Bicyclic Analogues of Exaltone (Cyclopentadecanone) and Muscone (3-Methylcyclopentadecanone)

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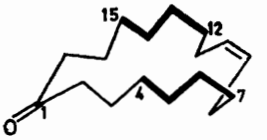
A series of unsubstituted and 3-methyl-substituted bicyclo[10.3.0]pentadecan-, bicyclo[9.3.1]pentadecan-, and bicyclo[10.4.0]hexadecan-ones have been prepared from readily available precursors. The bridging bond(s) of these ketones ensure that the preferred conformations of these compounds differ from the conformations likely to be adopted by exaltone and muscone. The odours of these bicyclic ketones are briefly discussed.

SOME 30 years ago, Ruzicka noted that certain androstenols [*e.g.* (1)] and civetone (2) were similar in two respects: they have a musk odour and the same number of carbon atoms on their perimeters.[1] Thus bridging of the cycloheptadecane ring to give the cyclopentaphenanthrene skeleton, had surprisingly little effect on the odour.

(1)



(2)

With this concept in mind, the synthesis and investigation of the odoriferous properties of some bicyclic analogues of cyclopentadecanone (exaltone) (3a or b) and 3-methylcyclopentadecanone (muscone) (4a or b) have

(3a) R = H
(4a) R = Me

(3b) R = H
(4b) R = Me

been carried out. One such bicyclic analogue of civetone, bicyclo[11.4.0]heptadecan-15-one has been prepared previously and shown to possess a musk odour.[2]

Bicyclic analogues of (3) and (4) are bicyclo[*m.n.*0]-pentadecanes where $m + n = 13$. The choice of $m = 10$ and $n = 3$ was expedited by the ready availability of cyclododecane derivatives and by the previous use of such compounds in efforts directed towards the synthesis of muscone (4) and closely related compounds.[3-8]

In the bicyclic analogues of muscone (4), the β-relation of the methyl substituent to the carbonyl group has been maintained, albeit across the bridging bond in (14). This is of considerable importance, for, of the isomeric methyl-substituted cyclopentadecanones,[9] the 3-methyl substituent of muscone itself confers the finest musk odour.

The two αβ-unsaturated ketones (8) and (20) were the first objectives. The former, having been used as a key intermediate in the synthesis of muscopyridine,[10a,†] was obtained by following the original route from cyclododecanone (5) *via* the alkylidenesuccinic half-ester (6), and the vinylogous β-keto-ester (7).

The preparation of the 1,4-diketone (19) which can be cyclised in alkali to the 3,4-disubstituted cyclopent-2-enone (20), represents the most direct route to this type of αβ-unsaturated ketone.[11] Attempts to prepare (19) by hydration of the propargylic ketone (16) [12] and by acid-catalysed ring opening of the furan (17) [prepared by the cyclisation [13] of the chloro-ketone (24)] failed; however, a third alternative, the condensation of the pyrrolidine enamine of cyclododecanone (19) [14] with bromoacetone, gave a reasonable yield [15] of the 1,4-diketone (19), the i.r. spectrum of which showed the presence of two carbonyl groups. Cyclisation of diketone (18) with ethanolic potassium hydroxide resulted in a good yield of the unsaturated ketone (20). On chromatography of the

† Ketone (8) has also been prepared by Nozaki *et al.*[4a] using a modification of the original route, and by Defaye *et al.*[10b] using an alternative method.

[1] V. Prelog and L. Ruzicka, *Helv. Chim. Acta*, 1944, **27**, 61; V. Prelog, L. Ruzicka, P. Meister, and P. Wieland, *ibid.*, 1945, **28**, 618; L. Ruzicka, P. Meister, and V. Prelog, *ibid.*, 1947, **30**, 867.

[2] V. Prelog, L. Ruzicka, and O. Metzler, *Helv. Chim. Acta*, 1947, **30**, 1883.

[3] G. Ohloff, J. Becker, and K. H. Schulte-Elte, *Helv. Chim. Acta*, 1967, **50**, 705; A. Eschenmoser, D. Felix, and G. Ohloff, *ibid.*, 1967, **50**, 708; D. Felix, J. Schreiber, G. Ohloff, and A. Eschenmoser, *ibid.*, 1971, **54**, 2896; Fr.P. 1,558,413 (*Chem. Abs.*, 1970, **72**, 42,961f).

[4] (*a*) H. Nozaki, T. Mori, R. Noyori, and M. Kawanisi, *Canad. J. Chem.*, 1967, **45**, 1804; (*b*) H. Nozaki, H. Yamamoto, and T. Mori, *ibid.*, 1969, **47**, 1107; (*c*) Jap.P. 04341-2/1969, 19903/1970 (*Chem. Abs.*, 1969, **71**, 49,399s, 21,748f; 1970, **73**, 98,494u); (*d*) T. Hiyama, Y. Ozaki, and H. Nozaki, *Chem. Letters*, 1972, 963.

[5] S. Bradamante, A. Marechesini, and G. Pagani, (*a*) *Chimica Industria*, 1971, **53**, 267; (*b*) *Tetrahedron Letters*, 1971, 4621; (*c*) A. Marchesini, S. Bradamante, R. Fusco, and G. Pagani, *ibid.*, 1971, 671; (*d*) A. Marchesini, U. M. Pagnoni, and A. Pinetti, *ibid.*, 1973, 4299.

[6] R. C. Cookson and R. Singh, *J. Chem. Soc.* (*C*), 1971, 1477; R. Baker, B. N. Blackett, and R. C. Cookson, *J.C.S. Chem. Comm.*, 1972, 802; R. Baker, R. C. Cookson, and J. R. Vinson, *ibid.*, 1974, 515.

[7] Ger. Offen, 2,165,113, 2,348,781 (*Chem. Abs.*, 1972, **77**, 126,143g; 1974, **81**, 25,208j).

[8] S. Abe, T. Eto, and Y. Tsujito, *Cosmetics and Perfumery*, 1973, **88**, No. 6, 67 review recent advances in this field.

[9] L. Ruzicka, H. Schinz, and M. Pfeiffer, *Helv. Chim. Acta*, 1928, **11**, 686; L. Ruzicka and M. Stoll, *ibid.*, 1934, **17**, 1308.

[10] (*a*) K. Biemann, G. Buchi, and B. H. Walker, *J. Amer. Chem. Soc.*, 1957, **79**, 5558; (*b*) G. Defaye, M. Fetizon, and M. C. Tromeur, *Compt. rend.*, 1967, **265***C*, 1489.

[11] R. A. Ellison, *Synthesis*, 1973, 397.

[12] A. M. Islam and R. A. Raphael, *J. Chem. Soc.*, 1952, 4086.

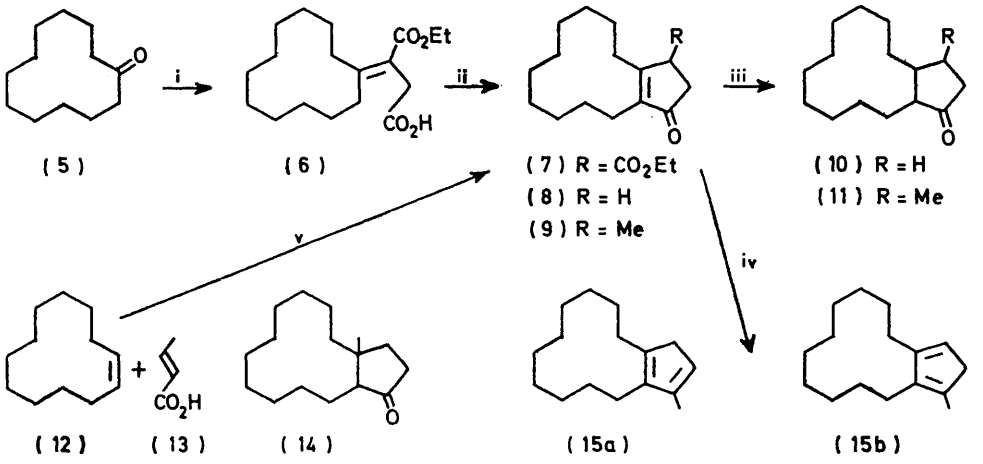
[13] E. J. Nienhouse, R. M. Irwin, and G. R. Finni, *J. Amer. Chem. Soc.*, 1967, **89**, 4557.

[14] K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *J. Org. Chem.*, 1963, **28**, 1464.

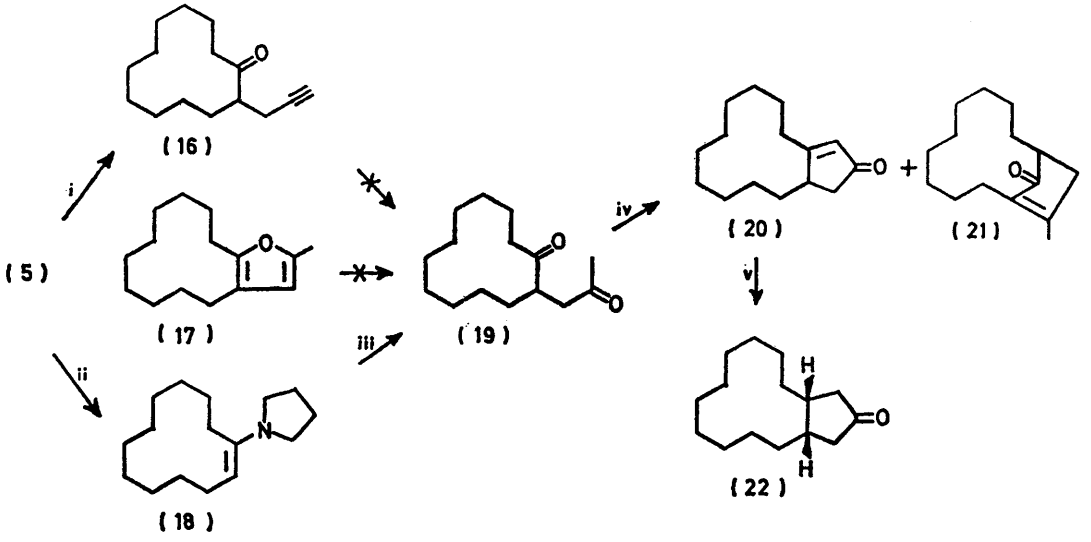
[15] H. E. Baumgarten, P. L. Creger, and E. E. Villars, *J. Amer. Chem. Soc.*, 1958, **80**, 6609.

mother liquors, the product (21) of cyclisation in the alternative manner was isolated as a viscous yellow oil.

On hydrogenation, the unsaturated ketones (8) and (20) yielded single isomeric forms, (10) and (22), of the corresponding saturated ketones. The stereochemistry at the ring junction of these ketones cannot be assumed to be *cis* as the course of hydrogenation of αβ-unsaturated ketones is influenced by the pH of the medium.[16] Furthermore, no definite conclusion can be drawn from the n.m.r. spectrum concerning the stereochemistry of the ring junction in (10). The 220 MHz spectrum is a complex of overlapping signals. The addition of the shift reagent [$^2H_{30}$]Eu(fod)$_3$ (0·09 mol. equiv.) separates the α-methylene and α-methine signals from the remainder. The latter signal is a doublet of triplets, *J ca.* 8·6 (d) and 5·5 Hz (t). Probably the large coupling involves one of the α-methylene protons in the twelve-membered ring but this cannot be established with certainty. Further addition of the shift reagent (0·19 and 0·29 mol. equiv.) yielded no further information owing to excessive line broadening. Some indication of the ring junction being *trans* is the small chemical shift difference between the two protons within the α-methylene group in the five-membered ring which remains small after the addition of more shift reagent.* Nozaki *et al.*[4a] have previously suggested that ketone (10) possesses a *trans* ring fusion on the basis of epimerisation studies.



Reagents: i, $(CH_2{\cdot}CO_2Et)_2$–KOBu^t; ii, PPA; iii, H_2; iv, Me_2CuLi–THF; v, PPA



Reagents: i, CH≡C·CH$_2$Br–NaH; ii, pyrrolidine–xylene; iii, CH$_3$·CO·CH$_2$Br; iv, KOH–EtOH; v, H_2

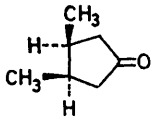
A comparison of the n.m.r. spectrum of (22) with those of *cis*- and *trans*-3,4-dimethylcyclopentanone (23a and b) [17] leads to the conclusion that the ring junction is

* If the ring junction is *cis*, an increase in the chemical shift difference between the two CH$_3$ protons would be expected, due to slightly preferred complexing of the reagent on one side of the molecule.

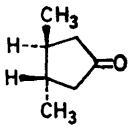
[16] R. L. Augustine, D. C. Migliorini, R. E. Foscante, C. S. Sodano, and M. J. Sisbarro, *J. Org. Chem.*, 1969, **34**, 1075, and refs. therein; I. Jardine, R. W. Howsam, and F. J. McQuillin, *J. Chem. Soc.* (*C*), 1969, 260, and refs. therein.

[17] J. M. Conia and M. L. Leriverend, *Bull. Soc. chim. France*, 1970, 2981.

almost certainly *cis*. The assignment of the stereochemistry of these model compounds was based on comparisons with literature data [18] and from the positions of



(23a)



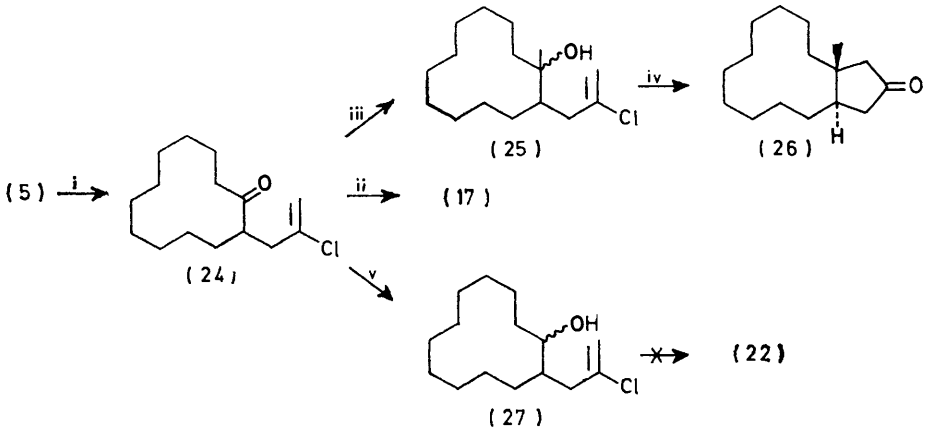
(23b)

the methyl signals, since the *trans*-dimethyl system is expected to absorb at lower field than the *cis*.[19]

It was expected that the β-methyl substituents of the ketones (14) and (26) could be introduced by reaction of the unsaturated ketones (8) and (20) with lithium dimethylcuprate.[20] When (8) was treated with this reagent in ether, the starting material was unchanged but, in refluxing tetrahydrofuran, reaction took place with formation of a compound showing no carbonyl and hydroxy-absorptions in the i.r. spectrum. On the basis of its mass (M^+ 218) and n.m.r. spectra [δ 1·92 (CH_3–C=C), 2·28 (allylic CH_2), 2·68 (=C–CH_2–C=), and 5·76 (=CH)] the product was identified as a trisubstituted cyclopentadiene. As the dehydration of the intermediate tertiary alcohol can occur directly or with rearrangement of the double bonds,[21] this material could be either of the dienes (15a and b), the spectroscopic data being insufficient to distinguish between them. This type of behaviour, although rare, is not unknown.[22]

The preparation of the ketone (26) by the reaction of the αβ-unsaturated ketone (20) with lithium dimethylcuprate was also unsatisfactory. However, (26) could be prepared by the chloro-olefin annulation method recently extended and rationalised by Lansbury.[23] Cyclododecanone (5) was condensed with 2,3-dichloropropene to yield the chloro-ketone (24), which was treated with an excess of methylmagnesium iodide to give a mixture of diastereoisomeric tertiary alcohols (25), directly cyclised in 90% sulphuric acid to the ketone (26). The methyl signal at δ 0·87 in the n.m.r. spectrum showed a long-range coupling of 0·85 Hz indicative of a *trans* ring junction.[24] The preparation of the ketone (22) (possibly with the opposite stereochemistry at the ring junction) seemed equally feasible by this route and to this end the chloro-ketone (24) was reduced to the corresponding alcohol (27); however attempts to cyclise this material in sulphuric acid, formic acid, and polyphosphoric acid led to a complex mixture which lacked any carbonyl absorption appropriate to a cyclopentanone.

The intermediate (7) had been considered as a suitable precursor to ketones in the 15-methylbicyclo[10.3.0]-pentadecane series. However, Dev has shown that 3-methyl-4,5,6,7-tetrahydroindan-1-one can be prepared from cyclohexene and crotonic acid (13) in a one step acylation–alkylation procedure.[25] Substitution of cyclododecene (12) for cyclohexene in this reaction gave a low



Reagents: i, CH_2=C(Cl)·CH_2Cl–$NaNH_2$; ii, 90% H_2SO_4; iii, MeMgI; iv, 90% H_2SO_4; v, $LiAlH_4$

yield of the αβ-unsaturated ketone (9). Catalytic hydrogenation yielded a mixture of two saturated ketones (11) whose stereochemistry at the ring junction is not established. The two isomers probably differ in the configuration of the methyl group with respect to the vicinal $[CH_2]_n$ substituent. The work of Pfeffer and Osman [19] suggests that the major component has its methyl group *trans* to the vicinal methylene chain and the minor one *cis*.

Two bicyclo[9.3.1]pentadecanones have also been prepared, both possessing methyl substituents β to the carbonyl group situated on the shortest bridge. In a further chloro-olefin reaction,[23] cyclododecanone (5) was condensed with 1,3-dichlorobut-2-ene to yield the chloro-ketone (28), which on treatment with 95% sulphuric acid

[18] C. Sablayrolles, R. Granger, J. P. Girard, H. Bodot, J. P. Aycard, and L. Bardet, *Org. Magnetic Resonance*, 1974, **6**, 161; W. C. M. C. Kokke and F. A. Varkevisser, *J. Org. Chem.*, 1974, **39**, 1539.

[19] P. E. Pfeffer and S. F. Osman, *J. Org. Chem.*, 1972, **37**, 2425.

[20] G. H. Posner, *Org. Reactions*, 1972, **19**, 1.

[21] S. McLean and P. Haynes, *Tetrahedron*, 1965, **21**, 2313, 2343.

[22] A. J. Birch and R. Robinson, *J. Chem. Soc.*, 1944, 503.

[23] P. T. Lansbury, *Accounts Chem. Res.*, 1972, **5**, 311.

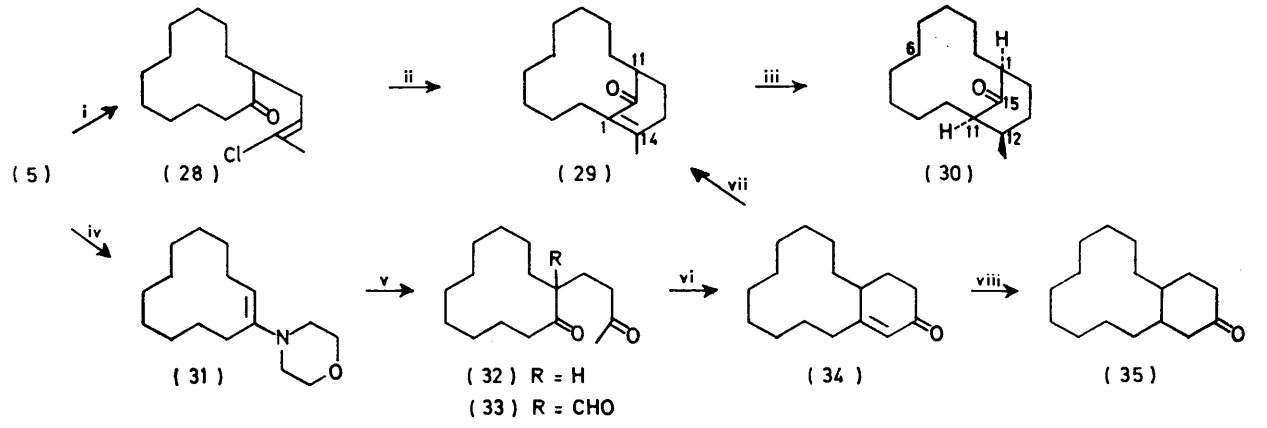
[24] L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance in Organic Chemistry,' Pergamon, 2nd edn., 1969, p. 334.

[25] S. Dev, *J. Indian Chem. Soc.*, 1957, **34**, 169.

gave an αβ-unsaturated ketone. This material did not react with Girard's Reagent T [26] and its n.m.r. spectrum showed a methyl signal at δ 1·84 (CH_3–C=C), indicating that the product was the enone (29). Further evidence for this structure was provided by the u.v. maximum at 251 nm, more appropriate to an αββ-trisubstituted cyclohexenone than to a ββ-disubstituted enone (34) which would be formed if the cyclisation occurred in the alternative manner. The reduced intensity of the absorption maximum of this bicyclic ketone (29) (log ε 4·10) and its analogue (21) (4·02) as compared with the fused enone (34) (4·22) [27] is caused by distortion of the chromophore.[28]

This particular condensation and cyclisation sequence, devised initially by Wichterle,[29] was superior both in yield and specificity when compared with our initial experiments using the Robinson annulation reaction. When the morpholine enamine of cyclododecanone (31) [30] (in preference to ethyl 2-oxocyclododecanecarboxylate) was condensed with methyl vinyl ketone in refluxing benzene, a mixture of products was obtained. On treatment with Girard's Reagent T, the 'non-ketonic' fraction was found to contain the enone (29); the ketonic fraction was treated with an excess of 2,4-dinitrophenylhydrazine and the products were chromatographed to yield (*a*) a red dinitrophenylhydrazone, m.p. 144—145°, $\lambda_{max.}$ ($CHCl_3$) 387 nm (log ε 4·47), identical with the dinitrophenylhydrazone (m.p. and mixed m.p.) of bicyclo-[10.4.0]hexadec-12-en-14-one (34), a ketone prepared by Whitehurst *et al.*[27] from the base-catalysed cyclisation of (33); and (*b*) a yellow monodinitrophenylhydrazone, m.p. 120°, $\lambda_{max.}$ ($CHCl_3$) 362 nm (log ε 4·37), M^+ 432, decomposed by the levulinic acid method [31] to give the intermediate 1,5-diketone (32). In later experiments, this δ-diketone was readily isolated when the enamine (31) and methyl vinyl ketone were left together at room temperature. On treatment with sodium methoxide in refluxing benzene,[27] the δ-diketone cyclised to the fused enone (34) in good yield.

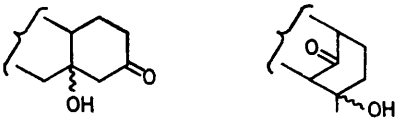
Neither the Wichterle nor the Robinson annulation sequence has been intensively investigated using medium sized ketones ($C_nH_{2n-2}O$) as starting materials. The results available [26,32] show that sulphuric acid-catalysed cyclisations almost invariably give bridged products ($6 \leqslant n \leqslant 15$) whereas the base-catalysed cyclisations yield fused enones when $n \leqslant 8$ and bicyclic enones when $n \geqslant 8$. The various factors affecting the cyclisation of cyclohexanone derivatives have been considered by



Reagents: i, CH_3·C(Cl)=CH·CH_2Cl–$NaNH_2$; ii, 95% H_2SO_4; iii, H_2; iv, morpholine–toluene; v, MeCO·CH=CH_2; vi, NaOMe–benzene; vii, 2N-KOH–MeOH; viii, H_2.

Buchanan,[33] who concluded that the bridged ketones are the products of kinetic control, whereas the fused enones are the thermodynamically more stable products.

With medium sized ring ketone derivatives ($8 \leqslant n \leqslant 12$), the steric environment of the intermediate ketols will



(36a) (36b)

have an important effect on the outcome of the cyclisations. Independent of the cyclisation medium, all the atoms of the original cycloalkanone ring become sp^3-hybridised during fused ketol formation (36a) and thus the *I*-strain is increased; [34] in contrast, during bicyclic ketol formation (36b) at least one sp^2-hybridised atom is maintained throughout the reaction and consequently the

[26] V. Prelog, *J. Chem. Soc.*, 1950, 420.
[27] V. Dave and J. S. Whitehurst, *J.C.S. Perkin I*, 1973, 393; *Tetrahedron*, 1974, **30**, 745.
[28] A. I. Scott, 'Interpretation of the Ultraviolet Spectra of Natural Products,' Pergamon, Oxford, 1964, p. 55.
[29] O. Wichterle, J. Prochazka, and J. Hofman, *Coll. Czech. Chem. Comm.*, 1948, **13**, 300.
[30] A. Kirrmann and C. Wakselman, *Compt. rend.*, 1965, **261***C*, 759.
[31] C. H. DePuy and B. W. Ponder, *J. Amer. Chem. Soc.*, 1959, **81**, 4629.
[32] V. Prelog, M. M. Wirth, and L. Ruzicka, *Helv. Chim. Acta*, 1946, **29**, 1425; V. Prelog, L. Ruzicka, P. Barman, and L. Frankiel, *ibid.*, 1948, **31**, 92; V. Prelog, P. Barman, and M. Zimmermann, *ibid.*, 1949, **32**, 1284.
[33] G. L. Buchanan, *Topics Carbocyclic Chem.*, 1969, **1**, 199; *Chem. Soc. Rev.*, 1974, **3**, 41.
[34] E. L. Eliel, 'Stereochemistry of Carbon Compounds,' McGraw-Hill, New York, 1962, pp. 265—269.

latter less sterically hindered mode will be the preferred method of cyclisation. In addition, models show that the favoured ' O-inside ' conformation of cyclododecanone [35] (and presumably its derivatives) will also promote bicyclic ketol formation.

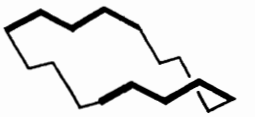
An outstanding anomaly is the cyclisation of the parent 1,5-diketone (32) and its formyl derivative (33) [27] to the fused αβ-unsaturated ketone (34) with sodium methoxide in refluxing benzene. Interestingly, under more vigorous alkaline conditions, it is possible to isomerise the fused enone (34) to the bridged enone (29). In the cyclododecane series, the bridged enone appears to be more stable than the fused enone, in complete contrast to the cyclohexane analogues.

Catalytic hydrogenation of the αβ-unsaturated ketone (29) gave two products (30) in the ratio 14 : 86 as deduced from the methyl n.m.r. signal (in [$^2H_6$]benzene). The 220 MHz spectrum of the major product indicates that both protons α to the carbonyl group are axial, leading to two about equally large couplings in the δ 2·71 signal (*J ca.* 12 Hz) and only one in the δ 2·90 signal (*J* 11·4 Hz). One large coupling involves a proton in each of the two methylene groups in the twelve-membered ring α to the ring junction with which the torsion angle approaches 180°. The methyl group must also be axial and all substituents are *cis* in the major product. The minor product is a stereoisomer.

Catalytic hydrogenation of the enone (34) under neutral, acidic, and basic conditions always yielded the corresponding saturated ketone (35) as a viscous liquid containing a mixture of stereoisomers. The single solid stereoisomer prepared by Ruzicka [2] could not be isolated.

The original observations on the structural relationship between civetone (2) and the androstenol (1) noted that these compounds possessed the same number of carbon atoms on their perimeters; this superficial resemblance can be placed on a much more rigorous foundation by conformational analysis. Dale [36] has shown that cyclooctadecane probably possesses an ideal rectangular conformation (C_{2h} symmetry) with two long parallel chains separated approximately by van der Waals radii, and bound at each end by bridges containing two carbon atoms (37); cyclohexadecane, on the other hand, must have bridges containing three carbon atoms joining the parallel chains to avoid torsional strain (D_{2d} symmetry) (38a) but may prefer to adopt some strain in order to improve van der Waals contacts (D_2 symmetry) (38b). The inherent strain in odd-membered cycloalkanes such as cycloheptadecane is probably distributed in the form of a pseudorotation and consequently civetone (2) could well exist in a conformation containing ' two-carbon bridges ' C-5 and -6; C-13 and -14, four ' corner ' atoms (C-4 and -7; C-12 and -15), and two methylene chains, one consisting of five carbon atoms containing the carbonyl group and one of four carbon atoms incorporating the double bond. Models show that the overall shape of

(37)



(38a)

(38b)

the conformations where C(4—7) and C(12—15) of civetone (2) correspond to C(6—8, 14) and C(12, 11, 9, 10) (steroid numbering) of the androstenol (1) are remarkably similar.

The correlation of three-dimensional structure with odour has been developed by a number of authors, Amoore in particular, and it has been suggested that the musk odorants fit a receptor site with the general shape of an elliptical flat-bottomed pan possessing axes of 1·15 and 0·90 nm.[37] The bicyclic ketones fit into the general elliptical pattern but from a conformational viewpoint do not appear particularly close to exaltone or muscone.

Unfortunately no crystallographic data are available for these two macrocyclic ketones; however, on the basis of arguments similar to those above, cyclopentadecanone is likely to adopt either a conformation with ' two carbon bridges ' joined by methylene chains containing three and four carbon atoms (3a) or one with ' three-carbon bridges ' joined by chains possessing two and three carbon atoms (3b). There is some evidence, however, that cyclopentadecanone is conformationally inhomogeneous;[35c] consequently both may well be present. The carbonyl group will take up a central position on the odd-membered chain β in relation to two corner atoms [35c,36,38] and the β-methyl group of muscone will then be placed in a sterically favoured corner position pointing out from the ring, the preferred position for a substituent (4a and b).

In contrast, the conformations adopted by the bicyclo-[10.3.0]pentadecanes are determined by the presence of the twelve-membered ring which possesses an essentially square conformation with ' two carbon bridges ' joined by ' two carbon chains ' (D_4 symmetry).[39] The five-membered ring fused to the twelve-membered ring gives

[35] (*a*) T. Burer and H. H. Gunthard, *Helv. Chim. Acta*, 1956, **39**, 356; (*b*) T. Ledaal, *Tetrahedron Letters*, 1967, 4397; 1968, 651; P. Kristiansen and T. Ledaal, *ibid.*, 1971, 2817, 4457; (*c*) F. A. L. Anet, A. K. Cheng, and J. Krane, *J. Amer. Chem. Soc.*, 1973, **95**, 7877.

[36] J. Dale, (*a*) *J. Chem. Soc.*, 1963, 93; (*b*) *Angew. Chem. Internat. Edn.*, 1966, **5**, 1000; (*c*) *Pure Appl. Chem.*, 1971, **25**, 469.

[37] J. E. Amoore, J. J. Johnston, and M. Rubin, *Scientific American*, 1964, February, p. 2; J. E. Amoore, *Ann. New York Acad. Sci.*, 1964, 457; *Cold Spring Harbour Symp. Quant. Biol.*, 1965, **30**, 623; see also ' Gustation and Olfaction,' eds. G. Ohloff and A. F. Thomas, Academic Press, 1971, for a general discussion of this topic.

[38] G. Borgen and J. Dale, *Chem. Comm.*, 1970, 1340.

[39] J. D. Dunitz and H. M. M. Shearer, *Helv. Chim. Acta*, 1960, **43**, 18; F. A. L. Anet, A. K. Cheng, and T. J. Wagner, *J. Amer. Chem. Soc.*, 1972, **94**, 9250.

these bicyclic ketones a wedge-shaped appearance with the rings in separate planes, quite different from the flatter disc-like shape of the macrocyclic ketones. Models show that *cis*-fusion of the rings causes severe steric interactions within the larger ring and suggests that *trans*-ring fusion will be strongly favoured. It is all the more surprising therefore to find that the n.m.r. data for the ketone (22) indicate a very probable *cis*-ring fusion.

The n.m.r. data for compounds (10) and (11) give no concrete evidence as to the nature of the ring fusion; however, *trans*-stereochemistry is likely as no epimerisation of these substituted cyclopentanones was observed upon treatment with alkali.[40] The ketone (10) has a wide choice of conformational alternatives depending on whether the three-carbon unit is fused to two ' bridging ' carbon atoms, or to a ' bridged ' atom and a ' corner ' atom. Further alternatives are introduced by the asymmetry of the three-carbon unit. However, the pseudorotation of the twelve-membered ring will interconvert these conformers and in energy terms there seems little to choose between them. The same argument can be applied to the substituted ketone (11) but not to the isomeric (26) where the quaternary carbon will of necessity be a corner atom to ensure that the methyl group points away from the cyclododecane ring.

The most conspicuous feature of all the αβ-unsaturated ketones [(8), (9), (20), (29), and (34)] is the effect of the sp^2-hybridised atoms on the conformation of the twelve-membered ring, as at least three and sometimes four carbon atoms are held in one plane. Its preferred symmetrical conformation cannot be reached and one which minimises the compression of the non-bonded atoms will be adopted.

The saturated ketones (30) and (35) provide an interesting contrast. The two rings in (30) are at a distinct angle to each other while (35) possesses a fairly planar structure with the most disc-like appearance of all the bicyclic ketones examined. Considered as substituted cyclohexanones, the 2,3,6-trisubstituted compound (30) has been shown by n.m.r. spectroscopy to have the expected 2,6-diequatorial substituents [41] and consequently the cyclododecane ring is forced to adopt a triangular conformation symmetrical about a line through C-13, C-15, and C-6 with one of the protons on C-3, C-6, and C-9 pointing inwards towards the oxygen atom. This alternative diamond-lattice conformation for the twelve-membered ring has been considered previously.[36c]

As catalytic hydrogenation of the unsaturated ketone (34) resulted in a stereoisomeric mixture of saturated ketones (35), it suggests there is only a small energy difference between the *cis*- and *trans*-forms. Other 3,4-disubstituted cyclohexanones exhibit similar behaviour.[42] The cyclododecane ring again approaches its preferred square conformation in both stereoisomers provided C-1 is of the corner atom type.

In conformational terms, it can be concluded that the ketones of the [10.3.0], [9.3.1], and [10.4.0] series are less similar to exaltone and muscone than is civetone to androstenol. When the twelve ketones were examined for odour (Table) it was all the more surprising to find that 15-methylbicyclo[10.3.0]pentadec-1(12)-en-13-one (9) and 1-methylbicyclo[10.3.0]pentadecan-14-one (26) possessed a distinct musk odour. The claims made for (10) as a musk odorant [4a] have not been confirmed in the present study. It appears that the correlation of structure with odour is still fraught with difficulties and possesses subtleties as yet unappreciated.

Structure	Compound	Odour
(8)	Bicyclo[10.3.0]pentadec-1(12)-en-13-one	Faint, sweet, woody
(9)	15-Methylbicyclo[10.3.0]pentadec-1(12)-en-13-one	Distinctly musky, with woody notes
(10)	Bicyclo[10.3.0]pentadecan-13-one	Faint, woody
(11)	15-Methylbicyclo[10.3.0]pentadecan-13-one	Faint, woody
(20)	Bicyclo[10.3.0]pentadec-1(15)-en-14-one	Weak, earthy
(22)	Bicyclo[10.3.0]pentadecan-14-one	Very faint, woody
(26)	1-Methylbicyclo[10.3.0]pentadecan-14-one	Distinctly musky, with sweet, woody notes
(29)	14-Methylbicyclo[9.3.1]pentadec-1(14)-en-15-one	Faint, woody
(30)	12-Methylbicyclo[9.3.1]pentadecan-15-one	Faint, sweet, woody
(34)	Bicyclo[10.4.0]hexadec-12-en-14-one	Almost odourless
(35)	Bicyclo[10.4.0]hexadecan-14-one	Faint, musky
	Bicyclo[9.4.1]hexadecan-16-one [4a]	Odourless

EXPERIMENTAL

I.r. spectra were measured with a Unicam SP 200 instrument and u.v. spectra with a Unicam SP 8000 instrument. ^{1}H N.m.r. spectra were recorded with a Varian A-60A or HR-220 instrument for solutions in carbon tetrachloride (unless otherwise stated), with tetramethylsilane as internal standard. Mass spectra were obtained with an A.E.I. MS 902 instrument at 70 eV. G.l.c. analyses were performed on a Pye 104 instrument [9 ft glass column packed with 3% FFAP or 3% OV-25 on Chromosorb G (100—120 mesh)]. DNPH = Dinitrophenylhydrazine; DNP = dinitrophenylhydrazone.

Bicyclo[10.3.0]*pentadec*-1(12)-*en*-13-*one* (8).—Bicyclo-[10.3.0]pentadec-1(12)-en-13-one [10a] was obtained as a pale yellow oil, b.p. 128—132° at 0·3 mmHg, 0·8—2·0 (16H, ring CH_2) and 1·95—2·65 (8H, CH_2·C=C and CH_2·CO).

Bicyclo[10.3.0]*pentadecan*-13-*one* (10).—The enone (8) (2·2 g) was catalytically hydrogenated over 5% palladium–carbon in 95% ethanol (15 ml). After removal of the catalyst and solvent, distillation gave *bicyclo*[10.3.0]*pentadecan*-13-*one* as an oil, b.p. 120—124° at 0·25 mmHg (2·0 g, 91%), n_D^{20} 1·5000; $\nu_{max.}$ (film) 1736 cm^{-1} (lit.,[4a] 1745; lit.,[4c] 1760

[40] D. Varech, C. Ouannes, and J. Jacques, *Bull. Soc. chim. France*, 1965, 1662.

[41] B. Rickborn, *J. Amer. Chem. Soc.*, 1962, **84**, 2414; W. D. Cotterill and M. J. T. Robinson, *Tetrahedron*, 1964, **20**, 765, 777; M. D. Brown, M. J. Cook, and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1971, 2358.

[42] R. Granger, J. P. Chapat, F. Simon, J. P. Girard, and J. Crassous, *Compt. rend.*, 1970, **270***C*, 869; N. L. Allinger and J. H. Siefert, *J. Amer. Chem. Soc.*, 1972, **94**, 8082.

cm^{-1}); δ 1·15—1·73 (20H, complex, ring CH_2), 1·75—2·40 (6H, complex); [$^2H_{30}$]Eu(fod)$_3$ addition (0·09 mol. equiv.) revealed 3·72 and 3·64 (partially overlapped distorted triplets, CO·CH_2), 3·33 (dt, J_d *ca.* 8·6, J_t *ca.* 5·5 Hz, CH·CO) (Found: M^+, 222·1981. $C_{15}H_{26}O$ requires M, 222·1984). The semicarbazone crystallised as needles (from ethanol), m.p. 198—199° (lit.,[4a] 197—198°) and the DNP was obtained as yellow needles (from ethanol), m.p. 153° (lit.,[4c] 147·5—148°).

2-*Prop*-2-*ynylcyclododecanone* (16).—Cyclododecanone (5) (18·2 g) was added over 0·5 h to a stirred suspension of sodium hydride (4·8 g; 50% suspension) in sodium-dried toluene (75 ml). The mixture was refluxed for 4 h and cooled to room temperature, and prop-2-ynyl bromide (11·9 g, 8·0 ml) was added dropwise over 0·5 h. The mixture was refluxed with stirring for a further 4 h, cooled to room temperature, and decomposed with glacial acetic acid (10 ml) followed by hydrochloric acid (1 : 1; 50 ml). The organic phase was separated, washed with water (1 × 100 ml), saturated sodium hydrogen carbonate solution (2 × 100 ml), and brine (1 × 100 ml), dried ($MgSO_4$), and concentrated (20·4 g). On distillation, after a fore-run of unchanged cyclododecanone, 2-*prop*-2-*ynylcyclododecanone* was obtained as an oil, b.p. 130—132° at 1·5 mmHg (5·0 g, 23%), n_D^{20} 1·4948; $\nu_{max.}$ (film) 3300, 2140, and 1703 cm^{-1}; δ 0·9—2·1 (18H, ring CH_2) and 1·85 (1H, t, J 2·6 Hz, C≡CH) (Found: M^+, 220·1819. $C_{15}H_{24}O$ requires M, 220·1827). All attempts to hydrate this material to the 1,4-diketone (19) by using red mercuric oxide–boron trifluoride ether complex–trichloroacetic acid–methanol [12] gave appreciable quantities of cyclododecanone.

14-*Methyl*-13-*oxabicyclo*[10.3.0]*pentadeca*-1(12),14-*diene* (17).—Sulphuric acid (95%; 7·5 ml) was added carefully with stirring to 2-(2-chloroprop-2-enyl)cyclododecanone (24) (6·4 g) (see later). A vigorous exothermic reaction ensued and the temperature was maintained below 35°. The mixture was stirred at room temperature for 2 h after the addition was complete, and then poured onto ice–water (250 ml). The acidic solution was neutralised with solid sodium hydrogen carbonate before the organic material was extracted with ether (3 × 50 ml). The extract was washed with brine (1 × 50 ml), dried ($MgSO_4$), and concentrated to give the crude furan (5·0 g). Distillation gave a yellow *oil*, b.p. 104—108° at 0·9 mmHg (3·7 g, 66%), n_D^{20} 1·5089; $\nu_{max.}$ (film) 3085, 1579, 1260, and 794 cm^{-1}; δ 0·9—2·0 (16H, ring CH_2), 2·19 (3H, C=C·CH_3), 2·19—2·70 (4H, CH_2·C=C·CH_2), and 5·65 (1H, C=CH) (Found: M^+, 220·1824. $C_{15}H_{24}O$ requires M, 220·1827). Attempts to hydrolyse this furan with 10 and 20% sulphuric acid in glacial acetic acid gave only traces of the 1,4-diketone (19).

2-*Acetonylcyclododecanone* (19).—A dried solution of bromoacetone (24·4 g, 15·0 ml) in benzene (150 ml) was added over 0·5 h to a stirred refluxing solution of 1-pyrrolidin-1-ylcyclododecene (18) [14] (41·8 g) in dry benzene (150 ml). The solution was refluxed with stirring for a further 1·5 h, cooled to room temperature, and stirred vigorously for 1 h with 10% hydrochloric acid (150 ml). The organic phase was separated, washed once with water, and concentrated (36·0 g). The dark brown oil obtained was steam-distilled for 6 h to remove the major portion of cyclododecanone. The residue was taken up in petroleum (b.p. 40—60°), dried ($MgSO_4$), and concentrated (21·8 g). Distillation (152—154° at 0·75 mmHg) gave an oil which solidified; crystallisation from petroleum (b.p. 40—60°) gave *needles*, m.p. 58·5—60·5° (15·4 g, 36%), $\nu_{max.}$(Nujol) 1712sh and 1705 cm^{-1}; δ 0·8—1·7 (18H, ring CH_2) and 2·07 (3H, s, CH_3CO) (Found: M^+, 238·1920. $C_{15}H_{26}O_2$ requires M, 238·1933). With DNPH solution, the diketone (19) gave *N*-(2,4-dinitroanilino)-14-methyl-13-azabicyclo[10.3.0]pentadeca-1(12),14-diene, yellow needles (from ethanol), m.p. 197°, $\lambda_{max.}$ ($CHCl_3$) 325 nm (log ε 4·19); δ ($CDCl_3$) 0·8—1·9 (16H, ring CH_2), 2·04 (3H, C=C·CH_3), 2·40 (4H, allylic CH_2), 5·85 (1H, C=CH), 6·20, 8·24, and 9·14 (3H, aromatic protons), and 9·95 (1H, N·NH·C); M^+ 400.

Bicyclo[10.3.0]*pentadec*-1(15)-*en*-14-*one* (20).—2-Acetonylcyclododecanone (19) (6·0 g) in ethanol (25 ml) was added to a stirred refluxing solution of potassium hydroxide (15·0 g) in ethanol (125 ml). The mixture was heated and stirred for 3 h, cooled, acidified with 10% sulphuric acid, diluted with water (100 ml), and extracted with ether (3 × 50 ml). The combined extracts were washed with saturated sodium hydrogen carbonate solution (2 × 50 ml) and brine (1 × 50 ml), dried ($MgSO_4$), and concentrated (4·8 g). Crystallisation from ethanol gave glistening *plates*, m.p. 95 96° (3·7 g, 68%), $\nu_{max.}$(Nujol) 1724 and 1693 (split C=O),[43] and 1615 cm^{-1}; $\lambda_{max.}$(EtOH) 231 nm (log ε 4·22); δ 0·8—1·9 (18H, ring CH_2) and 5·89 (1H, C=CH) (Found: M^+, 220·1824. $C_{15}H_{24}O$ requires M, 220·1827). The DNP was obtained as scarlet needles (from ethanol), m.p. 204°.

Chromatography of the concentrated crystallisation mother liquors on grade III neutral alumina [10% ether–petroleum (b.p. 40–60°) as eluant] yielded 13-methylbicyclo-[9.2.1]tetradec-1(13)-en-14-one (21) (70 mg) as a yellow oil, $\nu_{max.}$(film) 1698 and 1651 cm^{-1}; $\lambda_{max.}$(EtOH) 238 nm (log ε 4·02); δ 0·8—1·9 (16H, ring CH_2) and 2·03 (3H, C=C·CH_3); M^+ 220. This material did not react with DNPH solution.

Bicyclo[10.3.0]*pentadecan*-14-*one* (22).—The enone (20) (1·1 g) was catalytically hydrogenated as described for the enone (8). *Bicyclo*[10.3.0]*pentadecan*-14-*one* crystallised from petroleum (b.p. 40—60°) as flakes, m.p. 42—42·5° (1·0 g, 88%), $\nu_{max.}$ (Nujol) 1743 cm^{-1}; δ 1·2—1·7 (20H, complex, ring CH_2), 1·75 (2H, dd, *J ca.* 18 and *ca.* 6·8 Hz and long-range splitting < 2 Hz, CH of α-CH_2), 2·12 (2H, complex, ring junction protons), and 2·32 (2H, dd, J *ca.* 18 and *ca.* 7·3 Hz and long-range splitting of < 2 Hz, CH of α-CH_2) (Found: M^+, 222·1975. $C_{15}H_{26}O$ requires M, 222·1984). The DNP was obtained as yellow leaflets (from ethanol), m.p. 173—174°.

cis- *and* trans-3,4-*Dimethylcyclopentanone* (23).—The compounds were prepared and separated according to Conia *et al.*: [17] *cis*-isomer, δ 0·98 (6H, d, J 6·3 Hz, 2 CH_3), 1·84 (2H, dd, J 17·2 and 5·3 Hz and long-range splitting < 2 Hz, CH of α-CH_2), 2·21 (2H, distorted dd, J 17·2 and 7·1 Hz, CH of α-CH_2), and 2·33 (2H, complex, β-CH); *trans*-isomer, δ 1·125 (6H, d, J 5·8 Hz, 2 CH_3), 1·74 (4H, complex, 2α-H and 2β-H), and 2·335 (2H, complex, looking like a distorted quartet, 2α-H).

Reaction of Lithium Dimethylcuprate with the Enone (8).—Ethereal 1·59N-methyl-lithium (39·4 ml) was added to a stirred slurry of copper(I) iodide (6·0 g) in dry ether (120 ml). The resulting solution of lithium dimethylcuprate was stirred at 0° for 5 min, and bicyclo[10.3.0]pentadec-1(12)-en-13-one (8) (2·2 g) in dry tetrahydrofuran (75 ml) was added dropwise over 0·5 h. The temperature of the mixture was gradually raised (over 2 h) by distilling out the ether while adding further tetrahydrofuran and the solution was finally refluxed (65°) for 1 h. The mixture was cooled and poured into N-hydrochloric acid (100 ml). The organic material was

[43] P. Yates and L. L. Williams, *J. Amer. Chem. Soc.*, 1958, **80**, 5896.

taken up in ether (4 × 25 ml), separated, dried ($MgSO_4$), and concentrated to yield an orange-red oil (1·9 g). Distillation at 128—130° and 0·9 mmHg gave an oil, 13-methylbicyclo-[10.3.0]pentadeca-1(12),13-diene or -1(15),12-diene (15a or b) (1·1 g, 50%), n_D^{20} 1·5217; $\nu_{max.}$(film) 1645 cm^{-1}; $\lambda_{max.}$(EtOH) 245 nm (log ε 3·85); δ 0·8—1·8 (16H, ring CH_2), 1·92 (3H, C=C·CH_3), 2·28 (4H, allylic CH_2), 2·68 (2H, =C–CH_2–C=), and 5·76 (1H, C=CH); M^+ 218.

2-(2-*Chloroprop*-2-*enyl*)*cyclododecanone* (24).—Cyclododecanone (5) (18·2 g) was added in four portions over 1 h to a stirred mixture of sodamide (3·9 g) and sodium-dried benzene (50 ml). The mixture was refluxed for 15 h, cooled to room temperature, and then 2,3-dichloropropene (11·1 g) in dry benzene (10 ml) was added dropwise over 1 h. The mixture was refluxed for a further 4 h, cooled, and poured onto hydrochloric acid (1 : 1; 100 ml). The organic material was separated, washed with 10% sodium hydrogen carbonate solution (2 × 75 ml) and brine (1 × 50 ml), dried ($MgSO_4$), and concentrated (26·2 g). Distillation gave a fore-run of unchanged cyclododecanone followed by 2-(2-*chloroprop*-2-*enyl*)*cyclododecanone* as an oil which darkened; b.p. 148—152° at 2·0 mmHg (15·9 g, 62%), n_D^{20} 1·5029; $\nu_{max.}$(film) 1704, 1633, and 892 cm^{-1}, δ 0·8—1·9 (18H, ring CH_2) and 5·15 (2H, C=CH_2) (Found: M^+, 256·1584. $C_{15}H_{25}ClO$ requires M, 256·1594).

2-(2-*Chloroprop*-2-*enyl*)-1-*methylcyclododecanol* (25).—Under nitrogen, the Grignard reagent prepared from methyl iodide (7·1 g) and magnesium turnings (1·2 g) in dry ether (25 ml) was added over 0·5 h to a stirred mixture of 2-(2-chloroprop-2-enyl)cyclododecanone (24) (6·4 g) in dry ether (25 ml). The mixture was refluxed with stirring for 4 h, cooled, and hydrolysed with saturated aqueous ammonium chloride. The ethereal layer was separated, washed with brine (2 × 25 ml), dried ($MgSO_4$), and concentrated to yield the oily diastereoisomeric *chloro-alcohols* (6·8 g), $\nu_{max.}$(film) 3500, 1636, and 888 cm^{-1} (Found: M^+, 272·1897. $C_{16}H_{29}$-ClO requires M, 272·1907), δ 1·18 and 1·10 (each s, CH_3). Attempts to purify the alcohols led to decomposition; consequently they were cyclised directly to the ketone (26).

1-*Methylbicyclo*[10.3.0]*pentadecan*-14-*one* (26).—The crude chloro-alcohols (25) (5·5 g) were added with stirring to sulphuric acid (90%; 100 ml). The mixture was then stirred for a further 15 min, and decomposed by pouring onto ice-water (250 ml). The organic material was extracted with ether (3 × 25 ml) and the extract was washed with 10% sodium hydrogen carbonate solution (3 × 25 ml) and water (1 × 25 ml), dried ($MgSO_4$), and concentrated to yield a yellow oil (4·2 g). The portion (1·9 g) which distilled between 170 and 180° at 3—4 mmHg was redistilled (b.p. 137—141° at 0·75 mmHg) to give a slightly yellow oil (1·8 g) which solidified. 1-*Methylbicyclo*[10.3.0]*pentadecan*-14-*one* was obtained as prisms (from methanol), m.p. 44·5—45° (1·1 g, 23%), $\nu_{max.}$(melt) 1738 cm^{-1}; δ 0·87 (3H, d, J 0·85 Hz, W-coupling, CH_3) and 1·2—1·7 (20H, ring CH_2) (Found: M^+, 236·2131. $C_{16}H_{28}O$ requires M, 236·2140). The DNP was obtained as orange-yellow blades (from benzene–methanol), m.p. 164—165°.

2-(2-*Chloroprop*-2-*enyl*)*cyclododecanol* (27).—2-(2-Chloroprop-2-enyl)cyclododecanone (24) (3·2 g) was reduced to the corresponding alcohol with lithium aluminium hydride in dry ether. From petroleum (b.p. 60—80°), the *alcohol* (3·0 g, 92%) was obtained as needles, m.p. 87—88°, $\nu_{max.}$(Nujol) 3350, 1634, and 885 cm^{-1}; δ 1·0—2·1 (20H, ring CH_2), 3·76 (1H, m, C*H*·OH), and 5·18 (2H, C=CH_2) (Found: M^+, 258·1748. $C_{15}H_{27}ClO$ requires M, 258·1750). Attempts to cyclise this material to bicyclo[10.3.0]pentadecan-14-one (22) in sulphuric acid, formic acid, or polyphosphoric acid were unsuccessful.

15-*Methylbicyclo*[10.3.0]*pentadec*-1(12)-*en*-13-*one* (9).—Cyclododecene (12) (18·3 g; 90% pure) and crotonic acid (13) (8·6 g) were added to polyphosphoric acid [from phosphorus pentoxide (70·0 g) and orthophosphoric acid (30 ml)] at 60 °C. The reactants were stirred vigorously at this temperature for 2·5 h before the mixture became homogeneous and then stirred for a further 1·5 h. As much as possible of the flask's contents were poured onto ice–water (1 l) and ice–water (250 ml) was added to the remainder in the flask. The organic material was extracted with ether (3 × 75 ml) and the combined extracts were washed with 10% sodium hydrogen carbonate solution (3 × 100 ml) and brine (1 × 100 ml), dried ($MgSO_4$), and evaporated to leave a dark red oil (23·0 g). This was chromatographed on silica (deactivated with 15% water) [gradient elution with 0—35% ether–petroleum (b.p. 40—60°)] to give a fraction which contained the bicyclic ketone (7·3 g). Molecular distillation (100° at 0·1 mmHg) followed by crystallisation from pentane at 0 °C gave *nodules*, m.p. 48·5—50·5° (5·1 g, 22%), $\nu_{max.}$(Nujol) 1700 and 1635 cm^{-1}, $\lambda_{max.}$(EtOH) 236 nm (log ε 4·19); δ 1·16 (3H, d, J 7 Hz, CH_3) and 0·8—1·9 (16H, ring CH_2) (Found: M^+, 234·1979. $C_{16}H_{26}O$ requires M, 234·1984). The DNP crystallised as scarlet needles (from ethanol), m.p. 184–185°.

15-*Methylbicyclo*[10.3.0]*pentadecan*-13-*one* (11).—The enone (9) (1·2 g) was catalytically hydrogenated as described for the enone (8) to give an oil, b.p. 138—141° at 0·3 mmHg (0·8 g, 70%), n_D^{20} 1·4967, $\nu_{max.}$(film) 1737 cm^{-1}. The n.m.r. spectrum showed the presence of two isomers in a 75 : 25 ratio: major component δ 1·10 (3H, d, J 6·2 Hz, CH_3), 1·20—2·25 (*ca.* 20H, complex), 1·63 (1H, dd, J 11·0 and 17·6 Hz, CH of α-CH_2), and 2·36 (1H, dd, J 7·0 and 17·6 Hz, CH of α-CH_2); minor component δ 0·99 (3H, d, J 7·0 Hz, CH_3) and 2·16 (1H, dd, J 7·8 and 17·8 Hz, CH of α-CH_2); other signals of minor component obscured. The use of [$^2H_{30}$]Eu(fod)$_3$ did not give useful information: the signal for the α-CH at the ring junction remains overlapped by the α-CH_2 signals (Found: M^+, 236·2126. $C_{16}H_{28}O$ requires M, 236·2140). The DNP crystallised as yellow needles (from ethanol–ethyl acetate), m.p. 172—174°.

2-(3-*Chlorobut*-2-*enyl*)*cyclododecanone* (28).—This material was prepared in the same manner as 2-(2-chloroprop-2-enyl)-cyclododecanone (24). Cyclododecanone (5) (18·2 g) and 1,3-dichlorobut-2-ene (12·5 g) gave a faintly yellow *oil* which darkened, b.p. 172—178° at 2·0—2·5 mmHg (13·3 g, 49%), n_D^{20} 1·4998; $\nu_{max.}$(film) 1703, 1664, and 736 cm^{-1}; δ 0·7—1·9 (18H, ring CH_2), 2·07 (3H, m, *J ca.* 1 Hz, C=C·CH_3), and 5·39 (1H, tq, J_t 6, J_q *ca.* 1 Hz, C=CH) (Found: M^+, 270·1736. $C_{16}H_{27}ClO$ requires M, 270·1750).

14-*Methylbicyclo*[9.3.1]*pentadec*-1(14)-*en*-15-*one* (29).—This material was prepared in an identical fashion to the furan (17). Sulphuric acid (95%; 7·5 ml) and 2-(3-chlorobut-2-enyl)cyclododecanone (28) (6·8 g) gave a crude product (5·4 g). Distillation at 167—168° and 3·0 mmHg gave an oil (4·3 g) which solidified on cooling. Crystallisation from methanol gave *needles*, m.p. 49—51° (4·0 g, 68%), $\nu_{max.}$(Nujol) 1674 and 1632 cm^{-1}, $\lambda_{max.}$(EtOH) 251 nm (log ε 4·10); δ 0·9—1·65 (15H, complex, CH_2 and one CH of the large ring), 1·84 (3H, C=C·CH_3), 1·7—2·25 (6H, complex), 2·52br (1H, dt, J_d *ca.* 13, J_t *ca.* 6 Hz, H_{ax}-13), and 2·65br (1H, d, *J ca.* 13 Hz, H_{eq}-13) (Found: M^+, 234·1986. $C_{16}H_{26}O$ requires M, 234·1984). This material did not react with DNPH solution.

12-*Methylbicyclo*[9.3.1]*pentadecan*-15-*one* (30).—The enone (29) (2·3 g) was catalytically hydrogenated as described for the enone (8) to give *needles* (from methanol), m.p. 69—70° (2·2 g, 94%), $\nu_{max.}$(Nujol) 1710 cm^{-1}; δ 0·71 (3H, d, *J* 7·0 Hz, CH_3), 0·80—2·35 (23H, complex), 2·71 (1H, tdd, J_t *ca.* 12, J_d 5·0 and 2·5 Hz, H-1), and 2·90 (1H, ddd, *J* 11·4, 4·8, and 2·1 Hz, H-11); δ (C_6D_6) 0·74 (*J* 6·6 Hz) and 0·66 (*J* 7·0 Hz) (CH_3 signals in the ratio 14 : 86) (Found: M^+, 236·2123. $C_{16}H_{28}O$ requires *M*, 236·2140). This ketone did not react with DNPH solution.

Reaction of 1-*Morpholinocyclododecene*[30] *with Methyl Vinyl Ketone*.—Under nitrogen, at room temperature, methyl vinyl ketone (7·0 g) in dry benzene (25 ml) was added over 0·5 h to a stirred solution of 1-morpholinocyclododecene (31) (25·1 g) in dry benzene (25 ml). The mixture was refluxed for 6 h, the major portion of the benzene removed by distillation, aqueous methanol (1 : 1; 50 ml) added, and refluxing continued for a further 4 h. The flask's contents were transferred to a separating funnel, water (40 ml) was added, and the organic material was taken up in ether (2 × 50 ml); the extract was washed with brine (1 × 50 ml), dried ($MgSO_4$), and concentrated (18·6 g). Distillation removed cyclododecanone (10·8 g) (b.p. 60—96° at 0·002 mmHg) from the products (5·8 g) (b.p. 132—152° at 0·004 mmHg).

The products (500 mg) and Girard's Reagent T (750 mg) were refluxed for 1 h in glacial acetic acid (0·5 ml) and ethanol (5 ml). After cooling, 0·15N-sodium hydroxide (50 ml) was added and the aqueous solution was exhaustively extracted with ether (5 × 10 ml). The extract was dried and evaporated to yield a solid, which crystallised as needles (from methanol) (44 mg), m.p. 49—50°, identical with 14-methylbicyclo[9.3.1]pentadec-1(14)-en-15-one (29). The aqueous solution and concentrated hydrochloric acid (1 ml) were refluxed for 0·25 h, cooled, and thoroughly extracted with ether (5 × 10 ml). The combined extracts were dried and concentrated (yield 358 mg), and the product was treated with an excess of DNPH solution. The crystalline product (598 mg) was taken up in chloroform and chromatographed on grade III neutral alumina (10% chloroform–benzene as eluant). The first band eluted afforded bright red platelets (70 mg), m.p. 144—145° (from ethanol), $\lambda_{max.}$($CHCl_3$) 387 nm (log ε 4·47), identical with the DNP (m.p. and mixed m.p.) prepared from bicyclo[10.4.0]hexadec-12-en-14-one (34).[27] Attempts to decompose this material to the parent ketone were not successful.

Further elution gave a second band which, after evaporation and crystallisation from ethanol, gave sheaves of yellow needles (241 mg), m.p. 120°, $\lambda_{max.}$($CHCl_3$) 362 nm (log ε 4·37), M^+ 432. This material was warmed with levulinic acid (4·5 ml) and concentrated hydrochloric acid (0·5 ml) at 120 °C for 6 h. The cooled mixture was poured onto water (50 ml) and extracted with methylene chloride (25 ml). The organic extract was washed with 10% sodium hydrogen carbonate solution (3 × 50 ml) and brine (1 × 50 ml), dried ($MgSO_4$), and concentrated to yield a dark red oil (78 mg). Bulb-to-bulb distillation (160—170° at 1·5 mmHg) yielded a waxy solid, which crystallised from ethanol (yield 54 mg) to give 2-(3-*oxobutyl*)*cyclododecanone* (32), m.p. 58—59°, $\nu_{max.}$(Nujol) 1710sh and 1694 cm^{-1}; δ 1·0—2·0 (18H, ring CH_2), 2·05 (3H, s, $CO{\cdot}CH_3$), and 2·05—2·83 (5H, $CH_2{\cdot}CO{\cdot}CH{\cdot}CH_2{\cdot}CH_2{\cdot}CO$) (Found: M^+, 252·2075. $C_{16}H_{28}O_2$ requires *M*, 252·2089).

The intermediate 1,5-diketone became the major product when the enamine (31) and methyl vinyl ketone reacted together under different conditons. The enamine (31) (25·1 g) and methyl vinyl ketone (7·0 g; 90% solution in water) were left at room temperature under nitrogen for 3 days. The mixture was worked-up as previously described; distillation yielded cyclododecanone (11·8 g) (b.p. 100—110° at 1·5 mmHg) followed by the diketone (32) (15·9 g) (b.p. 164—168° at 1·5 mmHg). After crystallisation from ethanol, 2-(3-oxobutyl)cyclododecanone was obtained as needles, m.p. 59° (15·0 g, 60%).

Bicyclo[10.4.0]*hexadec*-12-*en*-14-*one* (34).—2-(3-Oxobutyl)-cyclododecanone (32) (2·5 g), sodium methoxide (1·6 g), and sodium-dried benzene (50 ml) were stirred and refluxed for 10 h. The mixture was cooled and acidified with 10% sulphuric acid, and the organic material was separated with the help of ether (50 ml). The extract was washed with saturated sodium hydrogen carbonate solution (2 × 50 ml) and brine (1 × 50 ml), dried ($MgSO_4$), and concentrated to yield a solid which crystallised from petroleum (b.p. 40—60°). The ketone (34), m.p. 77° (1·9 g, 83%), was obtained as needles identical with an authentic sample.[27]

Isomerisation of Bicyclo[10.4.0]*hexadec*-12-*en*-14-*one* (34).—Bicyclo[10.4.0]hexadec-12-en-14-one (34) (230 mg) was refluxed in ethanolic potassium hydroxide [from potassium hydroxide (250 mg) and ethanol (10 ml)] for 24 h. The mixture was worked up as in the previous experiment to give a product (220 mg) which contained 13% bicyclo[10.4.0]-hexadec-12-en-14-one (34), 20% 2-(3-oxobutyl)cyclododecanone (32), and 57% 14-methylbicyclo[9.3.1]pentadec-1(14)-en-15-one (29).

Bicyclo[10.4.0]*hexadecan*-14-*one* (35).—The enone (34) (0·6 g) was catalytically hydrogenated with 5% palladium–carbon in (i) 95% ethanol (15 ml), (ii) 95% ethanol (15 ml) containing concentrated hydrochloric acid (45 mg), and (iii) 95% ethanol (15 ml) containing potassium hydroxide (70 mg). As a mixture of stereoisomers was obtained in each case, the three products were combined and distilled at 160—162° and 3·5 mmHg to give *bicyclo*[10.4.0]*hexadecan*-14-*one* as a viscous oil (1·6 g, 92%), n_D^{20} 1·5508; $\nu_{max.}$(film) 1712 cm^{-1}, δ 1·0—2·0 (20H, ring CH_2) and 2·15 (4H, $CH_2{\cdot}CO{\cdot}CH_2$) (Found: M^+, 236·2130. $C_{16}H_{28}O$ requires *M*, 236·2140). Neither the DNP nor the semicarbazone of the stereoisomeric mixture had a sharp m.p.

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