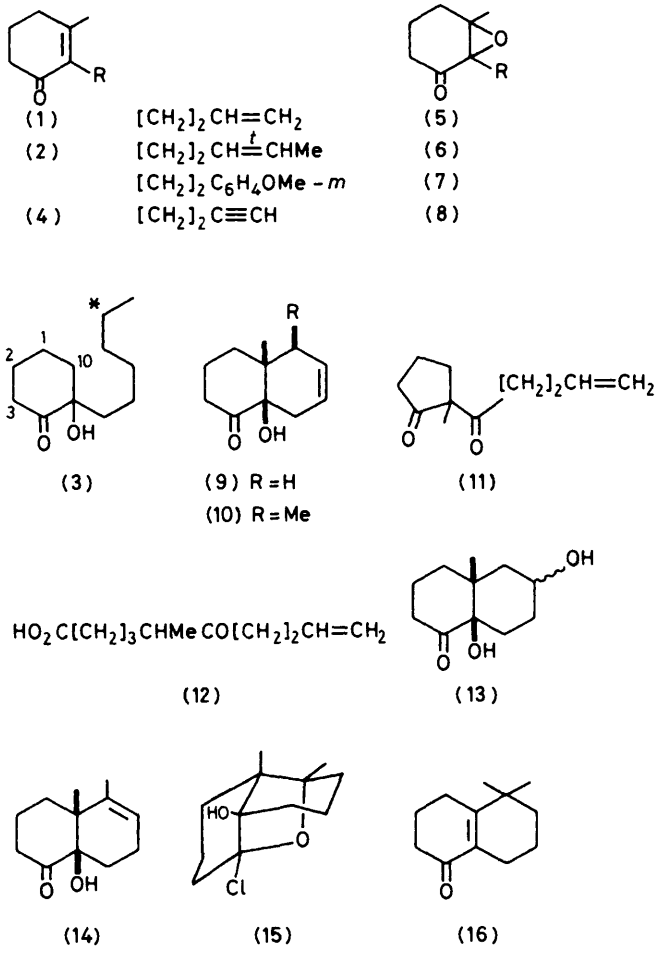
3-Methylcyclohex-2-enone Derivatives as Initiators of Cyclisation. Part 2.† Monocyclisations to Six-membered Rings

Joseph A. Amupitan, Enamul Huq, Michael Mellor, Edward G. Scovell, and James K. Sutherland *
Chemistry Department, The Victoria University of Manchester, Manchester M13 9PL

Cyclisation of 3-methylcyclohex-2-enones and the derived epoxides containing alkene, alkyne, and aryl side-chains yields bicyclo[4.4.0]decane derivatives when the alkene or alkyne is electronically biased towards six-membered ring formation and when the alkene is electronically unbiased.

We have examined the reaction of the epoxide (5) with a number of Lewis acids; varying quantities of cyclisation product (9) and ring-contracted dione (11) are formed. The structure of (11) derives from spectroscopic evidence [$\nu_{max.}$ ($CHCl_3$) 1 745 and 1 715 cm^{-1}; τ 4.3 (1 H, m), 5.1 (2 H, m), 8.7 (3 H, s)], alkaline hydrolysis to the acid (12) [τ 4.2 (1 H, m), 5.0 (2 H, m), 8.8 (3 H, d, J 7 Hz)], and precedent.[1] Spectroscopic data for (9) [$\nu_{max.}$ (CCl_4) 3 495 and 1 715 cm^{-1}; τ(300 MHz) 5.23 (1 H, m), 5.28 (1 H, m), and 9.15 (3 H, s)] established the part-structure (3), where C* is either C-1, -2, -3, or -10. The structures derived from C-1 and -2 bonding were rejected on mechanistic grounds leaving (9) and the bridged structure from C-3 bonding. The latter could be excluded by showing that the diols from borohydride reduction had a CH(OH) n.m.r. signal of greater multiplicity than the two singlets required for the isomers of the bridged structure. The *cis* ring junction in (9) follows from the existence of intramolecular hydrogen bonding. This is possible only in the ' non-steroid ' conformation of a *cis*-decalin as was confirmed by the absence of such bonding in the 5α- and 5β-hydroxycholestan-4-ones kindly donated to us by Dr. J. R. Bull, Pretoria. In the Table the ratio cyclisation : ring contraction for a variety of Lewis acids and solvents is summarised. If it is accepted that gas-phase metal–oxygen bond strengths [2] give a rough measure of Lewis acidity for oxygen then a trend for the stronger Lewis acids giving more cyclisation product is discernible. In line with this, $TiCl_4$–CH_2Cl_2 converted (5) into the ketol (9) (40%) and the diols (13) (23%) without any ring-contracted product. This effect could arise from the C–O–metal bond in the cyclisation transition state being stabilised to a greater extent than the $C{=}\overset{+}{O}$–metal bond in the ring-contraction transition state. In the latter case the stronger the O–metal bond, the less might be the resonance stabilisation. The enone (1) has been cyclised (using Ac_2O–$HClO_4$–EtOAc) to a decalone derivative.[3] This is a preparatively more useful reaction than the epoxide cyclisation.

The epoxide (6) was treated with $BF_3{\cdot}OEt_2$–CH_2Cl_2 at −20 °C to give a complex reaction mixture from which (10) (20%) [τ 4.30 (2 H, m), 9.00 (3 H, d, J 7 Hz), 9.15 (3 H, s)] and (14) (40%) [τ 4.63 (1 H, m), 8.35br (3 H, s), and 9.10 (3 H, s)] were isolated. The ketone (14) was reduced with $NaBH_4$ to a mixture of diols which on periodate oxidation gave a ketoaldehyde whose spectroscopic properties [$\nu_{max.}$ 1 730 and 1 715 cm^{-1}; τ 0.31 (1 H, t, J 1.5 Hz), 4.30 (1 H, m), 8.30 (3 H, t, J 1.6 Hz), and 8.83 (3 H, s)] established that the double bond was not allylic to the hydroxy-group in (14).‡ The two ketols (14) and (10) were again the major products using $TiCl_4$, BCl_3, and $SnCl_4$ as Lewis acids; the ratios of (14) : (10) were 3.4, 3.8, and 5.3 respectively. The experiment using BCl_3 was carried out at −20 °C in CH_2Cl_2. When the reaction was conducted at −78 °C small amounts of the previously mentioned compounds were formed, but a new major (84%) product appeared. It is formulated as (15) but only on mechanistic and spectroscopic grounds [$\nu_{max.}$ 3 600 cm^{-1}; mass spec. 1 H exchangeable with ^2H_2O; τ 8.79 (3 H, s) and 9.10 (3 H, s)]. Cyclisation of the enone (2) with $(CF_3CO)_2O$–CF_3CO_2H (which presumably occurs *via* the dienol trifluoroacetate) gave, after hydrolysis, the ketone (16) (23%) [$\lambda_{max.}$ (MeOH) 245 nm (ε 12 600); $\nu_{max.}$ 1 670 and 1 610 cm^{-1}; τ 8.91 (6 H, s)], the ketol (17) (26%) [$\nu_{max.}$ 3 600 and 1 710 cm^{-1}; τ 6.65 (1 H, m, $W_{\frac{1}{2}}$ 27 Hz), 9.00 (3 H, d, J 7 Hz), and 9.35 (3 H, s)] and the *cis*-isomer (18) (15%) [$\nu_{max.}$ 3 600 and 1 710 cm^{-1}; τ 6.55 (1 H, m, $W_{\frac{1}{2}}$ 25 Hz), 9.01 (3 H, s),



† Part 1, preceding paper.

‡ It was necessary to carry out this degradation to establish that an unexpected rearrangement observed in another cyclisation had not occurred here.

Table

Lewis acid	Solvent	Ratio (9) : (11) [a]
$TiCl_4$	CH_2Cl_2	∞
$AlCl_3$	CH_2Cl_2	3.0
$FeCl_3$	CH_2Cl_2	1.1
$SnCl_4$	CH_2Cl_2	0.6
$ZnCl_2$	CH_2Cl_2	0.3
BF_3·OEt_2	CH_2Cl_2	0.8
BF_3·OEt_2	C_6H_6	0.6
BF_3·OEt_2	Et_2O	0.1
$ZnCl_2$	Et_2O	0.1

[a] Ratios determined by g.l.c.

and 9.12 (3 H, d, *J* 8 Hz)]. The ring-junction stereochemistry of (17) and (18) is assigned using the chemical shifts of the angular methyl groups [4] while the $W_{\frac{1}{2}}$ of the CH(O) protons are in accord with the secondary methyl and the hydroxy-groups being equatorial. In the formation of (15) and (16) the initially formed secondary carbonium ion is transformed to a tertiary carbonium ion either by H^+ elimination–H^+ addition or by 1,2-hydride migration. In the formation of (16) the latter route was established by carrying out the cyclisation with $CF_3CO_2^2H$; one deuterium ($\nu_{max.}$ 2 170 cm^{-1}) was incorporated. On treatment with NaOH–H_2O–dioxan this deuterium was exchanged.

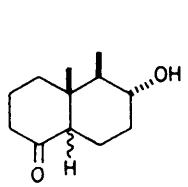
These results illustrate the difficulties of obtaining preparatively useful yields of cyclisation products when different termination mechanisms are evenly balanced. In the epoxide cyclisations control of the direction of elimination might be achieved using Fleming's device [5] of R_3Si elimination instead of H. This might also be applicable in the enone cyclisations and divert termination from the competing rearrangement and nucleophilic attack. Two participating groups which terminate cyclisation by a single mechanism are the acetylenic and aryl functions. Reaction of (7) with BF_3·OEt_2 or $SnCl_4$ in CH_2Cl_2 gave (19) (45%) [τ 2.95 (1 H, m), 3.30 (2 H, m), 8.63 (3 H, s)] and (20) (45%) [τ 2.90 (2 H, d, *J* 7 Hz), 3.30 (2 H, m), and 8.75 (3 H, s)].

A mixture of (19) and (20) was reduced to diols with $NaBH_4$ and oxidised with periodate to give the ketoaldehydes derived from (19) [$\lambda_{max.}$ (EtOH) 274 nm (ε 1 410); $\nu_{max.}$ 1 725 and 1 710 cm^{-1}; τ 0.49 (1 H, t, *J* 1.6 Hz), 2.93 (1 H, dd, *J* 8.5 and 7.5 Hz), 3.35 (2 H, m), 6.17 (3 H, s), and 8.54 (3 H, s)] and (20) [$\lambda_{max.}$ (EtOH) 279 nm (ε 1 440); $\nu_{max.}$ 1 730 and 1 710 cm^{-1}; τ 0.44 (1 H, t, *J* 1.5 Hz), 2.89 (1 H, d, *J* 8.5 Hz), 3.29 (1 H, dd, *J* 8.5 and 2.5 Hz), 3.43 (1 H, d, *J* 2.5 Hz), 6.26 (3 H, s), and 8.68 (3 H, s)].

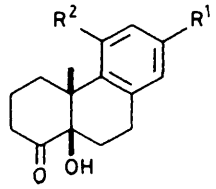
When $TiCl_4$ was used (19) and (20) were formed but the major product was formulated as the dihydrophenanthrene (21) (50%) [$\lambda_{max.}$ (EtOH) 278 nm (ε 29 800); τ 2.40 (2 H, dt), 2.90 (2 H, m), 3.20 (2 H, m), 6.20 (3 H, s), 7.20br (4 H, s), and 7.65 (3 H, s)]. It is not obvious why $TiCl_4$ should divert attack of the aryl ring from co-ordinated epoxide to co-ordinated carbonyl group.

Cyclisation of the acetylene (8) with BF_3·OEt_2 or $TiCl_4$ gave (22) (90%) [$\lambda_{max.}$ ($CHCl_3$) 3 480 and 1 715 cm^{-1}; τ 4.35 (1 H, s) and 9.05 (3 H, s)]. Degradation by borohydride reduction followed by periodate cleavage gave a keto-aldehyde whose properties supported structure (22).

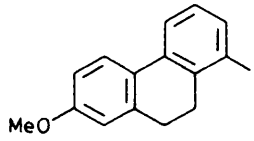
These experiments are in accord with prior results.[6] Where the alkene double bond is electronically unbiased then 6-*endo*-Trigonal-cyclisation formation is favoured over 5-*exo*-Trig. 6-*endo*-Digonal cyclisation is favoured only with a terminal alkyne.[7] Both *o*- and *p*-attack by the anisyl ring is not surprising but the equivalent rates of attack are and suggest an unselective and reactive cationic intermediate. From a preparative viewpoint only the alkyne cyclisations would appear to be useful.



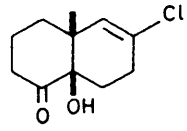
(17) (*trans*)
(18) (*cis*)



(19) R^1=H, R^2=OMe
(20) R^1=OMe, R^2=H



(21)



(22)

Experimental

M.p.s were determined on a Kofler block and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 257 instrument in $CHCl_3$ solution. N.m.r. spectra were recorded at 60 and 90 MHz on Perkin-Elmer R12B and R32 instruments using $CDCl_3$ as solvent. High-resolution mass spectra were measured on an AEI MS30 instrument on samples judged to be pure by t.l.c. The statement ' worked up in the usual way ' implies that the organic extract was washed with saturated brine, dried over Na_2SO_4 or $MgSO_4$, and the solvent evaporated under reduced pressure. G.l.c. was carried out on a Perkin-Elmer F11 using a 6 ft PEGA column.

Reaction of (5) *with* BF_3·OEt_2.—BF_3·OEt_2 (400 μl) was added to a stirred solution of (5) (120 mg) in CH_2Cl_2 (10 ml) at −20 °C under N_2. After 30 min water was added and the mixture extracted with CH_2Cl_2. Work-up in the usual way gave an oil (103 mg) which contained three major components by g.l.c. Chromatography on silica gel (12 g) and elution with light petroleum (b.p. 40—60 °C)–ether (7 : 3) gave the *dione* (11) (40 mg) (g.l.c. R_t 1.8 min/180 °C) (Found: C, 72.9; H, 8.9. $C_{11}H_{16}O_2$ requires C, 73.3; H, 8.8%) followed by the *ketol* (9) (30 mg) (g.l.c. R_t 4.25 min/180 °C (Found: C, 73.4; H, 9.0. $C_{11}H_{16}O_2$ requires C, 73.3; H, 8.8%). Reduction of (9) with sodium borohydride gave an oily mixture of *diols*, [τ 4.41 (2 H, m) and 6.22—6.60 (1 H, m)] (Found: M^+, 182.1311. $C_{11}H_{18}O_2$ requires *M*, 182.1307).

Reaction of (5) *with* $TiCl_4$.—$TiCl_4$ (250 μl) was added to a stirred solution of (5) (217 mg) in CH_2Cl_2 at −20 °C. Work-up as above gave an oil (196 mg) which was chromatographed on silica gel. Elution with light petroleum (b.p. 40—60 °C)–ether (1 : 1) first gave an oil (52 mg) (mainly starting material) followed by (9) (67 mg). Elution with ether gave the *diols* (13) (42 mg), m.p. 115—123 °C (ethyl acetate) (Found: C, 66.6; H, 9.1. $C_{11}H_{18}O_3$ requires C, 66.6; H, 9.2%).

Hydrolysis of the Dione (11).—The crude product (100 mg) from reaction of BF_3 and (5) was dissolved in EtOH (15 ml) and 2M-NaOH (15 ml) added. After being refluxed for 3 h the mixture was extracted with Et_2O and worked up in the

usual way to give (9). Acidification of the aqueous layer followed by Et_2O extraction and work-up in the usual way gave the acid (12) (35 mg) as an oil [*m/z* 198; τ 4.10 (1 H, m), 5.00 (2 H, m), and 8.80 (3 H, d, *J* 7 Hz)].

Reaction of (6) *with* BF_3·OEt_2.—BF_3·OEt_2 (0.5 ml) was added to a stirred solution of (6) (512 mg) in CH_2Cl_2 (35 ml) at −20 °C under a N_2 atmosphere. After 2 h no epoxide remained (t.l.c.) and the mixture was diluted with water, extracted with ether, and worked up in the usual way to give an oil (526 mg). G.l.c. showed five main peaks with R_t/150 °C 2.23, 4.35, 4.76, 6.35, and 8.87 min in a ratio 5 : 3 : 17 : 7 : 4. The crude product (512 mg) was dissolved in EtOH (20 ml) and 2M NaOH (20 ml) added. After 2 h reflux dilution with water, extraction with $CHCl_3$, and work-up in the usual way gave an oil (450 mg). G.l.c. showed that the second peak had disappeared. Chromatography on silica gel and elution with light petroleum (b.p. 40—60 °C)-Et_2O (1 : 1) gave the *ketol* (14) (202 mg) as an oil R_t (150 °C) 4.76 min (Found: C, 73.8; H, 9.2. $C_{12}H_{18}O_2$ requires C, 74.2; H, 9.3%) and the *isomer* (10) (105 mg) [R_t (150 °C) 6.35 min] (Found: C, 74.1; H, 9.4%).

Degradation of (14).—The ketol (14) (29 mg) in EtOH (1 ml) was reduced with $NaBH_4$ (40 mg). After addition of water the EtOH was evaporated off and the residue extracted with Et_2O and worked up in the usual way to give a mixture of oily *diols* (28 mg) (Found: M^+, 196.1464. $C_{12}H_{20}O_2$ requires *M*, 196.1463). The diols (19 mg) were dissolved in THF–water (3 : 1; 2 ml) and sodium periodate (54 mg) added. After being stirred overnight, the mixture was diluted with water and extracted with Et_2O; work-up in the usual way of the extract gave the *ketoaldehyde* (18 mg) (Found: M^+: 194.1308. $C_{12}H_{18}O_2$ requires *M*, 194.1307).

Reaction of (6) *with* BCl_3.—BCl_3 (>2 equiv.) was added to the epoxide (6) (160 mg) in CH_2Cl_2 (5 ml) at −78 °C. After 2 h dilution with water, extraction with Et_2O, and the usual work-up gave an oil which was chromatographed on silica gel. Elution with hexane–Et_2O (1 : 1) gave the *chloride* (15) (142 mg), m.p. 120—122 °C (light petroleum b.p. 60—80 °C) (Found: C, 62.7; H, 7.9; Cl, 15.0. $C_{12}H_{19}O_2Cl$ requires C, 62.5; H, 8.2; Cl, 15.4%).

Cyclisation of (2).—A mixture of CF_3CO_2H (8 ml) and $(CF_3CO)_2O$ (4 ml) was added to the ketone (2) (500 mg). After 12 h water was added and the mixture evaporated to dryness under reduced pressure. The residue was hydrolysed with $NaHCO_3$–MeOH. Addition of water, extraction with Et_2O, and the usual work-up procedure gave an oil (431 mg) which was separated by preparative t.l.c. on silica gel using hexane–Et_2O (1 : 1) into three fractions. In order of increasing polarity these were the *ketone* (16) (116 mg) (Found: M^+: 178.1358. $C_{12}H_{14}O$ requires *M*, 178.1358), the *cis*-isomer (18) (80 mg) (*m/z* 196), and the *trans*-isomer (17) (137 mg) (*m/z* 196).

Cyclisation of (7) *with* $SnCl_4$.—$SnCl_4$ (0.8 ml) was added to a solution of (7) (200 mg) in CH_2Cl_2 (10 ml) cooled to −20 °C under a N_2 atmosphere. After 2 h addition of water followed by extraction with Et_2O and work-up in the usual way gave a gum (205 mg). Chromatography on silica gel using light petroleum (b.p. 40—60 °C)-Et_2O (1 : 1) as eluant gave the *ketol* (20) (89 mg), m.p. 96—98 °C (Et_2O), $\nu_{max.}$ 3 480 and 1 710 cm^{-1} (Found: C, 74.1; H, 7.8. $C_{16}H_{20}O_3$ requires C, 73.8; H, 7.7%) and the *isomer* (19) (91 mg) m.p. 123—124 °C (Et_2O) $\nu_{max.}$ 3 480 and 1 710 cm^{-1} (Found: C, 73.8; H, 7.8%).

Similar results were obtained using BF_3·OEt_2.

Degradation of the Mixture of (19) *and* (20).—The mixture of ketols (19) and (20) (208 mg) obtained as above was reduced with $NaBH_4$ (202 mg) in EtOH (5 ml). The usual work-up gave a mixture of *diols* (202 mg) (Found: M^+, 262.1571. $C_{16}H_{22}O_3$ requires *M*, 262.1569). The diols (131 mg) in THF–water (3 : 1) (4 ml) were oxidized with sodium periodate (269 mg) to give an oil (125 mg). Chromatography on silica gel [light petroleum (b.p. 40—60 °C)-Et_2O] gave, first, the *ketoaldehyde* derived from (20) (46 mg) [$\nu_{max.}$ 1 725 and 1 710 cm^{-1}; $\lambda_{max.}$ 274 nm (ε 1 410); τ 0.49 (1 H, t, *J* 1.6 Hz), 2.93 (1 H, dd, *J* 8.5 and 7.5 Hz), 3.34 (2 H, m), and 8.54 (3 H, s) (Found: M^+, 260.1411. $C_{16}H_{20}O_3$ requires *M*, 260.1412)], then the ketoaldehyde [ex. (19)] (49 mg) [$\nu_{max.}$ 1 725 and 1 710 cm^{-1}; $\lambda_{max.}$ 279 nm (ε 1 440); τ 0.45 (1 H, t, *J* 1.5 Hz), 2.89 (1 H, d, *J* 8.5 Hz), 3.29 (1 H, dd, *J* 8.5 and 2.5 Hz), 3.43 (1 H, d, *J* 2.5 Hz), and 8.68 (3 H, s) (Found: M^+: 260.1414).

Cyclisation of (7) *with* $TiCl_4$.—The epoxide (7) (236 mg) was cyclised as above but using $TiCl_4$. A viscous gum (241 mg) was obtained which was chromatographed on silica gel [light petroleum (b.p. 40—60 °C)-Et_2O, 1 : 1] to give the *dihydrophenanthrene* (21) (120 mg), m.p. 70—71 °C (light petroleum b.p. 60—80 °C) (Found: M^+ 224.1196. $C_{16}H_{16}O$ requires *M*, 224.1201). Accurate combustion analyses (>1%) could not be obtained owing to facile oxidation of the compound. The ketols (19) and (20) were also isolated.

Cyclisation of (8).—BF_3·OEt_2 (0.8 ml) was added to a solution of (8) (175 mg) in CH_2Cl_2 (15 ml) at −20 °C under a N_2 atmosphere. After 3 h the reaction was worked up as before to give a brown oil (220 mg) which crystallised with time at ambient temperature. A sample was recrystallised from light petroleum (b.p. 40—60 °C), m.p. 84—85 °C (Found: C, 61.8; H, 7.1; Cl, 16.4. $C_{11}H_{15}ClO_2$ requires C, 61.5; H, 7.0; Cl, 16.5%).

Similar results were obtained on cyclisation with $TiCl_4$.

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References

1 H. O. House and R. L. Wasson, *J. Am. Chem. Soc.*, 1957, **79**, 1488.
2 L. Brewer and G. M. Rosenblatt, *Adv. High Temp. Chem.*, 1969, **2**.
3 J. L. Cooper and K. E. Harding, *Tetrahedron Lett.*, 1977, 3321.
4 L. M. Jackman and S. Sternhell, 'Applications of NMR Spectroscopy in Organic Chemistry,' Pergamon, Oxford and New York, 1969, 2nd edn., p. 243.
5 I. Fleming, A. Pearce, and R. L. Snowden, *J. Chem. Soc., Chem. Commun.*, 1976, 182.
6 For reviews see W. S. Johnson, *Bio-org. Chem.*, 1976, **5**, 51; E. E. van Tamelen, *Acc. Chem. Res.*, 1975, **8**, 152; J. K. Sutherland, *Chem. Soc. Rev.*, 1980, **9**, 265.
7 J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.

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