petroleum used had boiling range 40—60°. I.r. spectra were taken with a Perkin-Elmer 257 spectrophotometer and u.v. spectra were measured for solutions in ethanol with a Unicam SP 800 instrument. ^{1}H N.m.r. spectra were recorded with a Varian HA-100 spectrometer for solutions in deuteriochloroform, unless otherwise stated, with tetramethylsilane as internal standard. Mass spectra were recorded with an A.E.I. MS 902 instrument. Analytical g.l.c. was carried out with a Perkin-Elmer 881 gas chromatograph (nitrogen carrier gas; flow rate 30 ml./min.), by use of glass columns (6 ft. × 0·25 in. ext. diam.) packed with 1·5% XE60 or 5% Carbowax 20M on Chromosorb W (80—100 mesh). Preparative g.l.c. was performed with a Varian Aerograph 202-1C gas chromatograph by use of stainless steel columns (6 ft. × 0·25 in. int. diam.) with helium as the carrier gas (flow rate *ca.* 50 ml./min.) and a stationary phase of 20% Carbowax 20M on Chromosorb W (60—80 mesh). Preparative t.l.c. was carried out with 1 mm. plates (20 × 20 cm.) of Merck GF_{254} silica gel. After being washed with M-hydrochloric acid or 5% sodium hydrogen carbonate, as appropriate, organic extracts were shaken with saturated brine, dried (Na_2SO_4), and concentrated *in vacuo*.

trans-6-*Methylhept-2-en-4-one*.— 4-Methylpentan-2-one and acetaldehyde were condensed by the method of Luft [18] in the presence of M-potassium hydroxide in propan-2-ol, and the resultant ketol was dehydrated by slow distillation from oxalic acid dihydrate. Careful fractionation of this product through a 50 cm. column packed with glass helices afforded trans-6-*methylhept-2-en-4-one*, b.p. 77—78°/33 mm., t_R 5·1 min. (20M; 70°), $\nu_{max.}$ (film) 1695, 1675, and 1635 cm.$^{-1}$, $\lambda_{max.}$ 223 nm. (ε 13,000), δ(neat) 0·89 (6H, d, *J* 7 Hz, CMe_2), 1·83 (3H, dd, $J_{1,2}$ 7, $J_{1,3}$ 1·5 Hz, Me), 2·11 (1H, m, H-6), 2·36 (2H, d, *J* 6 Hz, H-5), 6·04 (1H, dq, $J_{3,2}$ 16, $J_{3,1}$ 1·5 Hz, H-3), and 6·78 (1H, dq, $J_{2,3}$ 16, $J_{2,1}$ 7 Hz, H-2) p.p.m. (Found: *M*, 126. $C_8H_{14}O$ requires *M*, 126).

1-*Methoxy-5-methyl-6-(1-oxo-3-methylbutyl)bicyclo*[2,2,2]-*oct-2-enes* (IV) *and* (V).—1-Methoxycyclohexa-1,4-diene was prepared by reduction of anisole with sodium–ethanol–ammonia in the usual way [14] and contained *ca.* 7% (by g.l.c.) of 1-methoxycyclohexene. *trans*-6-Methylhept-2-en-4-one (105 g.), 1-methoxycyclohexa-1,4-diene (105 g.), and hydroquinone (0·8 g.) were heated together in an evacuated sealed glass tube at 180° for 4 days to yield a 1 : 1 mixture (by g.l.c.) of (IV) and (V), b.p. 120—135°/2 mm. (151 g., 80%). Redistillation of this mixture on a spinning-band column gave the exo-*acyl adduct* (V), b.p. 125—126°/5 mm., t_R 5·5 min. (20M; 150°), $\nu_{max.}$ (film) 1700 cm.$^{-1}$, δ 0·76 (3H, d, *J* 7 Hz, *endo*-Me), 0·87 and 0·90 (each 3H, d, *J* 6 Hz, CMe_2), 1·1—2·8 (10H), 3·29 (3H, s, OMe), and 5·9—6·6 (2H, m, H-2 and -3) p.p.m. (Found: C, 76·5; H, 10·2%; *M*, 236. $C_{15}H_{24}O_2$ requires C, 76·2; H, 10·2%; *M*, 236), and the endo-*acyl adduct* (IV), b.p. 135—136°/5 mm., t_R 8·8 min. (20M, 150°), $\nu_{max.}$ (film) 1700 cm.$^{-1}$, δ 0·84 and 0·88 (each 3H, d, *J* 6 Hz, CMe_2), 1·03 (3H, d, *J* 7 Hz, *exo*-Me), 1·1—2·6 (10H), 3·24 (3H, s, OMe), and 6·1—6·5 (2H, m, H-2 and -3) p.p.m. (Found: C, 76·0; H, 10·2%; *M*, 236).

6-*Methyl*-2-(4-*oxocyclohex-2-enyl*)*heptan-4-one* (VI).—A mixture of the adducts (IV) and (V) (20 g.) in glacial acetic acid (100 ml.) was treated with 5M-perchloric acid (6 ml.) for 3 min., poured on to sodium hydrogen carbonate (250 g.), and diluted with water. Extraction with chloroform yielded the crude *cyclohexenone* (VI) (18·3 g., 96%). This product could not be distilled without decomposition but a sample was purified by preparative t.l.c. [light petroleum–ether (7 : 3)]. The pure material showed t_R 5·1 min. (20M; 210°), 3·0 min. (XE60; 180°), $\nu_{max.}$ (film) 1715 and 1685 cm.$^{-1}$, $\lambda_{max.}$ 228 nm. (ε 11,600), δ 0·89 (6H, d, *J* 6 Hz, CMe_2), 0·94 (3H, d, *J* 6 Hz, CMe), 1·4—2·8 (13H), 5·98 (1H, dd, $J_{3',2'}$ 10, $J_{3',1'}$ 2 Hz, H-3′), and 6·78br (1H, d, $J_{2',3'}$ 10 Hz, H-2′) p.p.m. (Found: *M*, 222·1611. $C_{14}H_{22}O_2$ requires *M*, 222·1620).

6-*Methyl*-2-(4-*oxocyclohexyl*)*heptan-4-one* (VII).—Crude (VI) (30 g.) in glacial acetic acid (400 ml.) was hydrogenated over 10% palladium–charcoal (0·5 g.) at 25° until uptake of hydrogen ceased. After removal of the catalyst, the solution was evaporated to dryness, diluted with water, and extracted with ether to yield the *saturated diketone* (VII) (30 g., 99%), which partly decomposed on distillation (b.p. 108—116°/0·3 mm.). A sample purified by preparative g.l.c. (20% 20M; 215°) showed t_R 4·0 min. (20M; 210°), $\nu_{max.}$ (film) 1710 cm.$^{-1}$, δ 0·89 (3H, d, *J* 6 Hz, CMe), 0·91 (6H, d, *J* 6 Hz, CMe_2), and 1·1—3·0 (15H) p.p.m. (Found: *M*, 22·1778. $C_{14}H_{24}O_2$ requires *M*, 224·1776).

2-(4-*Cyanocyclohex-3-enyl*)-6-*methylheptan-4-one* (IX; R = CN).—The diketone (VII) (10 g.) in redistilled acetone cyanohydrin (40 ml.) was treated with 3·5M-potassium carbonate (0·3 ml.) for 16 hr. at 25°. The brown solution was concentrated under vacuum, diluted with water, and worked up by ether extraction to give the crude cyanohydrin (VIII) (11·1 g.), $\nu_{max.}$ (film) 3460, 2240, and 1710 cm.$^{-1}$. To the crude cyanohydrin (200 mg.) in pyridine (2 ml.) was added phosphoryl chloride (0·5 ml.), and the solution was set aside at 25° for 16 hr., concentrated under vacuum, and diluted with water. Ether extraction afforded a residue which on preparative t.l.c. [light petroleum–ether (7 : 3)] and short-path distillation (0·3 mm.) yielded the *unsaturated nitrile* (IX; R = CN) (148 mg., 80%), t_R 8·8 min. (20M; 210°), $\nu_{max.}$ (film) 2220, 1710, and 1643 cm.$^{-1}$, δ 0·88 (3H, d, *J* 6 Hz, CMe), 0·92 (6H, d, *J* 6 Hz, CMe_2), 1·1—2·7 (13H), and 6·6 (1H, m, H-3′) p.p.m. (Found: C, 77·4; H, 9·9; N, 5·85%; *M*, 233. $C_{15}H_{23}NO$ requires C, 77·2; H, 9·9; N, 6·0%; *M*, 233).

2-(4-*Hydroxy-4-methoxycarbonylcyclohexyl*)-6-*methylheptan-4-one* (VIII; R = CO_2Me).—A solution of crude (VIII; R = CN) (2·51 g.) in dry methanol (30 ml.) was saturated at 0° with dry hydrogen chloride and left overnight at room temperature. After dilution with water (70 ml.) the mixture was stirred for 1 hr., and extracted with ether to yield a yellow oil (2·27 g., 80%). A portion of the product was purified by preparative t.l.c. [light petroleum–ether (1 : 1)] to afford the α-*hydroxy-ester* (VIII; R = CO_2Me), t_R 4·3 min. (XE60; 180°), t_R 25sh and 27 min. (20M; 190°), $\nu_{max.}$ (film) 3475, 1735, and 1710 cm.$^{-1}$, δ 0·93 (9H, d, *J* 6 Hz, CMe and CMe_2), 1·1—2·6 (15H), 2·92br and 2·98br (1H, each s, exchangeable, OH of C-4′ epimers), and 3·76 (3H, s, OMe) p.p.m. (Found: *M*, 284·1993. $C_{16}H_{28}O_4$ requires *M*, 284·1987).

Mixture of (±)-*Juvabione and its Diastereoisomer* (IX;

R = CO_2Me).—Treatment of the hydroxy-ester (VIII; R = CO_2Me) with phosphoryl chloride and pyridine, as already described, afforded the (±)-juvabione diastereoisomers (IX; R = CO_2Me) (93%). After preparative t.l.c. [light petroleum–ether (9 : 1); run three times] the product was indistinguishable by g.l.c. and t.l.c. from (±)-juvabione, prepared as described later, and had ^1H n.m.r., i.r., and mass spectra virtually identical with those of the racemic product.

6-*Methyl*-2-(1-*methyl*-4-*oxocyclohex*-2-*enyl*)*heptan*-4-*one*.—1-Methoxy-4-methylcyclohexa-1,4-diene was prepared by reduction of 1-methoxy-4-methylbenzene with sodium–ethanol–ammonia in the usual way,[14] and contained *ca.* 7% (by g.l.c.) of the tetrahydro-derivative. *trans*-6-Methylhept-2-en-4-one (120 g.), 1-methoxy-4-methylcyclohexa-1,4-diene (80 g.), and hydroquinone (0·8 g.) were heated together in an evacuated sealed glass tube at 180° for 5 days. The product, b.p. 122—132°/0·7 mm. (110 g.), $\nu_{max.}$ (film) 1710 cm.$^{-1}$, contained, together with several impurities (total *ca.* 25%), the expected Diels–Alder *adducts* [*ca.* 60%, t_R 8·0 min., and *ca.* 15%, t_R 12·0 min. (20M; 150°)] which were isolated by preparative g.l.c. (20% 20M; 180°); each displayed the expected mass spectrum including a molecular ion at *m/e* 250 and a base peak at *m/e* 124. The crude adduct mixture, which showed ^1H n.m.r. peaks at δ 3·29 and 3·26 p.p.m. in a ratio of *ca.* 4 : 1 (OMe of *exo*- and *endo*-acyl isomers, respectively), was treated with perchloric acid in acetic acid, as before, to give the corresponding *cyclohexenone*. A sample purified by preparative t.l.c. [light petroleum–ether (1 : 1)] showed t_R 5·3sh and 5·7 min. (20M; 210°), $\lambda_{max.}$ 228 nm. (ε 10,400), $\nu_{max.}$ (film) 1712 and 1680 cm.$^{-1}$, δ 0·93 (9H, d, *J* 6 Hz, CH*Me* and CMe_2), 1·14 and 1·16 (3H, two s, ratio *ca.* 4 : 1, CMe of diastereoisomers), 1·4—2·7 (10H), 5·89 (1H, d, *J* 10 Hz, H-3′), and 6·63br and 6·67br (1H, two 6d, ratio 1 : 4, each $J_{2',3'}$ 10 Hz, H-2′ of diastereoisomers) p.p.m. (Found: *M*, 236·1775. $C_{15}H_{24}O_2$ requires *M*, 236·1776).

6-*Methyl*-2-(1-*methyl*-4-*oxocyclohexyl*)*heptan*-4-*one*.—Hydrogenation of the cyclohexenone, in the usual manner, afforded the *saturated diketone*, which was purified by regeneration from its sodium hydrogen sulphite addition compound (50% overall yield from 1-methoxy-4-methylbenzene). The purified product showed t_R 5·2 min. (20M; 210°), $\nu_{max.}$ (film) 1713 cm.$^{-1}$, δ 0·89 (3H, d, *J* 6 Hz, CH*Me*), 0·93 (6H, d, *J* 6 Hz, CMe_2), 0·98 (3H, s, CMe), 1·68 (4H, m, two H-2′ and two H-6′), and 2·0—2·6 (10H) p.p.m. (Found: *M*, 238·1935. $C_{15}H_{26}O_2$ requires *M*, 238·1933).

2-(4-*Cyano*-1-*methylcyclohex*-3-*enyl*)-6-*methylheptan*-4-*one* (X; R = CN).—An exchange reaction of the diketone with acetone cyanohydrin led to the monocyanohydrin, $\nu_{max.}$ (film) 3445, 2240, and 1710 cm.$^{-1}$, in quantitative yield. The crude cyanohydrin, on dehydration with phosphoryl chloride, gave the *unsaturated nitrile* (X; R = CN) (75%). An analytical sample, prepared by preparative t.l.c. [light petroleum–ether (3 : 2)] followed by short-path distillation (0·3 mm.), had t_R 9·9 min. (20M; 210°), $\nu_{max.}$ 2215, 1720, and 1645 cm.$^{-1}$, δ 0·81 (3H, s, CMe), 0·93 (9H, d, *J* 6 Hz, CH*Me* and CMe_2), 1·2—2·7 (12H), and 6·55 (1H, m, H-3′) p.p.m. (Found: C, 77·8; H, 9·95; N, 5·8%; *M*, 247. $C_{16}H_{25}NO$ requires C, 77·7; H, 10·2; N, 5·7%; *M*, 247).

2-(4-*Hydroxy*-4-*methoxycarbonyl*-1-*methylcyclohexyl*)-6-*methylheptan*-4-*one*.—Methanolysis of the crude cyanohydrin gave the corresponding α-*hydroxy-ester* (70%); a sample purified by preparative t.l.c. [light petroleum–ether (1 : 1)] had t_R 4·2 and 5·5 min. (ratio 3 : 2) (XE60; 180°), $\nu_{max.}$ (film) 3500, 1730, and 1713 cm.$^{-1}$, δ 0·80 (3H, s, CMe), 0·85—1·0 (9H, m, CH*Me* and CMe_2), 1·1—2·65 (14H), 2·93 and 3·05 (1H, two s, ratio *ca.* 2 : 3, exchangeable, OH of C-4′ epimers), and 3·77 (3H, s, OMe) p.p.m. (Found: *M*, 298·2143. $C_{17}H_{30}O_4$ requires 298·2144).

Mixture of (±)-*Homojuvabione and its Diastereoisomer* (X; R = CO_2Me).—Dehydration of the α-hydroxy-ester, as before, gave a mixture containing some starting material. This mixture (2·05 g.) in pyridine (30 ml.) and phosphoryl chloride (3 ml.) was heated under reflux for 1 hr., and then worked up. The (±)-homojuvabione diastereoisomers (X; R = CO_2Me), purified by preparative t.l.c. [light petroleum–ether (3 : 2)], showed t_R 8·4 min. (20M; 210°), $\nu_{max.}$ (film) 1720sh, 1713, and 1655 cm.$^{-1}$, δ 0·79 (3H, s, CMe), 0·85—1·0 (9H, m, CH*Me* and CMe_2), 1·2—2·6 (12H), 3·72 (3H, s, OMe), and 6·90 (1H, m, H-3′) p.p.m. An analytical sample was prepared by short-path distillation (0·3 mm.) (Found: C, 73·1; H, 10·0%; *M*, 280. $C_{17}H_{28}O_3$ requires C, 72·8; H, 10·1%; *M*, 280).

1-*Methoxybicyclo*[2,2,2]*oct*-5-*ene*-2-*carbonitriles* (XI *and* XII; R = CN).—A mixture of 1-methoxycyclohexa-1,4-diene (30 g.), acrylonitrile (50 g.), and Methylene Blue (0·5 g.) was heated in an evacuated sealed glass tube at 150° for 4 days. The product was poured into ether, filtered from some polymeric material, and distilled to give the mixed adducts (28 g., 65%), b.p. 102—115°/0·75 mm. Redistillation of this mixture on a spinning-band column yielded, initially, the exo-*adduct* (XII; R = CN) (12 g.), b.p. 88—90°/0·8 mm., t_R 2·4 min. (XE60; 140°), $\nu_{max.}$ (film) 2240 cm.$^{-1}$, δ 1·1—2·2 (6H), 2·61 (2H, m, H-4 and -6), 3·41 (3H, s, OMe), 6·25—6·35 (2H, m, H-2 and -3) (Found: C, 73·6; H, 8·2; N, 8·7%; *M*, 163. $C_{10}H_{13}NO$ requires C, 73·6; H, 8·0; N, 8·6%; *M*, 163), followed by the endo-*adduct* (XI; R = CN) (11 g.), b.p. 102—104°/0·8 mm., t_R 3·8 min. (XE60; 140°), $\nu_{max.}$ (film) 2240 cm.$^{-1}$, δ 1·2—2·2 (6H), 2·60 (1H, m, H-4), 2·89 (1H, dd, *J* 4·5 and 10 Hz, H-6), 3·41 (3H, s, OMe), and 6·3—6·4 (2H, m, H-2 and -3) p.p.m. (Found: C, 73·7; H, 8·1; N, 8·6%; *M*, 163).

6-*Acetyl*-1-*methoxybicyclo*[2,2,2]*oct*-2-*enes* (XI and XII; R = Ac).—The mixed acrylonitrile adducts (XI and XII; R = CN) (100 mg.) were treated at 25° under nitrogen with 2M-methyl-lithium in ether (20 ml.). After 20 hr., excess of reagent was destroyed with saturated ammonium chloride solution and the product was isolated by extraction with ether. The residue (90 mg.) thus obtained showed two peaks of approximately equal areas on g.l.c. [t_R 3·0 and 4·5 min. (20M; 150°)], and was subjected to preparative g.l.c. (20% 20M; 180°). The peak of shorter retention time corresponded to the exo-*adduct* (XII; R = Ac), $\nu_{max.}$ (film) 1710 and 1615 cm.$^{-1}$, δ 1·2—2·05 (6H), 2·23 (3H, s, *exo*-Ac), 2·5 (1H, m, H-4), 2·89 (1H, dd, *J* 5 and 10 Hz, H-6), 3·36 (3H, s, OMe), and 6·15—6·5 (2H, m, H-2 and -3) p.p.m. (Found: *M*, 180·1149. $C_{11}H_{16}O_2$ requires *M*, 180·1159). The second peak corresponded to the endo-*adduct* (XI; R = Ac), $\nu_{max.}$ (film) 1705 and 1615 cm.$^{-1}$, δ 1·2—1·95 (6H), 2·12 (3H, s, *endo*-Ac), 2·56 (1H, m, H-4), 2·98 (1H, dd, *J* 5 and 10 Hz, H-6), 3·33 (3H, s, OMe), and 6·1—6·4 (2H, m, H-2 and -3) p.p.m. (Found: *M*, 180·1149). The mixture of adducts obtained by the method of Birch and Hill [13] from butenone and 1-methoxycyclohexa-1,3-diene was separated under the same conditions; each isomer was identical (g.l.c. and i.r. spectrum) with the corresponding one obtained here.

1-*Methoxy*-6-(3-*methyl*-1-*oxobutyl*)*bicyclo*[2,2,2]*oct*-2-*enes*

(XI and XII; R = $CO{\cdot}CH_2{\cdot}CHMe_2$).—A mixture of (XI and XII; R = Ac) (20 g.), 2-iodopropane (80 g.), sodium hydride (12 g.), and benzene (100 ml.) was heated under reflux for 16 hr., poured on to a mixture of ice (200 g.) and M-sulphuric acid (200 ml.), and extracted with benzene. The product, b.p. 135—149°/20 mm. (16 g.) was shown to be a 1 : 1 mixture by g.l.c. [t_R 5·0 and 8·0 min. (20M; 150°)]; a sample of each component was isolated by preparative g.l.c. (20% 20M; 200°). The *exo-adduct* (XII; R = $CO{\cdot}CH_2{\cdot}CHMe_2$), eluted first, showed $\nu_{max.}$ (film) 1707 and 1615 cm.$^{-1}$, δ 0·89 and 0·91 (each 3H, d, *J* 6 Hz, CMe_2), 1·0—2·7 (10H), 2·82 (1H, dd, *J* 5 and 11 Hz, H-6), 3·33 (3H, s, OMe), and 6·1—6·45 (2H, m, H-2 and -3) p.p.m. (Found: *M*, 222·1620. $C_{14}H_{22}O_2$ requires *M*, 222·1620). The second peak corresponded to the *endo-adduct* (XI; R = $CO{\cdot}CH_2{\cdot}CHMe_2$), $\nu_{max.}$ (film) 1710 and 1612 cm.$^{-1}$, δ 0·86 and 0·88 (each 3H, d, *J* 6 Hz, CMe_2), 1·2—2·65 (10H), 2·97 (1H, dd, *J* 6 and 9 Hz, H-6), 3·30 (3H, s, OMe), and 6·15—6·35 (2H, m, H-2 and -3) p.p.m. (Found: *M*, 222·1620).

5-Methyl-1-(4-oxocyclohex-2-enyl)hexan-3-one (XIII).—Perchloric acid treatment, as before, of the mixed adducts (XI and XII; R = $CO{\cdot}CH_2{\cdot}CHMe_2$) afforded in essentially quantitative yield the *cyclohexenone* (XIII); a sample purified by preparative t.l.c. [light petroleum–ether (3 : 2)] showed t_R 4·3 min. (20M; 210°), $\nu_{max.}$ (film) 1710 and 1680 cm.$^{-1}$, $\lambda_{max.}$ 227 nm. (ε 11,440), δ 0·94 (6H, d, *J* 6 Hz, CMe_2), 1·2—2·9 (12H), 5·97 (1H, dd, $J_{3',2'}$ 10, $J_{3',1'}$ 2·5 Hz, H-3'), and 6·83br (1H, d, $J_{2',3'}$ 10 Hz, H-2') p.p.m. (Found: *M*, 208·1462. $C_{13}H_{20}O_2$ requires *M*, 208·1463).

5-Methyl-1-(4-oxocyclohexyl)hexan-3-one.—Hydrogenation of (XIII), as before, afforded a quantitative yield of the *cyclohexanone*, t_R 3·6 min. (20M; 210°), $\nu_{max.}$ (film) 1710 cm.$^{-1}$, δ 0·93 (6H, d, *J* 6 Hz, CMe_2) and 1·1—2·9 (16H) p.p.m. A sample for mass spectrum was obtained by preparative g.l.c. (20% 20M; 215°) (Found: *M*, 210·1620. $C_{13}H_{22}O_2$ requires *M*, 210·1620).

1-(4-Cyanocyclohex-3-enyl)-5-methylhexan-3-one.—The diketone was treated with acetone cyanohydrin, followed by phosphoryl chloride and pyridine, as before, to yield the *unsaturated nitrile* (80%). The product, after preparative t.l.c. [light petroleum–ether (4 : 1)] and short-path distillation (0·1 mm.) showed t_R 7·8 min. (20M; 210°), $\nu_{max.}$ (film) 2220, 1710, and 1640 cm.$^{-1}$, δ 0·92 (6H, d, *J* 6 Hz, CMe_2), 1·1—2·6 (14H), and 6·57 (1H, m, H-3') p.p.m. (Found: C, 76·7; H, 9·5; N, 6·5%; *M*, 219. $C_{14}H_{21}NO$ requires C, 76·7; H, 9·65; N, 6·4%; *M*, 219).

1-(4-Hydroxy-4-methoxycarbonylcyclohexyl)-5-methylhexan-3-one.—Treatment of the diketone with acetone cyanohydrin, followed by reaction with methanol and hydrogen chloride, in the usual manner, afforded the *α-hydroxy-ester* (70%). After preparative t.l.c. [light petroleum–ether (1 : 1)] the product had t_R 3·9 min. (XE60; 180°), $\nu_{max.}$ (film) 3470, 1735, and 1710 cm.$^{-1}$, δ 0·92 (6H, d, *J* 6 Hz, CMe_2), 1·1—2·6 (16H), 2·93, and 2·99 (1H, two s, exchangeable, OH of C-4' epimers), and 3·75 (3H, s, OMe) p.p.m. (Found: *M*, 270·1826. $C_{15}H_{26}O_4$ requires *M*, 270·1831).

(±)-*Norjuvabione* (XIV).—Dehydration of the hydroxy-ester (200 mg.) in the usual way, followed by preparative t.l.c. [light petroleum–ether (4 : 1)] yielded (±)-*norjuvabione*. After short-path distillation (0·3 mm.) the product (155 mg.) showed t_R 6·7 min. (20M; 210°), $\nu_{max.}$ (film) 1720sh, 1710, and 1650 cm.$^{-1}$, δ 0·94 (6H, d, *J* 6 Hz, CMe_2), 1·1—2·6 (14H), 3·70 (3H, s, OMe), and 6·93 (1H, m, H-3') p.p.m. (Found: C, 71·3; H, 9·4%; *M*, 252. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%; *M*, 252).

(±)-*Nortodomatuic acid*.—A solution of (±)-norjuvabione (110 mg.) and potassium hydroxide (600 mg.) in methanol (15 ml.) was heated under reflux for 1 hr. in a nitrogen atmosphere. The solution was concentrated, diluted with M-sodium hydrogen carbonate, and washed with ether. The aqueous solution was acidified with 10M-hydrochloric acid and extracted with dichloromethane. The crystalline residue (100 mg.) thus obtained was recrystallized from light petroleum to give (±)-*nortodomatuic acid* as colourless flakes, m.p. 99—101°, $\nu_{max.}$ (Nujol) 3500—2300, 1710, 1675, and 1645 cm.$^{-1}$, δ 0·93 (6H, d, *J* 6 Hz, CMe_2), 1·1—2·6 (14H), 7·08 (1H, m, H-3'), 10·1br (1H, s, exchangeable, CO_2H) (Found: C, 70·75; H, 9·5%; *M*, 238. $C_{14}H_{22}O_3$ requires C, 70·6; H, 9·3%; *M*, 238).

2-(4-Hydroxycyclohex-2-enyl)-6-methylheptan-4-ols (XVII) and (XVIII).—Fission of each of the adducts (IV) and (V) with perchloric acid and acetic acid, in the usual way, led to (XV) and (XVI), respectively. Each of these isomeric cyclohexenones, as in the case of the mixture (VI), was indistinguishable from the other by g.l.c. or t.l.c., and all displayed virtually identical ^{1}H n.m.r., i.r., and mass spectra. A solution of (XV) (15 g.) in methanol (250 ml.) was added to a solution of sodium borohydride (10 g.) in M-sodium hydroxide (60 ml.) and set aside for 16 hr. at room temperature. The mixture was concentrated, diluted with water, and extracted with chloroform to yield the *diol* (XVII) as a viscous oil, b.p. 155—160°/1·3 mm., t_R 4·0 min. (XE60; 180°), $\nu_{max.}$ (film) 3350 cm.$^{-1}$, δ 0·95 (9H, d, *J* 6 Hz, CMe and CMe_2), 1·1—2·4 (11H), 2·65br and 3·4br (each 1H, s, exchangeable, two OH), 3·7 and 4·2 (each 1H, m, H-4 and -4'), and 5·5—5·9 (2H, m, H-2' and -3') p.p.m. (Found: C, 74·6; H, 11·8%. $C_{14}H_{26}O_2$ requires C, 74·3; H, 11·6%). The mass spectrum did not show a molecular ion, but included peaks at *m/e* 208 (25%, $M - H_2O$) and 190 (22%, $M - 2H_2O$).

Similarly, reduction of (XVI) afforded the corresponding *diol* (XVIII), b.p. 155—160°/1·3 mm., t_R 4·0 min. (XE60; 180°), $\nu_{max.}$ (film) 3350 cm.$^{-1}$, δ 0·90 (9H, d, *J* 6 Hz, CMe and CMe_2), 1·1—2·5 (11H), 3·24br (2H, s, exchangeable, two OH), 3·65 and 4·1 (each 1H, m, H-4 and -4'), and 5·3—5·8 (2H, m, H-2' and -3') p.p.m. (Found: C, 74·4; H, 11·4%). The mass spectrum showed a very weak molecular ion (*m/e* 226, 0·7%), as well as peaks at 208 (40%) and 190 (28%).

3-Isobutyl-5-methyl-2-oxabicyclo[4,4,0]*decan-9-one* (XX), (XXI), *and* (XXII).—A solution of (XVIII) (2·08 g.) in chloroform (40 ml.) was stirred with active manganese dioxide (Beacon Chemical Industries) for 1·5 hr. at 25°, filtered, and concentrated to a yellow gum, which contained two products (g.l.c.; ratio *ca.* 5 : 1), together with some starting material. This mixture of keto-ethers (XX) and (XXI) was chromatographed on silica gel, with benzene–chloroform as eluant, to give initially the major *keto-ether* (1·02 g., 50%), τ_R 1·7 min. (XE60; 170°), m.p. 59·5—60·5° (from light petroleum), $\nu_{max.}$ (Nujol) 1720sh, 1710 cm.$^{-1}$, δ 0·85 (6H, d, *J* 6 Hz, CMe_2), 0·95 (3H, d, *J* 6 Hz, CMe), 1·1—2·7 (13H) [including 2·46 (2H, d, *J* 4 Hz, two H-10)], 3·35 (1H, m, H-3), and 3·80 (1H, m, $w_{\frac{1}{2}}$ 9 Hz, H-1 p.p.m.); irradiation at δ 2·46 p.p.m. (H-10) caused the multiplet at 3·80 to narrow (to $w_{\frac{1}{2}}$ 4 Hz) (Found: C, 75·3; H, 10·9%; *M*, 224. $C_{14}H_{24}O_2$ requires C, 74·95; H, 10·8%; *M*, 224). Further elution gave the minor *keto-ether* (0·20 g., 10%), m.p. 57·5—58·0° (from light petroleum), t_R 2·6 min.

(XE60; 170°), $\nu_{max.}$ (Nujol) 1710 cm.$^{-1}$, δ 0·91 (6H, d, *J* 6 Hz, CMe_2), 0·95 (3H, d, *J* 6 Hz, CMe), 1·1—2·6 (13H), and 3·9—4·2 (2H, m, H-1 and -3), δ (C_6D_6) 0·72 (3H, d, *J* 6·5 Hz CMe), 0·91 (6H, d, *J* 6 Hz, CMe_2), 1·0—2·5 (13H) [including 2·06 (2H, d, *J* 4 Hz, two H-10)], 3·63 (1H, m, $w_{\frac{1}{2}}$ 9 Hz; H-1), and 3·85 (1H, m, H-3 p.p.m.); irradiation at δ 2·06 p.p.m. (H-10) caused the multiplet at 3·63 (H-1) to narrow (to $w_{\frac{1}{2}}$ 5 Hz) (Found: C, 74·8; H, 10·7%; *M*, 224).

On similar treatment the diol (XVIII) afforded a mixture (*ca.* 2 : 1 by g.l.c.) of the *keto-ethers* (XXII) (32%) together with the 6-*methyl*-2-(4-*oxocyclohex*-2-*enyl*)*heptan*-4-*ol* (XIX) (34%). The latter product, which spontaneously rearranged in essentially quantitative yield to the keto-ethers (XXII) even when kept in the refrigerator, showed t_R 4·2 min. (XE60; 170°), $\nu_{max.}$ (film) 3430 and 1675 cm.$^{-1}$, δ 0·92 (6H, d, *J* 6·5 Hz, CMe_2), 0·94 (3H, d, *J* 6 Hz, CMe), 1·1—2·8 (12H), 3·75 (1H, m, H-4), 6·00 (1H, dd, $J_{3',2'}$ 10, $J_{3',1'}$ 2·5 Hz, H-3′), and 6·84br (1H, d, $J_{2',3'}$ 10 Hz, H-2′) p.p.m. (Found: *M*, 224). Fractional crystallization of (XXII) from light petroleum gave colourless needles, m.p. 75·5—76·5°, t_R 1·3 min. (XE60; 170°), $\nu_{max.}$ (Nujol) 1715 cm.$^{-1}$, δ 0·85 (6H, d, *J* 6 Hz, CMe_2), 1·1—2·7 (16H) [including 1·17 (*ca.* 3H, d, *J* 6 Hz, CMe) and 2·42 (*ca.* 2H, d, *J* 3·5 Hz, two H-10)], 3·55 (1H, m, H-3), and 4·08 (1H, m, $w_{\frac{1}{2}}$ 9 Hz, H-1) p.p.m.; irradiation at δ 2·42 p.p.m. caused the multiplet at 4·08 to narrow (to $w_{\frac{1}{2}}$ 5 Hz) (Found: C, 75·2; H, 10·75%; *M*, 224). The mother liquors contained this product, as well as the minor product, t_R 1·5 min. (XE60; 170°).

Methyl 9-*Hydroxy*-3-*isobutyl*-5-*methyl*-2-*oxabicyclo*[4,4,0]-*decane*-9-*carboxylate* (XXIII; R = CO_2Me).—To a stirred and ice-cooled solution of the keto-ether, m.p. 59·5—60·5° (2·24 g.), and potassium cyanide (11·2 g.) in 95% ethanol (60 ml.) was added 17M-acetic acid (13·5 ml.) during 40 min. After a further 1 hr. at 25° the mixture was treated with 10M-hydrochloric acid (0·2 ml.) and concentrated under vacuum. The residue was diluted with water and extracted with ether to yield the crude cyanohydrin (XX; R = CN), $\nu_{max.}$ (film) 3420 and 2240 cm.$^{-1}$. Methanolysis of this cyanohydrin in the usual manner afforded the α-*hydroxy*-*ester* (90%), which was purified by chromatography on silica gel. The product, eluted with benzene–chloroform (1 : 4), showed t_R 2·3 min. (XE60; 190°), $\nu_{max.}$ (film) 3470 and 1735 cm.$^{-1}$, δ 0·90 (6H, d, *J* 6·5 Hz, CMe_2), 0·96 (3H, d, *J* 6 Hz, CMe), 1·1—2·3 (13H), 3·35 and 3·9 (each 1H, m, H-1 and -3), 3·75 (3H, s, OMe), and 4·72 (1H, s, exchangeable, OH) p.p.m. (Found: *M*, 284·1990. $C_{16}H_{28}O_4$ requires *M*, 284·1987).

Methyl 3-*Isobutyl*-5-*methyl*-2-*oxabicyclo*[4,4,0]*dec*-8- *and* 9-*ene*-9-*carboxylates* (XXV) *and* (XXIV).—Dehydration of (XXIII; R = CO_2Me) in the usual way, followed by chromatography of the crude product on silica gel yielded initially the *unsaturated ester* (XXIV) (50%), t_R 3·3 min. (XE60; 170°), $\nu_{max.}$ (film) 1720 and 1655 cm.$^{-1}$, δ 0·89 (6H, d, *J* 6 Hz, CMe_2), 0·97 (3H, d, *J* 6·5 Hz, CMe), 1·1—2·8 (11H), 3·4 (1H, m, H-3), 3·69 (3H, s, OMe), 3·87 (1H, dd; $J_{1.10}$ 5·5, $J_{1.6}$ 2 Hz, H-1), and 6·88 (1H, dd, $J_{10.1}$ 5·5, $J_{10.8}$ *ca.* 1·5 Hz, H-10) p.p.m.; irradiation at δ 6·88 p.p.m. (H-10) caused the doublet of doublets at 3·87 to become a slightly broadened singlet, $w_{\frac{1}{2}}$ 4·5 Hz, whereas irradiation at δ 3·87 p.p.m. (H-1) caused the doublet of doublets at 6·88 to collapse to an apparent singlet, $w_{\frac{1}{2}}$ 5 Hz (Found: *M*, 266·1874. $C_{16}H_{26}O_3$ requires *M*, 266·1882). Further elution yielded the second *unsaturated ester* (XXV) (24%), t_R 3·6 min. (XE60; 170°), $\nu_{max.}$ (film) 1715 and 1660 cm.$^{-1}$, δ 0·88 (6H, d, *J* 6 Hz, CMe_2), 0·93 (3H, d, *J* 6·5 Hz, CMe), 1·0—2·6 (11H), 3·4 and 3·75 (each 1H, m, H-1 and -3), 3·68 (3H, s, OMe), and 6·96 (1H, m, H-8) p.p.m. (Found: *M*, 266·1874).

Methyl 4-(3-*Hydroxy*-2,6-*dimethylhexyl*)*cyclohex*-1-*enecarboxylate* (XXVII).—To a stirred solution of (XXIV) (95 mg.) in tetrahydrofuran (1·5 ml.) and liquid ammonia (20 ml.) was added calcium (23·5 mg.) to give a deep blue solution. After 4 min., the blue colouration was discharged by addition of sodium benzoate and the solvents were evaporated off. The residue was diluted with water; extraction with chloroform afforded the crude hydrogenolysis product, which on silica gel chromatography with benzene–chloroform as eluant yielded the pure *alcohol* (XXVII) (65 mg., 67%), t_R 5·8 min. (XE60; 180°), $\nu_{max.}$ (film) 3430, 1710, and 1650 cm.$^{-1}$, δ 0·93 (9H, d, *J* 6 Hz, CMe and CMe_2), 1·0—2·8 (14H), 3·64 (1H, m, H-4), 3·70 (3H, s, OMe), and 6·95 (1H, m, H-3′) p.p.m. (Found: *M*, 268·2038. $C_{16}H_{28}O_3$ requires *M*, 268·2038).

(±)-*Juvabione* [(Ib) *and its enantiomer*].—A solution of (XXXII) (50 mg.) in acetone (2 ml.) was treated with a slight excess of Jones reagent at 0°. After 5 min. the excess of oxidant was destroyed by the addition of two drops of propan-2-ol and the mixture was concentrated, diluted with water, and extracted with chloroform. The residue thus obtained was purified by preparative t.l.c. [light petroleum–ether (4 : 1)] followed by short-path distillation (0·1 mm.) to yield (±)-juvabione (42 mg.), t_R 2·9 min. (XE60; 190°), 7·5 min. (20M; 210°), $\nu_{max.}$ (film) 1722sh, 1712, 1650, 1255, 1085, 1035, 925, 805, 745, and 715 cm.$^{-1}$, δ 0·88 (3H, d, *J* 6 Hz, CMe), 0·91 (6H, d, *J* 6 Hz, CMe_2), 1·1—2·8 (13H), 3·70 (3H, s, OMe), and 6·95 (1H, m, H-3′) p.p.m., *m/e* 266 (3%, M^+), 234 (30), 209 (3), 207 (3), 206 (9), 181 (3), 177 (9), 167 (32), 166 (32), 151 (5), 149 (6), 139 (21), 137 (10), 135 (23), 134 (100), 127 (22), 125 (3), 121 (4), 107 (30), 85 (19), 79 (19), 59 (5), and 57 (22) (Found: C, 72·25; H, 9·9. $C_{16}H_{26}O_3$ requires C, 72·1; H, 9·8%; *M*, 266). These values are in agreement with the specta published for (+)-juvabione [2] and for (±)-juvabione.[7]

(±)-*Todomatuic Acid*.—On alkaline hydrolysis, as already described, (±)-juvabione yielded (±)-todomatuic acid (90%), m.p. 60—63°; after two recrystallizations from light petroleum the product had m.p. 66—67°, $\nu_{max.}$ (Nujol) 3200—2500, 1710, 1690, 1652, 1648, 1278, 955, 945, 925, 785, 745, and 710 cm.$^{-1}$ δ(CCl_4) 0·87 (3H, d, *J* 6 Hz, CMe), 0·90 (6H, d, *J* 6 Hz, CMe_2), 1·1—2·8 (13H), 7·02 (1H, m, H-3′), and 11·0br (1H, s, exchangeable CO_2H) p.p.m., *m/e* 252 (2%, M^+), 234 (22), 206 (12), 195 (5), 177 (13), 152 (60), 134 (100), 127 (38), 107 (28), 101 (13), 86 (33), 79 (19), and 57 (40) (Found: C, 71·7; H, 9·3. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%). These values agree with the published figures.[7]

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