3-Methylcyclohex-2-enone Derivatives as Initiators of Cyclisation. Part 4.† Some Bicyclisations

Joseph A. Amupitan, Roy L. Beddoes, Owen S. Mills, and James K. Sutherland *
Chemistry Department, The University of Manchester, Manchester M13 9PL

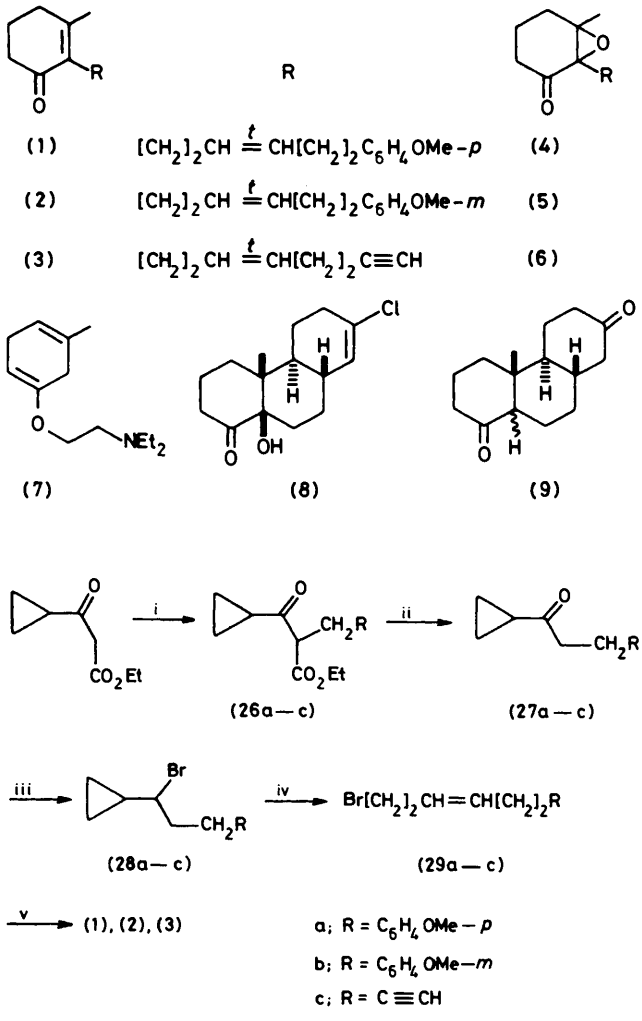
Hydrochrysene and hydrophenanthrene derivatives (8)—(14) have been prepared by cyclisation of 2-substituted 3-methylcyclohexen-2-ones and the derived 2,3-epoxides. Cyclisation of the epoxides does not give preparatively useful yields of bicyclised compounds, the major products being monocyclised compounds. Cyclisation of the α,β-unsaturated ketones with trifluoroacetic anhydride–trifluoroacetic acid gives high yields of bicyclised products. The stereochemistry of two cyclisation products has been determined by *X*-ray crystallography.

The results which we obtained in monocyclisations [1] prompted us to test these methods for the consecutive formation of two rings. The highest yields and minimal number of products were obtained previously when anisyl and ethynyl groups participate in cyclisation; thus we determined to use these groups for the termination of cyclisation and to synthesise the enones (1), (2), and (3). The bromides corresponding to the enone side-chains were prepared essentially by the Julia–Johnson procedures [2] and used to alkylate (7) by the procedure which we have developed (Scheme). The epoxides (4), (5), and (6) were prepared by the House–Wasson method.[3]

Cyclisation of the enyne (6) with BCl_3–CH_2Cl_2 at −78 °C gave a mixture from which the crystalline ketol (8) (35%) [$\nu_{max.}$ 3 585 and 1 710 cm^{-1}; τ 4.52 (1 H, m), and 9.01 (3 H, s)] was isolated. The related enone (3) cyclised with $(CF_3CO)_2O$–CF_3CO_2H to give, after hydrolysis, a 4 : 6 mixture of *cis*- and *trans*-isomers (9) (40%) [$\nu_{max.}$ 1 710 cm^{-1}; τ 9.28(s) and 8.94(s)] which we separated with difficulty. Equilibration (K_2CO_3–MeOH) produced a 1 : 1 mixture.

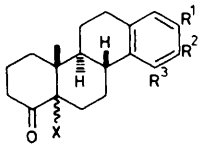
Reaction of the epoxides (4) and (5) with BCl_3–CH_2Cl_2 was disappointing. The tetracycle (10) [$\nu_{max.}$ 3 590 and 1 710 cm^{-1}; τ 3.04 (1 H, d, *J* 8.5 Hz), 3.80 (1 H, d, *J* 2.5 Hz), 3.34 (1 H, dd, *J* 8.5 and 2.5 Hz), and 8.92 (3 H, s)] was formed in only 4% yield from (4). The major product (51%) arose from formation of one ring and has been assigned structure (15) [$\nu_{max.}$ 3 600 cm^{-1}; τ 3.05 (4 H, m) and 9.08 (3 H, s)]. Three other products were isolated but not completely characterised; spectroscopic data are in accord with these being the chlorohydrin (16) (3%), the cyclopentanone (18) (18%), and the bicycle (20) (10%). A similar pattern resulted from cyclisation of (5); the major product (21) (57%) [$\nu_{max.}$ 3 560 and 1 710 cm^{-1}; τ 2.80 (1 H, m), 3.28 (3 H, m), 5.82 (1 H, m, $W_{\frac{1}{2}}$, 23 Hz), and 9.03 (3 H, s)] arose from monocyclisation and the tetracycle (11) [$\nu_{max.}$ 3 590 and 1 710 cm^{-1}; τ 2.82 (1 H, d, *J* 9 Hz), 3.29 (1 H, dd, *J* 9 and 3 Hz), 3.40 (1 H, d, *J* 3 Hz), and 8.93 (3 H, s)] was formed in only 9% yield. Other, not fully characterised, products were the ring-contracted ketone (19) (14%) and the chlorohydrin (17) (17%). The properties of (15) and the cyclisation product from the epoxide of 3-methyl-2-pent-3-enylcyclohex-2-enone [1] make it clear that they have similar structures and although these have not been rigorously established it is evident that either an elimination-addition or hydride migration has occurred in the initially formed cation (22). Precedent would favour the latter.[4] If it is accepted that the pathway followed by the cation (22; R = Me) is 'normal' then the cyclisation of (4) is also 'normal' and the *m*-anisyl group somehow facilitates nucleophilic attack by Cl^-.

Cyclisation of the enones (1) and (2) with $(CF_3CO)_2O$–CF_3CO_2H at 0 °C was much more effective; [1,5] (1) gave, after hydrolysis, the ketone (12) (81%) [$\nu_{max.}$ 1 710 cm^{-1}; τ 2.98 (1 H, d, *J* 8.4 Hz), 3.10 (1 H, d, *J* 2.4 Hz), 3.28 (1 H, dd, *J* 8.4 and 2.4 Hz), and 9.22 (3 H, s)] while (2) yielded (13) (56%) [$\nu_{max.}$ 1 710 cm^{-1}; τ 2.75 (1 H, d, *J* 8.4 Hz), 3.24 (1 H, dd, *J* 8.4 and 2.4 Hz), 3.34 (1 H, d, *J* 2.4 Hz), 9.22 (3 H, s)] and (14) (14%)

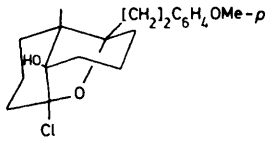


Scheme. *Reagents:* i, NaOEt–THF, RCH_2Cl, −40°; ii, KOH–EtOH, 25 °C; iii, $NaBH_4$–EtOH; collidine–LiBr–PBr_3–Et_2O, −40 °C; iv, $ZnBr_2$–Et_2O; v, Bu^nLi–THF–(7), −78 °C; HCl–Me_2CO

† Part 3, preceding paper.



(10) X = β–OH, R^2 = OMe, R^1 = R^3 = H
(11) X = β–OH, R^1 = OMe, R^2 = R^3 = H
(12) X = α–H, R^2 = OMe, R^1 = R^3 = H
(13) X = α–H, R^1 = OMe, R^2 = R^3 = H
(14) X = α–H, R^3 = OMe, R^1 = R^2 = H



(15)

[$\nu_{max.}$ 1 710 cm^{-1}; τ 2.82 (1 H, d, *J* 6.7 Hz), 3.2—3.5 (2 H, m), and 9.20 (3 H, s)].

In order to compare these initiators of cyclisation with those developed by Johnson,[1] the ketone (1) was treated with methyl-lithium to give the alcohol (23). Cyclisation with formic acid–pentane gave the crystalline hydrochrysene (24) (60%) [τ 3.05 (1 H, d, *J* 8 Hz), 3.16 (1 H, d, *J* 3 Hz), 3.38 (1 H, dd, *J* 8 and 3 Hz), 6.26 (3 H, s), 8.39 (3 H, s), and 8.99 (3 H, s)].

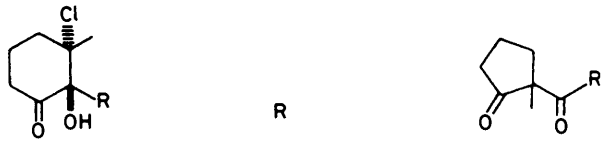
The structures postulated for the various bicyclisation products are consistent with the spectroscopic and analytical data quoted, but are not rigorously established; in particular, we wished to prove diaxial opening of the epoxide and the *trans* B-C ring junction. To put the structures beyond doubt one compound from each series was chosen for structure determination by *X*-ray diffraction.

Accordingly we have studied the structures of the ketol (8) and the ketone (13). In the case of (8), Figure 1 clearly shows the *cis*-fusion of the cyclohexanone ring and the *trans*-fusion of the cyclohexene. Use of the Crystal Structure Search and Retrieval system revealed no other similar ketone for structural comparison. The ketol (25), whose structure was recently reported,[6] is *trans*-fused. Examination of the geometry of (8) shows no feature, bond length, bond angle, or torsion angle, which might be regarded as unusual.

The structure of the ketone (13), shown in Figure 2, clearly shows the *trans*-fusion geometry, with no abnormal feature; (13) is akin to the structure (26) reported some years ago.[7]

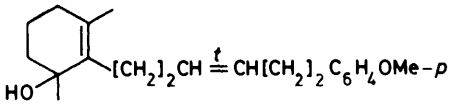
These structures establish that there is initial diaxial ring-opening in the epoxide cyclisations and that formation of the rings in both series occurs by antiperiplanar additions to the *E*-alkenes *via* chair-like transition states.

These results on bicyclisations show up a real difference between the cyclisations induced by epoxide ring-opening and those induced by the various types of allylic cations. In monocyclisations both initiators gave similar results in terms of amount of cyclisation,[4,8] but bicyclisation using Lewis acid-epoxide initiation, is a minor pathway—the bulk of the product arises from monocyclisation. Clearly different reagents and solvents are being used to form the different initiators but the epoxyketone functions may also play a part, as Johnson [9] has recently described substantial amounts of bi- and tri-cyclisation using allylic alcohols and Lewis acids in chlorinated hydrocarbon solvents. It is possible to devise mechanisms whereby Lewis acid complexed to epoxide or ketone can quench cyclisation at the monocyclised stage but we shall not discuss them further, since they are not particularly convincing.

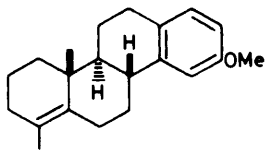


(16) $[CH_2]_2CH{=}CH[CH_2]_2C_6H_4OMe$-*p* (18)
(17) $[CH_2]_2CH{=}CH[CH_2]_2C_6H_4OMe$-*m* (19)

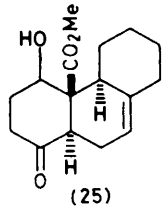
(20) R = $[CH_2]_2C_6H_4OMe$-*p* (22)
(21) R = $[CH_2]_2C_6H_4OMe$-*m*



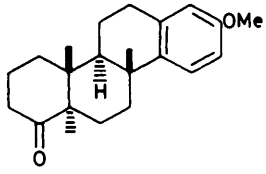
(23)



(24)



(25)



(26)

Experimental

For general comments see Part 1.[10]

Preparation of the Cyclopropyl Ketone (27a).—Freshly prepared dry NaOEt (ex. 1.32 g Na) was dissolved in dry tetrahydrofuran (40 ml) under N_2. After cooling to −40 °C a solution of cyclopropyl ethoxycarbonylmethyl ketone [2] (9 g) in tetrahydrofuran (150 ml) was added. Stirring was continued for 1 h with the addition of a further portion of tetrahydrofuran (60 ml). *p*-Methoxybenzyl chloride (9.024 g) in tetrahydrofuran (100 ml) was added with stirring during 0.5 h. The stirred solution was allowed to rise to ambient temperature overnight. Solvent was removed under reduced pressure and water added to the residue followed by 2M-HCl. Work-up in the usual way gave a mixture (14.58 g), which was dissolved in 95% EtOH and added to KOH (2.5 g) in 95% EtOH (30 ml). After stirring for 15 min the crystalline *dialkylated ester* (2.51 g) separated, m.p. 86—88 °C (MeOH) (Found: C, 72.9; H, 7.1. $C_{24}H_{28}O_5$ requires C, 72.7; H, 7.1%). After filtration the solution was stirred overnight and then the EtOH removed under reduced pressure. After acidification with 2M-HCl, work-up in the usual way gave a mixture of the ketoacid and ketone (9.92 g) which was heated on a steam-bath for 1 h to yield the ketone (27a) (7.86 g) (Found: M^+, 204.1150. $C_{13}H_{16}O_2$ requires *M*, 204.1157), τ 3.10 (4 H, m), 6.30 (3 H, s), 7.20 (4 H, s), 8.20 (1 H, m), and 9.15 (4 H, m); $\nu_{max.}$ 1 680 cm^{-1}.

Preparation of the Bromide (29a).—The ketone (27a) (3.3 g) in MeOH (15 ml) was cooled to 0 °C and $NaBH_4$ (1 g) added

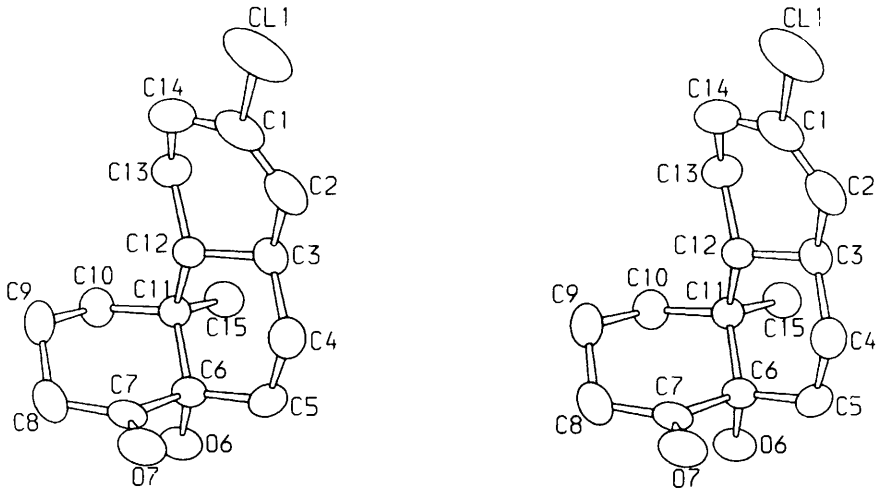


Figure 1. Stereoview of (8)

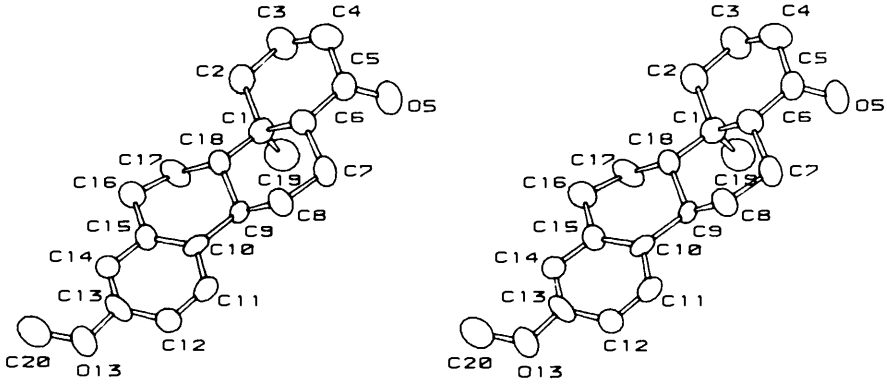


Figure 2. Stereoview of (13)

portionwise. After 1.5 h the MeOH was removed under reduced pressure and the residue dissolved in water. Work-up in the usual way gave the alcohol (2.98 g) which was dissolved in anhydrous Et_2O and collidine (1.45 g) and anhydrous LiBr (1.22 g) added. The stirred mixture was cooled to −40 °C and PBr_3 (1.6 g) added. After addition was complete the temperature was raised to 0 °C and kept there for 1.5 h. Collidine (2.5 ml) was added, followed by water. Extraction with pentane and work-up in the usual way gave the *bromide* (28a) (3.2 g) which was added to a stirred suspension of anhydrous $ZnBr_2$ (4.8 g) in Et_2O (15 ml) at −40 °C. The mixture was warmed to 0 °C and after 1.5 h pentane and brine were added. Work-up in the usual way gave a pale yellow oil which, on distillation 100 °C (bath) at 0.1 mmHg gave the *bromide* (29a) (2.8 g) (Found: M^+, 270.0463. $C_{13}H_{17}{}^{81}BrO$ requires M, 270.0463), τ 3.10 (4 H, m), 4.55 (2 H, m), 6.30 (3 H, s), 6.70 (2 H, t), and 7.50 (6 H, m), $\nu_{max.}$ 1 250 cm^{-1}.

Preparation of the Ketone (1).—Bu^{n}Li (9.3 ml of 1.5 M solution in hexane) was added to a solution of the enol ether [10] (7) (2.71 g) in tetrahydrofuran (20 ml) at −78 °C under N_2. After stirring for 1 h $(Me_2N)_3PO$ (2.49 g) in tetrahydrofuran (5 ml) was added and, after 5 min, the bromide (29a) (3.4 g). The mixture was allowed to warm to room temperature and worked up in the usual way to give the crude alkylation product which was immediately dissolved in Me_2CO (20 ml) and 2M HCl (15 ml) added under N_2. After 2 h work-up in the usual way yielded the *ketone* (1) (3.7 g) τ 3.05 (4 H, m), 4.58 (2 H, m), 6.25 (3 H, s), and 8.20 (3 H, s); $\nu_{max.}$ 1 670 cm^{-1}; M^+ 298.

Preparation of the Epoxide (4).—6M-NaOH (3.33 ml) was added during 5 min to the ketone (1) (3 g) in MeOH (25 ml) containing 30% H_2O_2 (3.4 ml). After 6 h and 8 h additional quantities of 30% H_2O_2 and 6M-NaOH were added and the reaction worked up in the usual way after 14 h to give the *epoxide* (4) (2.4 g), τ 3.10 (4 H, m), 4.60 (2 H, m), 6.34 (3 H, s), and 8.60 (3 H, s); $\nu_{max.}$ 1 700 and 1 245 cm^{-1}; M^+, 314.

Preparation of the Ketones (2) *and* (3) *and the Epoxides* (5) *and* (6).—These were synthesised by similar experimental methods. *m*-Methoxybenzylbromide ⟶ 16% dialkylation product + 72% (26b) ⟶ 74% (24b) (Found: C, 77.1; H, 8.0. $C_{13}H_{16}O_2$ requires C, 76.5; H, 7.8%), τ 2.90 (1 H, m), 3.33 (3 H, m), 6.35 (3 H, s), 7.30 (4 H, m), 8.20 (1 H, m), and 9.20 (4 H, m); ⟶ 56% (29b) (Found: C, 58.1; H, 6.2; Br, 29.5. $C_{13}H_{17}BrO$ requires C, 58.0; H, 6.3; Br, 29.7%), τ 2.85 (1 H, m), 3.25 (3 H, m), 4.52 (2 H, m), 6.25 (3 H, s), *and 6.18 (2 H,* t); ⟶ 86% (2) (Found: C, 80.1; H, 8.7%; M^+, 298.1930. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.7%; M, 298.1933), τ 3.10 (4 H, m), 4.55 (2 H, m), 6.25 (3 H, s), and 8.20 (3 H, s); $\nu_{max.}$ 1 660 cm^{-1}; ⟶ 75% (3), τ 3.15 (4 H, m), 4.55 (2 H, m), 6.20 (3 H, s), and 8.60 (3 H, s); $\nu_{max.}$ 1 700 cm^{-1}.

3-Bromopropyne ⟶ 3% dialkylation product, m.p. 80—

Table 1. Structural parameters and e.s.d.s for (8).

Atom	Crystal co-ordinates x/a	y/b	z/c
Cl(1)	0.618 4(1)	0.756 8(1)	−0.122 5(1)
O(6)	0.881 2(2)	0.704 6(2)	0.488 4(1)
O(7)	0.447 4(2)	0.452 7(2)	0.377 5(1)
C(1)	0.732 0(4)	0.768 7(3)	0.000 7(2)
C(2)	0.691 4(3)	0.853 7(3)	0.079 6(2)
C(3)	0.775 9(3)	0.858 6(3)	0.188 3(1)
C(4)	0.617 2(3)	0.832 2(3)	0.267 7(2)
C(5)	0.696 3(3)	0.826 7(3)	0.377 2(2)
C(6)	0.787 6(3)	0.687 2(2)	0.386 6(1)
C(7)	0.624 7(3)	0.485 5(3)	0.376 7(1)
C(8)	0.695 4(3)	0.333 6(3)	0.373 8(2)
C(9)	0.862 9(3)	0.366 7(3)	0.299 0(2)
C(10)	1.026 9(3)	0.561 7(3)	0.316 8(2)
C(11)	0.953 7(2)	0.716 6(2)	0.307 6(1)
C(12)	0.857 4(3)	0.710 7(2)	0.198 1(1)
C(13)	0.992 1(4)	0.721 3(3)	0.107 8(2)
C(14)	0.869 8(4)	0.675 4(4)	0.005 0(2)
C(15)	1.135 6(3)	0.902 4(3)	0.333 2(2)
H(2)	0.601 1(34)	0.912 2(31)	0.068 8(17)
H(3)	0.891 2(34)	0.983 7(32)	0.203 1(17)
H(41)	0.498 0(35)	0.713 2(32)	0.247 7(17)
H(42)	0.569 8(33)	0.931 8(31)	0.262 4(17)
H(51)	0.585 5(34)	0.801 8(31)	0.424 3(17)
H(52)	0.800 7(35)	0.950 0(33)	0.400 6(17)
H(6)	0.789 8(35)	0.687 1(31)	0.524 8(18)
H(81)	0.580 4(35)	0.213 3(33)	0.358 2(17)
H(82)	0.751 5(34)	0.329 5(31)	0.442 8(18)
H(91)	0.807 3(34)	0.343 1(30)	0.226 0(18)
H(92)	0.918 7(34)	0.274 1(33)	0.307 4(17)
H(101)	1.135 7(34)	0.579 3(30)	0.269 6(17)
H(102)	1.090 8(34)	0.572 6(30)	0.387 7(18)
H(12)	0.738 6(34)	0.588 5(32)	0.189 7(17)
H(131)	1.056 4(34)	0.634 8(32)	0.117 2(17)
H(132)	1.098 3(34)	0.851 6(33)	0.106 3(17)
H(141)	0.791 6(34)	0.540 8(33)	0.005 7(17)
H(142)	0.953 6(34)	0.712 5(30)	0.054 1(18)
H(151)	1.102 0(33)	1.012 5(33)	0.335 5(17)
H(152)	1.237 3(34)	0.920 0(30)	0.283 6(18)
H(153)	1.197 5(34)	0.899 8(30)	0.401 3(18)

Table 2. Structural parameters and e.s.d.s for (13).

Atom	Crystal co-ordinates x/a	y/b	z/c
C(1)	0.478 8(15)	1.171 5(9)	0.835 3(6)
C(2)	0.305 5(16)	1.250 9(10)	0.827 6(6)
C(3)	0.375 1(20)	1.358 8(10)	0.816 6(7)
C(4)	0.552 5(19)	1.389 5(9)	0.877 4(7)
C(5)	0.718 1(17)	1.310 9(9)	0.895 5(6)
C(6)	0.644 4(16)	1.204 4(8)	0.903 2(6)
C(7)	0.824 6(17)	1.128 8(9)	0.924 6(6)
C(8)	0.736 1(16)	1.026 1(8)	0.941 5(6)
C(9)	0.576 3(14)	0.988 2(8)	0.877 1(5)
C(10)	0.492 4(14)	0.881 9(8)	0.888 5(5)
C(11)	0.628 3(14)	0.803 7(9)	0.922 9(5)
C(12)	0.562 9(16)	0.707 9(9)	0.936 9(6)
C(13)	0.354 5(18)	0.686 9(9)	0.915 3(6)
C(14)	0.217 7(16)	0.759 9(9)	0.881 0(6)
C(15)	0.288 2(15)	0.854 6(8)	0.866 6(5)
C(16)	0.133 3(16)	0.930 2(9)	0.827 0(6)
C(17)	0.228 9(18)	1.020 5(9)	0.797 1(6)
C(18)	0.400 1(15)	1.066 8(8)	0.855 9(5)
C(19)	0.563 0(20)	1.168 0(10)	0.767 9(6)
C(20)	0.101 1(23)	0.564 1(10)	0.914 3(8)
O(5)	0.898 1(14)	1.330 4(7)	0.899 6(6)
O(13)	0.304 4(13)	0.590 9(6)	0.930 5(5)
H(191)	0.6693	1.1144	0.7691
H(201)	0.0227	0.5845	0.8569
H(21)	0.2475	1.2490	0.8748
H(22)	0.1868	1.2307	0.7832
H(31)	0.2521	1.4089	0.8149
H(32)	0.4200	1.3628	0.7669
H(41)	0.6174	1.4567	0.8623
H(42)	0.4975	1.4045	0.9239
H(6)	0.5711	1.2056	0.9467
H(71)	0.8979	1.1203	0.8818
H(72)	0.9295	1.1551	0.9710
H(81)	0.8549	0.9728	0.9546
H(82)	0.6680	1.0345	0.9861
H(9)	0.6466	0.9828	0.8329
H(11)	0.7853	0.8201	0.9385
H(12)	0.6670	0.6527	0.9630
H(14)	0.0605	0.7435	0.8660
H(161)	0.0466	0.9570	0.8629
H(162)	0.0339	0.8932	0.7837
H(171)	0.1162	1.0756	0.7786
H(172)	0.2903	0.9965	0.7535
H(18)	0.3402	1.0780	0.9020
H(192)	0.4424	1.1548	0.7228
H(193)	0.6292	1.2385	0.7613
H(202)	0.0876	0.4855	0.9202
H(203)	0.0248	9.6011	0.9492

81 °C (MeOH) (Found: C, 72.8; H, 6.9. $C_{14}H_{16}O_3$ requires C, 72.4; H, 6.9%) + 78% (26c) ⟶ 53% (27c) (Found: C, 78.3; H, 8.1. $C_8H_{10}O$ requires C, 78.7; H, 8.2%); ⟶ 51% (29c), τ 4.40 (2 H, m), 6.65 (2 H, t), and 7.95 (1 H, m); ⟶ 75% (3) (Found: C, 83.7; H, 9.6. $C_{15}H_{20}O$ requires C, 83.3; H, 9.3%), τ 4.35 (2 H, m) and 8.15br (4 H, s), $\nu_{max.}$ 1 660 cm^{-1}; ⟶ 65% (6), τ 4.55 (2 H, m) and 8.60 (3 H, s).

Cyclisation of the Epoxide (4) *with* BCl_3.—The epoxide (4) (320 mg) in CH_2Cl_2 (2 ml) was added during 5 min to a solution of BCl_3 (*ca.* 5 equiv.) in CH_2Cl_2 (15 ml) cooled to −78 °C. After 2 h saturated aqueous $NaHCO_3$ (5 ml) was added and the cooling bath removed. Work-up in the usual way gave an oil (342 mg) which was chromatographed on silica gel. Elution with Et_2O–hexane (1 : 2) gave five fractions; the first was an oil (46 mg), $\nu_{max.}$ 1 745 and 1 710 cm^{-1}, believed to be (*18*). *Fraction 2 was an oil* (13 mg), τ 4.52 (2 H, m) and 8.5 (3 H, s), believed to be (16). Fraction (3) (128 mg) was the *tricyclic chloride* (15), m.p. 126—127 °C; light petroleum (b.p. 60—80 °C) (Found: C, 68.9; H, 7.9. $C_{20}H_{27}ClO_3$ requires C, 68.5; H, 7.7%). Fraction 4 gave the *bicyclic chloride* (16) (30 mg), m.p. 140—143 °C (Found: M^+, 350.1648. $C_{20}H_{27}ClO_3$ requires M, 350.1649), τ 3.04 (4 H, m), 5.30 (1 H, $W_{\frac{1}{2}}$ 22 Hz), 6.23 (3 H, s), and 9.26 (3 H, s); $\nu_{max.}$ 3 590 and 1 710 cm^{-1}. Fraction 5 gave the *tetracycle* (10) (11 mg), m.p. 143—145 °C (CCl_4) (Found: M^+, 314.1885. $C_{20}H_{26}O_3$ requires M, 314.1882).

Cyclisation of the Epoxide (5) *with* BCl_3.—The epoxide (5) (200 mg) in CH_2Cl_2 (2.5 ml) was added to CH_2Cl_2 (10 ml) containing BCl_3 (*ca.* 5 equiv.) cooled to −78 °C. After 1 h saturated aqueous $NaHCO_3$ (5 ml) was added and the mixture allowed to warm to room temperature. Work-up in the usual way gave an oil (210 mg) which on preparative t.l.c. with Et_2O–light petroleum (b.p. 40—60 °C, 1 : 1) gave four fractions. Fraction R_F 0.75 was an oil believed to be the cyclopentanone (19) (30 mg), $\nu_{max.}$ 1 745 and 1 710 cm^{-1}. A fraction R_F 0.54 had properties consistent with those expected for the chlorohydrin (17) (42 mg). The *chloride* (21) (120 mg), m.p. 152—153 °C (Found: M^+, 350.1647. $C_{20}H_{27}ClO_3$ requires M, 350.1649) had R_F 0.40. The fraction R_F 0.25 gave the *tetracycle*

(11) (20 mg), m.p. 180—182 °C (Found M^+, 314.1883. $C_{20}H_{26}O_3$ requires M, 314.1882).

Cyclisation of the Epoxide (6).—The epoxide (6) (200 mg) in CH_2Cl_2 (6 ml) was added to BCl_3 (0.4 ml) in CH_2Cl_2 (15 ml) cooled to −78 °C. After 1.5 h work-up as before gave a dark brown oil (204 mg) which was chromatographed on silica gel with Et_2O–hexane (1 : 1) as eluant. An oily first fraction (42 mg) was followed by the *tricycle* (8) (88 mg), m.p. 185 °C (Found: C, 67.5; H, 8.1%; M^+, 268.1230. $C_{15}H_{21}ClO_2$ requires C, 67.2; H, 7.8%; M^+, 268.1229).

Cyclisation of the Enone (1) *with* CF_3CO_2H–$(CF_3CO)_2O$.—The ketone (1) (500 mg) was dissolved in CF_3CO_2H (10 ml) and $(CF_3CO)_2O$ (5 ml) cooled to 0 °C. After 8 h water (10 ml) was added and the solvents removed under reduced pressure. The residue was dissolved in 10% KOH–MeOH (5 ml). After 1 h work-up in the usual way gave a product (445 mg) which was chromatographed on Grade 1 alumina. Elution with Et_2O–CH_2Cl_2 (2 : 1) gave the *tetracyclic ketone* (12) (405 mg), m.p. 141—143 °C (Et_2O) (Found: C, 80.9; H, 8.9% M^+, 298.1937. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.7%; M^+, 298.1933).

Cyclisation of Enone (2).—The ketone (2) (500 mg) was cyclised and the reaction worked up as in the previous experiment. Crystallisation of the product (470 mg) from Et_2O gave the *isomer* (13) (285 mg), m.p. 155—157 °C (Found: C, 79.8; H, 8.8. $C_{20}H_{26}O_2$ requires C, 80.5; H, 8.7%). Preparative t.l.c. using the mother liquors gave *isomer* (14) (68 mg), m.p. 98—100 °C (Found M^+ 298.1929. $C_{20}H_{26}O_2$ requires M, 298.1933).

Cyclisation of Enone (3).—The ketone (3) (500 mg) was cyclised and the reaction worked up as in the previous experiments. Preparative t.l.c. [Four elutions with hexane–Et_2O (2 : 1) on silica] gave the trans-*isomer* (9) (119 mg), m.p. 68—69 °C (Found: M^+, 234.1617. $C_{15}H_{22}O_2$ requires M, 234.1620) and the cis-*isomer* (9) (88 mg), m.p. 52—55 °C. Treatment of the latter with K_2CO_3–MeOH gave a 1 : 1 mixture of the two isomers.

Cyclisation of the Alcohol (23).—Methyl-lithium (5 ml of a 1.5M ethereal solution) was added to the ketone (1) (300 mg) in Et_2O (15 ml) at −78 °C. After 1 h the mixture was worked up in the usual way to give the *alcohol* (23) [τ 3.05 (4 H, m), 4.52 (2 H, m), 6.23 (3 H, s), 8.35 (3 H, s), and 8.72 (3 H, s); M^+ 314) which was dissolved in pentane (15 ml) and anhydrous formic acid (10 ml; freshly distilled from phthalic anhydride) added. After 1 h work-up in the usual way gave an oil (270 mg) which on crystallisation from MeOH gave the *tetracycle* (24), m.p. 74—75 °C (Found: C, 84.4; H, 9.7%; M^+, 296.2142. $C_{21}H_{28}O$ requires C, 85.1; H, 9.5%; M, 296.2140).

Crystal Data.—$C_{20}H_{26}O_2$ (13), M = 298.2, Monoclinic, a = 6.708(1), b = 13.210(5), c = 18.943(5) A, β = 103.14(2)°, U = 1 634.6 A^3, Z = 4, D_c = 1.21 g cm^{-3}, μ(Mo-K_α) = 0.9 cm^{-1}, space group $P2_1/c$ (No. 14).

Data were collected with a CAD-4 computer-controller Kappa axis diffractometer from a crystal of dimensions 0.26 × 0.1 × 0.12 mm which was cut from a larger mass. Measurements were made between θ limits of 1 and 25°. The measurement technique used was the θ—2θ scan and the count time for any reflexion was limited to a maximum of 300 s. The crystal orientation was checked every 100 reflexions and standards measured approximately every 30 min. In this way some 3019 reflexions were measured.

The structure was solved through application of MULTAN 76; the set which exhibited the highest combined figure of merit gave all the non-hydrogen atoms except C(20) which was subsequently found from a difference map. No information additional to the atomic composition of the unit cell was supplied. Refinement proceeded through isotropic and anisotropic models. The crystals diffracted rather weakly and the final R-value was 0.079 for 791 reflexions with $F_o > 3\sigma(F)$ and a model incorporating anisotropic vibrations for the non-hydrogen atoms. A parabolic weighting scheme $\omega^{-1} = 4.84 - 0.0556\ F_o + 0.00043\ F_o^2$ was used in the final refinement cycles. Atomic co-ordinates are given in Table 2; values of temperature factors and a list of F_o and F_c have been submitted for deposition.

The determination has established the configuration (with its enantiomer) shown in Figure 2.

Crystal data. $C_{15}H_{21}ClO_2$ (8), M = 268.6, Triclinic, a = 7.312(1), b = 7.935(1), c = 12.905(3) Å, α = 92.01(2), β = 91.60(2), γ = 114.54(1) °, U = 680.0 A^3, Z = 2, D_c = 1.31 g cm^{-3}, μ(M-K_α) = 2.9 cm^{-1}, space group $P\bar{1}$ (No. 2).

The method of data collection was similar to that described for compound (13) save that the crystal dimension was 0.32 × 0.08 × 0.5 mm. 2 265 Reflexions were measured of which 1 815 had $F > 3\sigma(F)$ and the structure solved through application of MULTAN 76. The structure found corresponded to the set with the smallest psi zero figure of merit. Isotropic and anisotropic refinement converged after 20 least-squares cycles. During the final cycles hydrogen atom positions found from difference Fourier syntheses were also refined and a parabolic weighting scheme used, given by $\omega^{-1} = 0.316 - 0.0113F + 0.00062F^2$. The final R value was 0.0355.

Atomic co-ordinates are given in Table 1; bond lengths, values of temperature factor coefficients, and a list of $F_{obs.}$ and $F_{calc.}$ are available as a Supplementary publication (Sup No. 23530 (35 pp.).*

The structure determination firmly establishes the configuration shown in Figure 1.†

Acknowledgement

We thank the University of Ahmadu Bello, Zaria, Nigeria, for leave of absence to J. A. and the S.E.R.C. for financial support.

References

1 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.
2 K. A. Parker and W. S. Johnson, *J. Am. Chem. Soc.*, 1974, **96**, 2556.
3 H. O. House and R. L. Wasson, *J. Am. Chem. Soc.*, 1957, **79**, 1488.
4 J. A. Amupitan, E. Huq, M. Mellor, E. G. Scovell, and J. K. Sutherland, *J. Chem. Soc., Perkin Trans. 1*, 1983, 751.
5 J. L. Cooper and K. E. Harding, *Tetrahedron Lett.*, 1977, 3321.
6 A. Mugnoli, A. Moretto, F. Orsini, and F. Pelizzoni, *Acta Crystallogr.*, 1981, **C84**, 37.
7 R. E. Ireland, M. I. Dawson, C. J. Kowalski, C. A. Lipinski, D. R. Marshall, J. W. Tilley, J. Bordner, and B. L. Trus, *J. Org. Chem.*, 1975, **40**, 973.
8 J. A. Amupitan, E. G. Scovell, and J. K. Sutherland, *J. Chem. Soc., Perkin Trans. 1*, 1983, preceding paper.
9 W. S. Johnson, C. E. Ward, S. G. Boots, M. B. Gravestock, R. L. Markezich, B. E. McCarry, D. A. Okorie, and R. J. Parry, *J. Am. Chem. Soc.*, 1981, **103**, 88.
10 J. A. Amupitan, E. Huq, M. Mellor, E. G. Scovell, and J. K. Sutherland, *J. Chem. Soc., Perkin Trans. 1*, 1983, 747.

* For details of the Supplementary publications scheme see Notice to Authors No. 7, *J. Chem. Soc., Perkin Trans. 1*, 1982, Index issue.
† The compound (8) was racemic. The molecule drawn is the enantiomer to that shown in the Scheme.

Received 27th July 1982; *Paper* 2/1296