The cyclisation of humulene 6,7- and 9,10-epoxides catalysed by tetracyanoethylene

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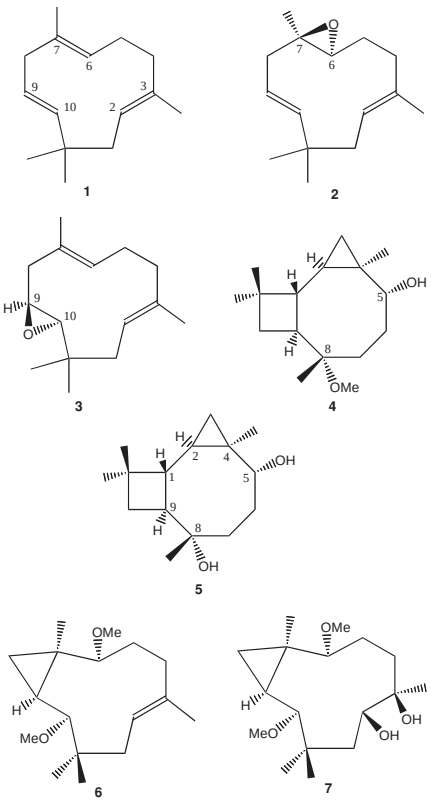
The cyclisation of humulene 6,7- and 9,10-epoxides catalysed by methanolic tetracyanoethylene has been examined and the structure of a cyclisation product established by X-ray crystallography.

Keywords: epoxides, humulene, terpenoids, tetracyanoethylene, crystal structures

Cyclisations of the 11-membered ring of the sesquiterpenoid triene humulene (**1**) play a central role in the biosynthesis of many polycyclic sesquiterpenoids.[1] The majority of these cyclisations and subsequent skeletal rearrangements are of a carbocationic character. The conformations of the flexible ring system[2] and the cyclisations of humulene and its epoxides in the presence of mineral and Lewis acids have been studied in this context.[3-9] Tetracyanoethylene (TCNE) has been examined[10,11] as a mild π-acid catalyst in the cyclisation of caryophyllene oxide to the clovanes. In this paper we report the cyclisation of humulene 6,7- and 9,10-epoxides catalysed by TCNE in methanol.

Humulene (**1**) was obtained from oil of hops[12,13] via its silver nitrate adduct. Reaction of humulene with one molar equivalent of *m*-chloroperbenzoic acid gave, as the major component, humulene 6,7-epoxide (**2**), and, as the minor component, the 9,10-epoxide (**3**). In prior work the 2,3-epoxide had also been reported as a minor component.[14] A small amount of the 2,3:6,7-diepoxide was also isolated.

The TCNE catalysed cyclisation of humulene 6,7-epoxide (**2**) gave a complex mixture of products from which one major component was obtained by careful chromatography. The ^{13}C NMR spectrum of the product **4**, $C_{16}H_{28}O_2$ (see Table 1)



1 **2** **3** **4** **5** **6** **7**

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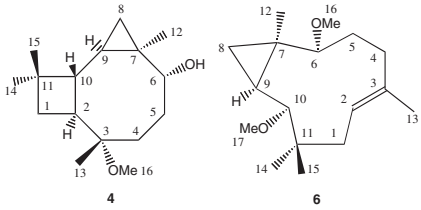
Table 1 ^{13}C NMR data for cyclisation products

Carbon atom*	Compound **4**	**6**	**7**
1	35.0	40.5	43.4
2	48.8	124.5	70.4
3	77.4	132.7	74.7
4	34.8	38.5	33.7
5	30.2	28.2	25.3
6	74.4	92.1	89.7
7	19.8	24.5	22.7
8	18.1	19.0	19.5
9	17.2	19.7	20.0
10	48.1	85.4	87.7
11	34.5	41.6	40.8
12	15.8	14.5	16.8
13	30.3	30.0	31.2
14	22.1	16.2	17.0
15	23.9	29.6	27.7
16	54.9	56.4	55.5
17		60.6	58.3

*Compounds **4**, **6** and **7** are numbered following the system used for humulene. Atom shifts may therefore be compared across the Table. In the text they are numbered systematically, following the Baeyer rules. The numbering used *in Table* 1 is shown in the two structures below.



4 **6**

did not contain any alkene resonances and hence the product was tricyclic. The ^{1}H NMR spectrum bore marked similarities to the known[7] acid-catalysed cyclisation product **5**, which was prepared for comparison purposes. Signals at δ_H 0.17 (1H, t, *J* 4.5 Hz, 3β-H), 0.44 (1H,dd, *J* 4.5 and 7.9 Hz,3α-H) and 0.64 (1H, ddd, *J* 4.5, 7.9 and 10.9 Hz, 2α-H) were assigned to the protons of a cyclopropane ring. There was a three-proton singlet at δ_H 3.13 assigned to a methyl ether and a C**H**(OH) resonance at δ_H 3.22 (1H, dd, *J* 5.5 and 11.2 Hz; δ_C 74.4). Examination of the ^{1}H:^{1}H 2D COSY spectrum led to the identification of the fragments [HOC(5)H–C(6)H_2–C(7)H_2] and [C(10)H_2–C(9)H–C(1)H–C(2)H–C(3)H_2] and hence the structure **4** was assigned to this compound. The stereochemistry followed from nOe enhancements which are summarised in Fig. 1. This cyclisation product is the methyl ether of a minor acid-catalysed cyclisation product (tricyclohumuladiol).[7] Under acidic conditions tricyclohumuladiol under goes further rearrangement.[7]

The major product **6**, $C_{17}H_{30}O_2$, from the TCNE catalysed cyclisation of humulene 9,10-epoxide **3**, retained an alkene [δ_H 5.23 (1H, dt, *J* 16.1, 1.6 Hz)] and possessed the high-field ^{1}H NMR signals characteristic of a cyclopropane ring [δ_H 0.57

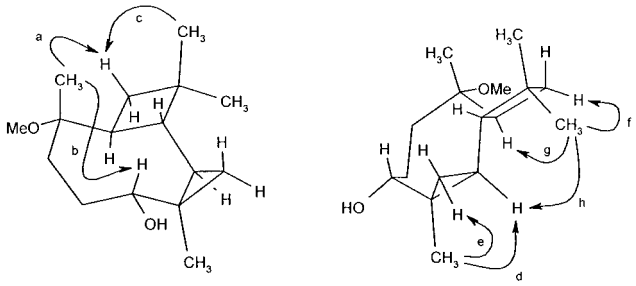


Fig. 1 nOe enhancements observed in compound **4**. a = 5.6; b = 7.4; c = 3.0; d = 4.7; e = 3.2; f = 2.7; g = 5.2; h = 6.6 %.

(1H, dd, *J* 4.7, 6.2 Hz), 0.79 (1H, dd, *J* 4.7 and 9.9 Hz) and 0.91 (1H, td, *J* 6.2 and 9.9 Hz)]. There were two methoxyl signals (δ_H 3.33 and 3.34). The structure of the product was established by osmylation of the alkene to give a crystalline diol which was suitable for X-ray crystallography (see Fig. 2). This established the structure of the diol to be 2α,9α-dimethoxy-1,5,8,8-tetramethylbicyclo[8.1.0]undecane-5β,6β-diol (**7**). The cyclisation product was therefore **6**. The second methoxyl group has probably been inserted as a result of displacement of the hydroxyl group adjacent to the cyclopropyl ring. The cyclopropane ring could provide stabilisation for the incipient carbocation. The methyl ether would then be formed by quenching the carbocation with methanol.

In conclusion, the major products which were obtained from the reaction of humulene 6,7- and 9,10-epoxides were those of cyclisation. These milder conditions did not lead to the skeletal rearrangements that occurred under the more vigorous mineral acid conditions.

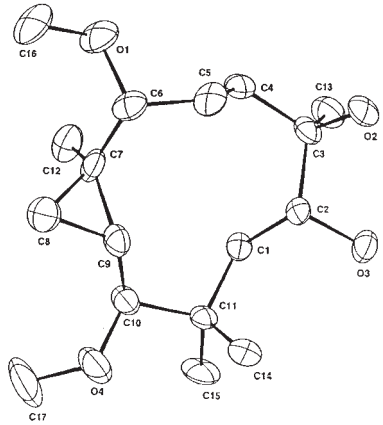


Fig. 2 X-Ray crystal structure of compound **7** (hydrogen atoms omitted).

Experimental

Silica for chromatography was Merck 9385. Light petroleum refers to the fraction b.p. 60–80 °C. ^{1}H and ^{13}C NMR spectra were determined at 300 and 75 MHz respectively for solutions in deuteriochloroform. IR spectra were determined as nujol mulls. Mass spectra were determined on a Fisons Autospec mass spectrometer. Extracts were dried over sodium sulfate. Humulene was obtained from oil of hops by crystallisation of the silver nitrate adduct and steam distillation.[12,13]

Epoxidation of humulene (**1**): A solution of humulene (2.0 g) in dichloromethane (125 cm^3) was cooled to 0 °C and treated with *m*-chloroperbenzoic acid (1.7 g) in portions. The mixture was left at room temperature for 48 h. The solution was washed with aqueous sodium sulfite, water and brine and dried. The solvent was evaporated and the residue was chromatographed on silica. Elution with 2.5% ethyl acetate : light petroleum gave 9,10-epoxy-3,7,11,11-tetramethylcycloundec-2,6-diene (humulene 9,10-epoxide, **3**) (73 mg) as an oil (lit.,[14] oil); IR: ν_{max}/cm^{-1} 1667; NMR: δ_H 0.74 (3H, s), 1.07 (3H, s), 1.54 (3H, s), 1.64 (3H, s), 2.72 (1H, dd, *J* = 4.2 and 12.7 Hz), 2.93 (1H, dt, *J* = 3.3 and 9.5 Hz), 4.92 (1H, d, *J* = 10.8 Hz), 4.99 (1H, t, *J* = 7.0 Hz). Further elution with 5% ethyl acetate:light petroleum gave 6,7-epoxy-3,7,11,11-tetramethylcycloundeca-2,9-diene (**2**) (1.62 g) as an oil (lit.,[14] oil), IR: ν_{max}/cm^{-1} 1667; NMR: δ_H 1.01 (3H, s), 1.04 (3H, s), 1.23 (3H, s), 1.49 (3H, s), 2.46 (1H, dd, *J* = 2.6 and 9.6 Hz), 2.52 (2H, d, *J* = 5.0 Hz), 4.92 (1H, br.t, *J* = 7.3 Hz), 5.08 (1H, d, *J* = 16.0 Hz), 5.21 (1H, dt, *J* = 16.0 and 7.7 Hz). Further elution with 10% ethyl acetate:light petroleum gave 2,3:6,7-diepoxy-3,7,11,11-tetramethylcycloundec-9-ene (270 mg) which crystallised from light petroleum as needles, m.p. 101–104 °C (lit.[14] 102–104 °C); IR: ν_{max}/cm^{-1} 1642; NMR: δ_H 1.06 (3H, s), 1.17 (3H, s), 1.28 (6H, s), 2.46 (2H, d, *J* = 9.5 Hz), 2.62 (1H, dd, *J* = 4.9 and 12.2 Hz), 2.72 (1H, m), 5.29 (1H, d, *J* = 16.0 Hz), 5.47 (1H, dt, *J* = 16.0 and 7.6 Hz).

Reaction of humulene-6,7-epoxide (**2**) *with TCNE*: A solution of humulene 6,7-epoxide (1.0 g) in methanol (10 cm^3) was treated with TCNE (58 mg) for 24 h. The solvent was evaporated and the residue was chromatographed on silica. Elution with 20% ethyl acetate: light petroleum gave 8α-methoxy-4,8,11,11-tetramethyltricyclo-[7.2.0.0^{2,4}]undecan-5α-ol (**4**) (144 mg) as an oil. IR: ν_{max}/cm^{-1} 3386; NMR: δ_H (500 MHz) 0.17 (1H, t, *J* = 4.8 Hz, 3β-H), 0.44 (1H, dd, *J* = 4.8 and 7.9 Hz, 3α-H), 0.64 (1H, ddd, *J* = 5.2, 7.9 and 10.9 Hz, 2α-H), 0.97 (3H, s), 0.99 (3H, s), 1.04 (3H, s), 1.09 (3H, s), 1.38 (1H, t, *J* = 10.5 Hz, 10β-H), 1.51 (1H, ddd, *J* = 0.4, 7.8 and 10.5 Hz, 10α-H), 2.09 (1H, ddd, *J* = 7.8, 10.8, 10.9 Hz, 9α-H), 3.13 (3H, s, OMe), 3.22 (1H, dd, *J* = 5.1 and 11.2 Hz, 5β-H). (Found: M$^+$ 252.2080; $C_{16}H_{28}O_2$ requires 252.2089)

Reaction of humulene-9,10-epoxide (**3**) *with TCNE*: A solution of humulene 9,10-epoxide (250 mg) in methanol (10 cm^3) was treated with TCNE (12 mg) for 24 h. The solvent was evaporated and the residue was chromatographed on silica. Elution with 15% ethyl acetate:light petroleum gave 2,9-dimethoxy-1,5,8,8-tetramethyl-bicyclo[8.1.0]undec-5-ene (**6**) (96 mg) as an oil. NMR: δ_H (500 MHz) 0.57 (1H, dd, *J* = 4.7 and 6.2 Hz, 8-H), 0.79 (1H, dd, *J* = 4.7 and 9.9 Hz, 8-H), 0.64 (1H,dd, *J* = 6.2 and 9.9 Hz, 9-H), 0.96 (3H, s), 1.06 (6H, s), 1.64 (3H, s), 2.24 (1H, dd, *J* = 2.4 and 10.3 Hz, 6-H), 2.52 (1H, d, *J* = 6.3 Hz, 10-H), 3.33 (3H, s, OMe), 3.34 (3H, s, OMe). (Found: M$^+$ 266.2257; $C_{17}H_{30}O_2$ requires 266.2248)

CAUTION: The vapour of osmium tetraoxide is hazardous and this reaction must be carried out in an efficient fume cupboard.

Osmylation reaction: A stock solution of osmium tetraoxide (1 g) in *t*-butanol (80 cm^3) containing *t*-butyl hydroperoxide (2 cm^3) was prepared. A solution of 2,9-dimethoxy-1,5,8,8-tetramethylbicyclo [8.1.0]undec-5-ene (**6**) (75 mg) in *t*-butanol (10 cm^3) and water (10 cm^3) was treated with potassium hexacyanoferrate(III) (600 mg), potassium carbonate (375 mg) and 1,4-diazabicyclo[2.2.2]octane (55 mg) followed by the above osmium tetraoxide solution (1 cm^3) for 24 h. Sodium sulfite (75 mg) was then added and the mixture was left overnight. The reaction mixture was filtered and the residue extracted with ethyl acetate. The extract was dried and the solvent evaporated. The residue crystallised from petrol to give 2α,9α-dimethoxy-1,5,8, 8-tetramethylbicyclo[8.1.0]undecane-5β,6β-diol (**7**) (30 mg), m.p. 118–120 °C. IR: ν_{max}/cm^{-1} 3525, 3402; NMR: δ_H 1.07 (3H, s), 1.17 (6H, s), 1.26 (3H, s), 2.50 (1H, d, *J* = 9.5 Hz 10β-H), 2.67 (1H, br s, 6β-H), 3.36 (3H, s, OMe), 3.43 (3H, s, OMe), 3.94 (1H, d, *J* = 8.5 Hz, 2α-H). (Found: C, 66.1; H,10.4; $C_{17}H_{32}O_4$ requires C, 66.0; H, 10.7 %)

X-Ray crystal data and structure determination: Compound **7**, $C_{17}H_{32}O_4$, M_r 300.4, monoclinic, space group $P2_1/c$ (No.14), *a* = 17.181(6), *b* = 9.575(6), *c* = 10.969(6) Å, α = γ = 90°, β = 107.62(3)°, *V* = 1719.8(16)^3, *Z* = 4, D_{calc} 1.16 g.cm^{-3}, μ = 0.64 mm^{-1}, F(000) = 664, crystal size 0.4 × 0.2 × 0.05 mm^3. Data were collected on an Enraf-Nonius CAD4 diffractometer for 2 < θ < 50° and –17 ≤ *h* ≤ 16, 0 ≤ *k* ≤ 9, 0 ≤ *l* ≤ 10. 1880 reflections were collected of which 1771 were independent and 993 with $I > 2\sigma(I)$ were used in the refinement. The structure was solved using direct methods and refined using SHELXL-97. The final R indices were [$I > 2\sigma(I)$] R_1 = 0.077, wR_2 = 0.194 and (all data), R_1 = 0.144 and wR_2 = 0.239. The largest difference peak and hole was 0.20 and –0.20 e Å^{-3}.

Crystallographic details for compound **7** have been deposited at the Cambridge Crystallographic Data Centre as CCDC no. 235 187.

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