

Acid-catalysed Cyclisation of Humulene

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Extended treatment of humulene [(*E,E,E*)-2,6,6,9-tetramethylcycloundeca-1,4,8-triene] (1) with aqueous sulphuric acid-acetone gives 10-isopropyl-3,7-dimethylbicyclo[5.3.0]deca-2,10-diene (3). A time-dependent product analysis has revealed the initial formation of humulol (11) which then rearranges to a series of bicyclo[5.3.0]decanes terminating in (3).

SEVERAL groups have suggested that humulene (1) is the key biogenetic precursor of a number of fungally-derived sesquiterpenoids.^{1-4†} In the present study, we sought experimental evidence in support of these proposed *in vivo* cyclisations summarised in Scheme 1.‡

Rearrangement Conditions and Product Analysis.—Cyclisation reactions attempted in aqueous sulphuric acid with rapid stirring to emulsify the organic material were not reproducible; the extent of rearrangement seemed to depend upon the stirring rate. However, addition of an equal volume of acetone produced a homogeneous reaction mixture which was held at reflux, sampled at intervals, and the product mixtures analysed by g.l.c. procedures chosen to balance the maximum resolution of hydrocarbon products with suitable retention times for the alcohol products.

RESULTS

A total of seventeen products were detected of which only five were formed in significant quantities.§ The Figure shows the major trends over the full reaction span with the g.l.c. retention times (R_t) of the products expressed relative to that of humulene ($R_t = 1.00$).

Compound R_t 0.54 (3).—Presumably this hydrocarbon

† Note added in proof: A hitherto unknown sesquiterpene skeleton has been found in the structure of 'africanol' derived from marine invertebrates. This framework has been rationalised by yet another cyclisation reaction of humulene (B. Tursch, J. C. Braekman, D. Daloz, P. Fritz, A. Kelem, R. Carlsson, and D. Losman, *Tetrahedron Letters*, 1974, 747).

‡ Variants within this framework have been proposed and received partial experimental support; see refs. 1c and 2d.

§ After the completion of experimental work described in this paper, Y. Naha and Y. Hirose reported in preliminary form similar results from different reaction conditions (*Chem. Letters*, 1973, 133, 727).

¹ Hirsutic acid, coriolin, coriolin-B, and coriolin-C: (a) N. G. Heatley, M. A. Jennings, and H. W. Florey, *Brit. J. Exp. Pathol.*, 1947, **28**, 35; (b) F. W. Comer, F. McCapra, I. H. Qureshi, J. Trotter, and A. I. Scott, *Chem. Comm.*, 1965, 310; (c) F. W. Comer, F. McCapra, I. H. Qureshi, and A. I. Scott, *Tetrahedron*, 1967, **23**, 4761; (d) P. T. Lansbury, N. Y. Wang, and J. E. Rhodes, *Tetrahedron Letters*, 1971, 2056; 1972, 2056; (e) S. Takahashi, H. Naganawa, H. Iinuma, and T. Takita, *ibid.*, 1971, 1955 and references cited therein; (f) T. K. Sarkar, *J.C.S. Perkin I*, 1973, 2454; (g) T. C. Feline, G. Mellows, R. B. Jones, and L. Phillips, *J.C.S. Chem. Comm.*, 1974, 63.

($C_{15}H_{24}$) is the humulene rearrangement product, 'bicyclohumulene' briefly described by Dev.⁵ The u.v. spectrum [λ_{max} , 244 nm (ϵ 11,400)] indicated a conjugated heteroannular diene, whose structure was more clearly defined by the ¹H n.m.r. spectrum (Experimental section) which at first sight pointed to the structure of δ -selinene (2). The corresponding mass spectrum reinforced this view showing a strong molecular ion at m/e 204 with a base peak at 189

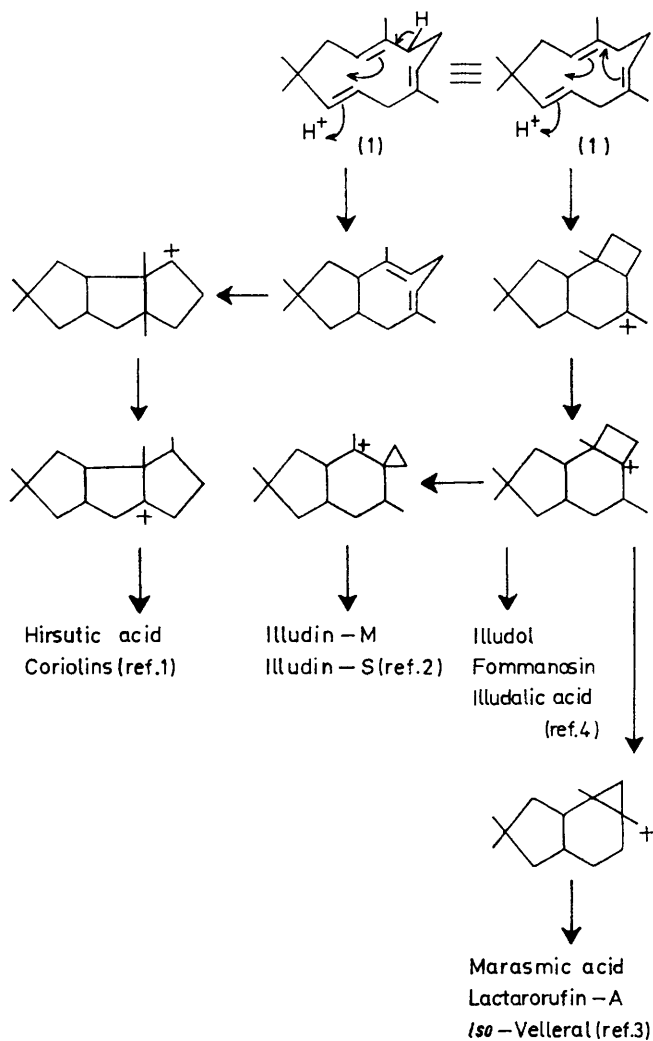
² Illudin-M, illudin-S, and dihydroilludin-S: (a) M. Anchel, A. Hervey, and W. J. Robins, *Proc. Nat. Acad. Sci. U.S.A.*, 1950, **36**, 300; (b) T. C. McMorris and M. Anchel, *J. Amer. Chem. Soc.*, 1963, **85**, 831; 1965, **87**, 1594; (c) K. Nakanishi, M. Ohashi, M. Tada, and Y. Yamada, *Tetrahedron*, 1965, **21**, 1231; (d) J. R. Hanson and T. Marten, *J.C.S. Chem. Comm.*, 1973, 171; (e) T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, F. Sakan, and K. Miyano, *Tetrahedron Letters*, 1971, 2049; (f) M. Anchel, T. C. McMorris, and P. Singh, *Phytochemistry*, 1970, **11**, 2339; (g) H. Navada and K. Nakanishi, *Chem. Comm.*, 1970, 310; (h) A. Ichihara, H. Shirahama, and T. Matsumoto, *Tetrahedron Letters*, 1969, 3965; (i) A. Turnsaki, H. Shirahama, and T. Matsumoto, *Chem. Letters*, 1973, 1293; (j) A. Banerji, G. Ramakrishnan, and M. S. Chadha, *Tetrahedron Letters*, 1974, 1369.

³ Marasmic acid; *iso*-vellerol, lactarorufin-A, etc.: (a) F. Kavanagh, A. Hervey, and W. J. Robins, *Proc. Nat. Acad. Sci. U.S.A.*, 1949, **35**, 343; (b) J. J. Dugan, P. de Mayo, M. Nisbet, J. R. Robinson, and M. Anchel, *J. Amer. Chem. Soc.*, 1965, **87**, 2768; 1966, **88**, 2838; (c) G. A. Sim and P. D. Cradwick, *Chem. Comm.*, 1971, 431; (d) D. Helmlinger, P. de Mayo, M. Nye, L. Westfelt, and R. B. Yeats, *Tetrahedron Letters*, 1970, 349; (e) S. R. Wilson and R. B. Turner, *J. Org. Chem.*, 1973, **38**, 2870; (f) G. Magnusson, S. Thoreu, and B. Wickberg, *Tetrahedron Letters*, 1972, 1105; (g) W. M. Danielski and M. Kocor, *Bull. Acad. Polon. Sci. Sér. Sci. chim.*, 1971, **19**, 553; (h) W. M. Danielski, A. Ejchart, J. Jurczak, L. Kozerki, and J. S. Pyrek, *ibid.*, 1972, **20**, 131; (i) S. Nozoe, H. Matsumoto, and S. Urano, *Tetrahedron Letters*, 1971, 3125.

⁴ Illudol, fommanosin, illudoic acid-A, illudalic acid, illudinine, and illudacetic acid: (a) see ref. 3a; (b) T. C. McMorris, M. S. R. Nair, and M. Anchel, *J. Amer. Chem. Soc.*, 1967, **89**, 4562; (c) T. C. McMorris, M. S. R. Nair, P. Singh, and M. Anchel, *Phytochemistry*, 1971, **10**, 1611; (d) S. Kagawa, S. Matsumoto, S. Nishida, S. Yu, J. Morita, A. Ichihara, H. Shirahama, and T. Matsumoto, *Tetrahedron Letters*, 1969, 3913; (e) T. Matsumoto, K. Miyano, S. Kagawa, S. Yu, J. Ogawa, and A. Ichihara, *ibid.*, 1971, 3521; (f) C. Basset, R. T. Sherwood, J. A. Keplen, and P. B. Hamilton, *Phytopathology*, 1967, **57**, 1046; (g) J. A. Kepler, M. E. Wall, J. E. Mason, C. Bassett, A. T. McPhail, and G. A. Sim, *J. Amer. Chem. Soc.*, 1967, **89**, 1260; (h) M. S. R. Nair, H. Takeshita, T. C. McMorris, and M. Anchel, *J. Org. Chem.*, 1969, **34**, 240; (i) M. S. R. Nair and M. Anchel, *Tetrahedron Letters*, 1972, 2753; (j) K. Miyano, Y. Ohfune, S. Azuma, and T. Matsumoto, *Tetrahedron Letters*, 1974, 1645.

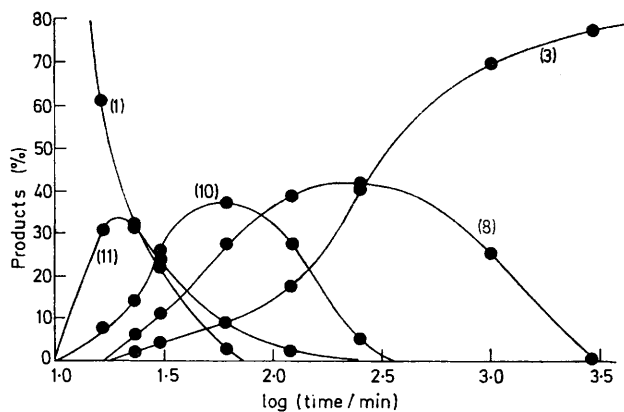
⁵ Sukh Dev, *Current Sci.*, 1951, **20**, 296.

($M - 15$) and a further large peak at 161 ($M - 43$). However the molecular absorptivity remained suspiciously



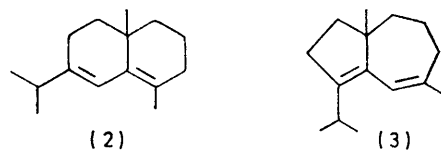
SCHEME 1

'low' even after repeated purification and comparison with an authentic sample of (2) showed that indeed they were not identical.

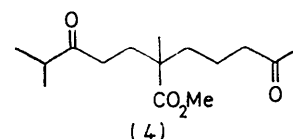


Log (time) variable plot of the reaction of humulene in H_2SO_4 -acetone-water

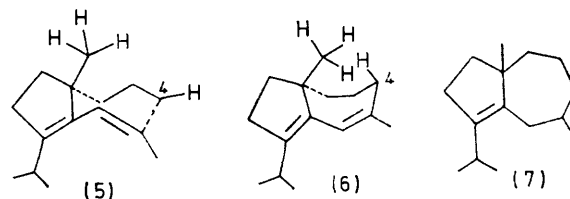
The hydrocarbon (R_t 0.54) does not form a silver nitrate adduct and attempted preparation of a dibromide gave two compounds both of which were liquids. Selenium dehydrogenation gave in a low yield a liquid azulene, λ_{max} 228 (ϵ 15,000), 230 (15,200), 283 (20,000), and 302 nm (5750).



Based on the foregoing data and consideration of probable cyclisation modes of humulene, structure (3) was tentatively assigned to the hydrocarbon and confirmed by oxidative ozonolysis followed by esterification with diazomethane to give a diketo-methyl ester (4) identical in all respects except rotation (g.l.c., i.r., 1H n.m.r., and mass spectra) with the corresponding compound prepared by ruthenium tetroxide oxidation⁶ of δ -selinene (2).

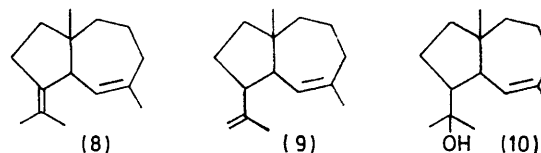


An explanation of the 'low' extinction coefficient might lie in the preferred conformation of this molecule. A Dreiding model of (3) shows that when the diene function is in a planar arrangement (6) there is a serious repulsive interaction between the ring junction methyl group and a proton at C-4, whereas in any of the less crowded (preferred) conformations [*e.g.* (5)] the diene function is distorted out of planarity to a greater or lesser extent.



Catalytic reduction of (4) even under forcing conditions resulted only in the absorption of 1 mol. equiv. of hydrogen to give (7).

Compound R_t 0.89 (8).—The mass spectrum * of (8) is almost identical with that of (3) and the n.m.r. spectrum (Experimental section) showed signals fully compatible with the structure 10-isopropylidene-3,7-dimethylbicyclo-[5.3.0]dec-2-ene (8). The *trans*-stereochemistry depicted in (8) is based on the shielded tertiary methyl signal at τ 9.25.



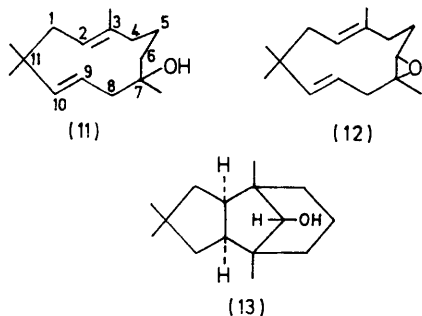
From a study of molecular models it can be seen that the *trans*-stereochemistry forces this methyl group directly above the shielding zone of the 2,3-double bond.

* The published mass spectra of the related selinadienes are noticeably different from those of (3) and (8); see M. G. Moshanas and E. D. Lund, *The Flavour Industry*, 1970, 375.

Compound R_t 0.70 (9).—It was noticed that the diene (8) slowly rearranged to the hydrocarbon R_t 0.70 which was formed in minor quantities throughout the humulene rearrangement. It was isolated by column chromatography on AgNO_3 -alumina and n.m.r. spectroscopy confirmed its structure as (9). Unlike (3), catalytic hydrogenation of (8) and (9) proceeded to completion with the production of 8-isopropyl-1,5-dimethylbicyclo[5.3.0]-decane.

Compound R_t 3.45 (10).—This compound was isolated by column chromatography on silica and its i.r. (ν_{max} 3608 cm^{-1}) and n.m.r. (Experimental section) spectra permitted the structure assignment shown in (10). The mass spectrum of (10) is very similar to those of (3) and (8) with the additional molecular ion at m/e 224 and associated α -cleavage peaks at m/e 59 and 207. Dehydration of (10) with KHSO_4 gave the expected products (8) and (9) in ratios dependent on the reaction conditions, e.g. at 140–150° (9) was found to the extent of 90%; at 170–180° the (9) : (8) ratio was 3 : 2; and at 190–200° (8) predominated along with a little (9) and 10% of (3).

Compound R_t 6.10 (11).—The alcohol R_t 6.10 was best isolated from a 17 min reaction mixture by column chromatography over alumina. The n.m.r. spectrum was very similar to that of humulene-1,2-epoxide⁷ (12) and this alcohol was therefore assigned structure (11), humulol,⁸ which is confirmed by its mass spectral fragmentation pattern. It is notable that (11) could not be prepared from (12) either by treatment with lithium aluminium hydride in refluxing ether or tetrahydrofuran or with lithium in ethylamine.⁹



Compound R_t 4.45 (13).—This alcohol was identified as ' α -caryophyllene alcohol' (13) by comparison with an authentic sample.¹⁰

DISCUSSION

Prior to the present study, the structures of humulene rearrangement products have suggested cyclisation pathways markedly different to the proposed *in vivo* processes (see above); Sutherland¹¹ and McKervery¹² have reported the formation of the tricyclohumulene skeleton

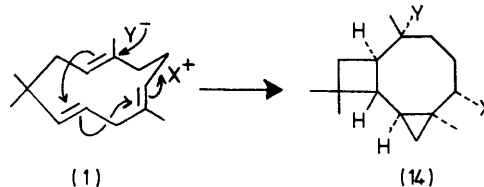
⁶ D. M. Piatak, H. B. Bhat, and E. Caspi, *J. Org. Chem.*, 1969, **34**, 112.

⁷ N. P. Damodaran and Sukh Dev, *Tetrahedron*, 1968, **24**, 4123.

⁸ (a) R. G. Buttery, W. H. McFadden, R. E. Lundin, and M. P. Kealy, *J. Inst. Brewing*, 1946, **70**, 396; (b) R. G. Buttery, R. E. Lundin, and L. C. Ling, *Agric. Food Chem.*, 1967, **15**, 58; (c) R. G. Buttery and L. C. Ling, *Brewers Digest*, 1966, 71; (d) Y. Naya and M. Kotake, *Bull. Chem. Soc. Japan*, 1969, **42**, 2405.

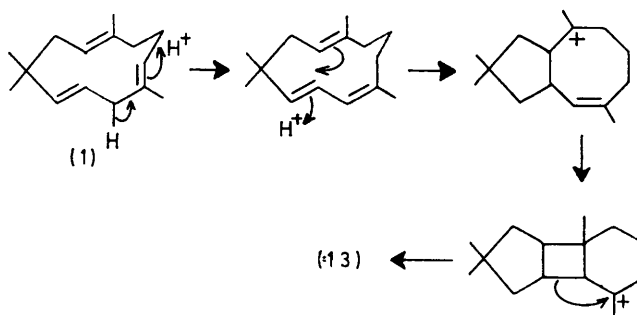
⁹ J. Fried, J. W. Brown, and L. Borkenhagen, *Tetrahedron Letters*, 1965, 2499.

(14) from treatment of humulene with HOBr [to give (14; $\text{X} = \text{Br}$, $\text{Y} = \text{OH}$)] and from the corresponding 6,7-epoxide (12) with aqueous sulphuric acid [to give (14; $\text{X} = \text{OH}$, $\text{Y} = \text{OH}$)].



SCHEME 2

Similarly the structure⁹ of ' α -caryophyllene alcohol' (13) prompted the mechanism^{10g} (Scheme 3) which formed the basis of its 3-step synthesis.^{10f}



SCHEME 3

As a result of the present study it is possible to construct yet another reaction pathway for the acid-cyclisation of humulene (Scheme 4) which is supported by the behaviour of the individual rearrangement products.

The compounds (8) and (9) both react to form (3) when subjected to acid treatment for 50 h. The tertiary alcohol (10) has been dehydrated to (8) and (9) and on acid treatment has been converted into (3), (8), and (9). The diene alcohol (11), as expected, rearranges to all the other reaction products including humulene. It is also suspected that an isomer of humulene [(15)?]¹³ is formed, mainly on the basis of a slight shortening of the retention time and broadening of the humulene g.l.c. peak. It is obvious from the Figure that (11) is formed very rapidly in this particular reaction medium, a finding fully in accord with Sutherland's strain calcu-

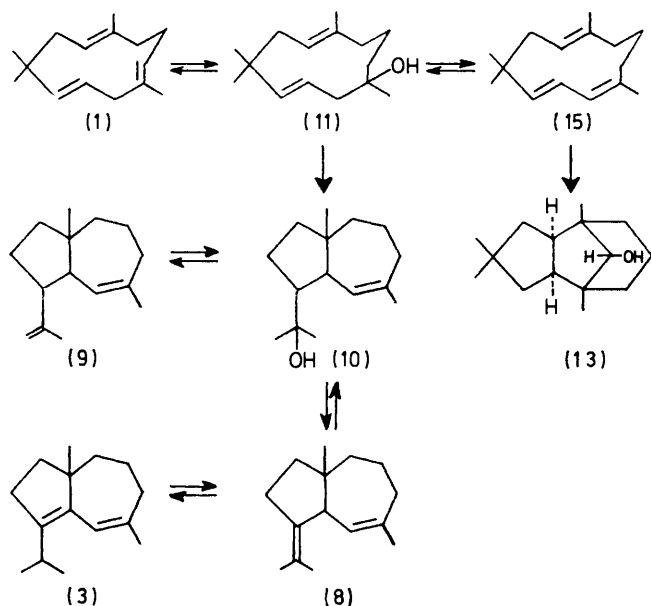
¹⁰ (a) J. Bell and G. G. Henderson, *J. Chem. Soc.*, 1930, 1971; (b) A. Nickon, J. R. Mahajan, and F. J. McGuire, *J. Org. Chem.*, 1961, **26**, 3617; (c) K. W. Gemmill, W. Parker, J. S. Roberts, and G. A. Sim, *J. Amer. Chem. Soc.*, 1964, **86**, 1438; (d) A. Nickon, F. J. McGuire, J. R. Mahajan, B. Umezawa, and S. A. Navany, *ibid.*, 1964, **86**, 1437; (e) A. Nickon, T. Iwadare, F. J. McGuire, J. R. Mahajan, S. A. Narang, and B. Umezawa, *ibid.*, 1970, **92**, 1688; (f) E. J. Corey and S. Nozoe, *ibid.*, 1964, **86**, 1652; (g) J. B. Stothers, C. T. Tan, A. Nickon, F. Huang, R. Sridhar, and R. Weglein, *ibid.*, 1972, **94**, 8581.

¹¹ J. M. Greenwood, M. D. Solomon, J. K. Sutherland, and A. Torre, *J. Chem. Soc. (C)*, 1968, 3004.

¹² M. A. McKervery and J. R. Wright, *Chem. Comm.*, 1970, 117.

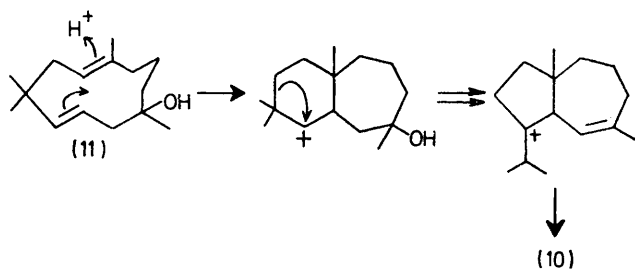
¹³ (a) S. P. Damodaran and Sukh Dev, *Tetrahedron Letters*, 1965, 1977; (b) Sukh Dev, J. E. Anderson, V. Cormier, N. P. Damodaran, and J. C. Roberts, *J. Amer. Chem. Soc.*, 1968, **90**, 1246.

lations.¹⁴ A mechanism for the conversion of (11) into (10) is shown in Scheme 5 and although it might be argued that (10) could be formed directly from humulene, examination of models demonstrates the necessary



SCHEME 4

intermediacy of (11) or (15). The geometry of humulene¹⁵ does not permit the interaction of the 4,5- and 8,9-double bonds required for the formation of (10) whereas such overlap is attainable in both (11) and (15).

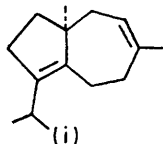


SCHEME 5

Whether the diene (15) or the alcohol (11) or both is/are the precursor(s) of (10) must remain for the moment a matter of speculation, although the apparently preferred conformation of (15) suggests the cyclisation (Scheme 3) which leads to α -caryophyllene alcohol (13).

† For details of Supplementary Publications, see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1973, Index issue.

‡ This quartet signal for the isopropyl group is perhaps unexpected but (–)-daucene (i) exhibits a similar pattern



(P. Naegeli and R. Kaiser, *Tetrahedron Letters*, 1972, 2013; see also T. Irie, K. Yamamoto, and T. Masamune, *Bull. Chem. Soc. Japan*, 1964, **37**, 1053).

It is therefore tempting to propose that (11) is the precursor of the bicyclodecane system whereas (15) is the precursor of the α -caryophyllene skeleton.

It remains to be seen whether the bicyclohumulenes discovered in this work will be found to occur in nature and whether reaction conditions can be developed for the cyclisation of humulene to the fungally-derived sesquiterpenoids.

EXPERIMENTAL

I.r. spectra were recorded on Perkin-Elmer 157G and 457G spectrophotometers. N.m.r. spectra were determined in carbon tetrachloride or deuteriochloroform solution with a Perkin-Elmer R10 spectrometer employing tetramethylsilane as an internal standard. The mass spectra of compounds marked with an asterisk were determined by P.C.M.U. at Harwell and are listed in Supplementary Publication No. SUP 20996 (8 pp.).† Analytical g.l.c. was performed with a Perkin-Elmer model F11 employing a 2 m stainless steel column; packing, 15% Carbowax 20M on Chromosorb W 80–100 at 120°; carrier gas, nitrogen; inlet pressure, 20 lb in⁻². Peak areas were measured with an Allbrit Planimeter. Preparative g.l.c. separations were carried out using a Perkin-Elmer F21 with 3 × 0.9 m aluminium columns (1 cm i.d.), packing, Carbowax 20M on Chromosorb A 60–80; the first two columns from the inlet had 5% liquid phase and the third 15%.

Acid-catalysed Rearrangement of Humulene—Humulene (0.3 g) was heated to 54° in a vigorously stirred solution of acetone (125 ml), water (125 ml), and concentrated sulphuric acid (48 g).

At appropriate intervals, the reaction was quenched in ice-water then thoroughly extracted with ether (3 × 50 ml). The combined ether extracts were washed with a saturated solution of sodium hydrogen carbonate (2 × 50 ml), water (50 ml), and then dried (MgSO₄). After removal of the solvent, the residue was analysed by g.l.c. and the results are shown in the Table.

Isolation of 10-Isopropyl-3,7-dimethylbicyclo[5.3.0]dec-2,10-diene (3).—The products from a large scale rearrangement of humulene (2.7 g) were passed down an alumina column (type H, 80 g) and eluted with light petroleum to give the diene (3)* (1.8 g, 67%), b.p. 53° at 0.2 mmHg (Found: C, 87.9; H, 11.8. C₁₅H₂₄ requires C, 88.15; H, 11.85), λ_{max} (EtOH) 244 nm (ϵ 11,420), ν_{max} 2960, 2920, 2860, 2730, 1470, 1375, 1370, 1360, 1335, 1325, 1305, 1298, 1180, 1145, 1135, 1105, 1040, 1030, 955, 920, and 865 cm⁻¹, τ (CCl₄) 4.08br (1H, s, C=C-CH=C), 7.4 (1H, sept, Me₂CH-C=C), 7.6–8.1 (4H, m, CH₂-C=C), 8.22br (3H, s, CH₃-C=C), 8.35–8.7 (6H, m), 9.02 (3H, d, *J* 6.9 Hz), 9.04 (3H, d, *J* 6.9 Hz) (non-equivalent Me₂CH),‡ and 9.05 (3H, s, tertiary Me).

Dehydrogenation of (3).—A mixture of (3) (900 mg) and selenium (900 mg) was heated to 300° for 10 h. The mixture was taken up in light petroleum and shaken with 85% orthophosphoric acid. The acidic solution was then diluted with water and extracted with petroleum (3 × 10 ml) to give an intense blue solution which was dried (MgSO₄). After removal of the solvent, the residual oil

¹⁴ F. H. Allen, E. D. Brown, D. Rogers, and J. K. Sutherland, *Chem. Comm.*, 1967, 1116.

¹⁵ (a) A. T. McPhail and G. A. Sim, *J. Chem. Soc. (B)*, 1966, 112; (b) M. E. Cradwick, P. D. Cradwick, and G. A. Sim, *J.C.S. Perkin II*, 1973, 404; (c) P. D. Cradwick and G. A. Sim, *Chem. Comm.*, 1971, 431; (d) See ref. 13b.

was purified by p.l.c. to give an intense blue oil (4 mg) (presumably 1-isopropyl-7-methylazulene), ν_{\max} (iso-octane) 228 (ϵ 14,940), 230 (ϵ 15,190), 283 (ϵ 20,000), and 302 nm (ϵ 5750).

Hydrogenation of (3).—The diene (3) (200 mg) was dissolved in glacial acetic acid (20 ml) and hydrogenated over Adams platinum catalyst (10 mg) until uptake ceased. The solution was then filtered and the solvent removed *in vacuo* to give 8-isopropyl-1,5-dimethylbicyclo[5.3.0]dec-7-ene (7),* τ (CCl₄) 7.4 (1H, sept), 7.6–8.8 (m), 8.9, 9.0, 9.01, 9.02, and 9.10 (methyly).

Ozonolysis of (3).—A solution of the diene (3) (1 g) in methylene chloride (100 ml) and pyridine (0.8 g) was ozonised at -70° until a blue colour persisted and was then set aside at room temperature overnight.

The mixture was washed with water (100 ml), 2N-HCl (100 ml), and dried (MgSO₄). Removal of the solvent

limonene and β -selinene. Fractional distillation afforded β -selinene (0.43 g), b.p. 130° at 10 mmHg, identical with an authentic sample kindly provided by Dr. Green, Wye College.

Preparation of δ -Selinene.— β -Selinene (0.43 g) was mixed with formic acid (3 ml) and the rapidly stirred solution was heated at 40° for 2 h. The mixture was then diluted with water, extracted with ether (3 \times 10 ml), and the combined ethereal extracts washed with saturated solution of sodium hydrogen carbonate (2 \times 25 ml), water (25 ml), and dried. Removal of the solvent gave δ -selinene (0.32 g), τ (CCl₄) 3.95 (1H, s), 8.4 (3H, s), 8.95 (6H, d), and 9.10 (3H, s), identical with a sample kindly provided by Professor Y. Hirose.

Oxidation of δ -Selinene with Ruthenium Tetraoxide.—To a stirred mixture of ruthenium dioxide (200 mg) in acetone (70 ml) and sodium periodate (1.6 g) in water (minimum

Product distribution (%) from reaction of humulene in acetone-water-H₂SO₄

Compound	R_t^*	Distribution (%) after time								
		15 min	23 min	30 min	1 h	2 h	4 h 7 min	12 h 6 min	48 h	
(3)	0.54	T	1.74	3.89	8.79	18.3	40.23	65.79	78.87	
	0.63						T	T	11.27	
(9)	0.70	T	6.27	9.90	5.80	6.7	5.75	2.63	T	
	0.85		3.48	S		T				
(8)	0.89	T	6.27	10.95	27.24	38.35	42.53	26.32	T	
	(1)	1.00	61.2	31.36	21.20	3.16	T			
	1.05					T	2.87	5.26	T	
	1.12	T	2.79	1.1	T	T	T		2.82	
	1.20								T	
	1.30		T	1.06	1.41	0.8	2.87	T	T	
	1.42		T	T	0.35	0.6	T			
	1.66		T	T	0.35	0.7	T			
(10)	3.45	8.2	13.94	24.10	37.26	28.34	5.75			
	3.80			T	1.76		T			
(13)	4.45		2.44	3.18	2.11	2.4	T	T	7.04	
	5.45			T	1.93	2.2	T			
(11)	6.10	30.6	31.71	22.97	9.67	1.7				

T = a trace quantity too small to integrate. S = shoulder on the preceding peak—area included in the preceding peak.

* R_t = retention time relative to humulene ($R_t = 1.00$).

gave an oil which was dissolved in ether and washed with 2N-NaOH (50 ml) and the aqueous alkaline layer was then acidified and thoroughly extracted with ether; the combined ether extracts were dried (MgSO₄) and evaporated to give 2,6-dimethyl-3,10-dioxoundecane-6-carboxylic acid (liquid; 0.7 g), ν_{\max} 2970, 2950, 2870, 1720, 1705, 1465, 1455, 1445, 1435, 1410, 1380, 1350, 1120, and 1070 cm⁻¹, τ (CCl₄) -0.8br (1H, s), 7.1–7.8 (5H, part of a septet is apparent), 7.9 (3H, s), 8.0–8.6 (6H, m), and 8.92 (9H, d, *J* 7 Hz, isopropyl and tertiary Me, superimposed on leading peak of isopropyl doublet).

Treatment of this acid with diazomethane gave methyl 2,6-dimethyl-3,10-dioxoundecane-6-carboxylate (4),* ν_{\max} 2970, 2935, 2865, 1730, 1720, 1460, 1380, 1120, and 1070 cm⁻¹, τ (CCl₄) 6.35 (3H, s), 7.2–7.85 (m containing a septet integrating for 5H), 7.93 (3H, s), 8.1–8.8 (6H, m), and 8.93 (9H, d, *J* 7 Hz, tertiary Me superimposed on the inner isopropyl signal).

Extraction of β -Selinene from Celery Seeds.—Celery seeds (Superb Red variety; 454 g) were crushed with a mortar and pestle and the pulp was extracted with ether. The seed residue was refluxed with ether for 24 h and the ether removed and combined with the pulp ethereal extract. After removal of the ether the residual oil was passed down an alumina column (200 g). Elution with light petroleum gave an oil (4 g), which was a mixture containing mainly

amount for dissolution), under an N₂ atmosphere, was added alternately a solution of δ -selinene (2.2 g, 11.3 mmol) in acetone (100 ml), and a solution of sodium periodate (30.0 g) in water (160 ml) and acetone (160 ml). This addition was regulated to take ca. 2 h and the mixture was stirred overnight. The precipitated solids were then filtered off and the acetone evaporated off *in vacuo*. A small amount of dilute HCl was added to ensure acidity, and the solution was extracted three times with ether. The combined ethereal extracts were washed thoroughly with brine and then extracted with 2N-NaOH solution. The alkaline solution was acidified with 2N-HCl and extracted three times with ether. The combined ethereal extracts were washed thoroughly with brine, dried (MgSO₄), and the ether evaporated *in vacuo* to give a gummy acid (2.1 g, 75%).

The crude acid was esterified with diazomethane to give the crude ester (1.50 g, 68%), a portion (273 mg) of which was purified by p.l.c. [0.5 mm silica gel (Merck GF₂₅₄ type 60), light petroleum-ethyl acetate-ether (5 : 3 : 2)] to give pure ester (118 mg, 43%) which exhibited identical spectroscopic (i.r., n.m.r., mass) and chromatographic (g.l.c. and t.l.c.) properties with the ester prepared from (3) by ozonolysis.

*Isolation of 10-Isopropylidene-3,7-dimethylbicyclo[5.3. dec-2-ene (8).**—This compound was isolated by pre-

parative g.l.c. (manifold temperature 250°, connecting line 250°, oven temperature 180°, injection block 180°, nitrogen flow rate 20 lb in⁻², flow of carrier gas to the injection block 10 ml min⁻¹), ν_{\max} (CCl₄) 2960, 2930, 2860, 1450, 1440, 1375, 1170, 920, and 870 cm⁻¹, τ (CCl₄) 4.58 (1H, d, *J* 6 Hz, CH=CCH₃), 6.85br (1H, s, C=C-CH-C=C), 8.23 (3H, apparent t, *J* 2 Hz, CH₃C=C), 8.40 (6H, q, *J* 2 Hz, Me₂C=C), and 9.25 (3H, s, tertiary Me).

Isolation of 10-Isopropenyl-3,7-dimethylbicyclo[5.3.0]dec-2-ene (9).—Humulene (3.0 g) was treated for 130 min under the foregoing aqueous acid conditions and the hydrocarbon products were isolated by chromatography on silica gel (100 g). The diene (9) was then isolated by further chromatography of the hydrocarbons on silver nitrate (25%)–silica gel using light petroleum as the eluant. The liquid diene exhibited ν_{\max} (liquid film) 2960, 2920, 2850, 1640, 1450, 1373, 1260, 1200, 890, and 865 cm⁻¹, τ (CCl₄) 4.9 (1H, s), 5.3 (2H, slightly split s, *J* ca. 1 Hz), 8.30 (3H, s), 8.33 (3H, s), and 9.20 (3H, s).

Isolation of the Alcohol (10).—Humulene (3.0 g) was treated for 130 min under the foregoing aqueous acidic conditions and absorbed on silica gel (100 g). Elution with light petroleum–ether (3:2) gave 10-(1-hydroxy-1-methyl-ethyl)-3,7-dimethylbicyclo[5.3.0]dec-2-ene (10) * (3.45 g) (Found: C, 80.85; H, 11.55. C₁₅H₂₆O requires C, 81.0; H, 11.8%), ν_{\max} (CCl₄) 3608, 2970, 2930, 2900, 2860, 1470,

1453, 1387, 1380, 1370, and 940 cm⁻¹, τ (CCl₄) 4.75 (1H, d, *J* 5 Hz, CH=CCH₃), 8.3 (3H, finely split s, 3 lines, *J* 2 Hz, CH₃C=CH), 8.90br (6H, s, Me₂COH), and 9.25 (3H, s, Me).

Dehydration of (10).—The tertiary alcohol (10) (164.5 mg) and KHSO₄ (150 mg) were heated to 170–180° for 1.5 h to give the hydrocarbons (8) and (9) in the ratio of 2:3.

*Isolation of Humulol [(1E,5E)-1,4,4,8-Tetramethylcyclo-undeca-1,5-dien-8-ol] (11).**—Humulene (2.5 g) was treated for 17 min under the foregoing aqueous acidic conditions and the crude product absorbed on silica gel (100 g). Elution with light petroleum–ether (3:2) gave the tertiary alcohol (10) and subsequent elution with light petroleum–ether (1:1) gave humulol (11) (324 mg) (Found: C, 80.9; H, 11.85. C₁₅H₂₆O requires C, 81.0; H, 11.8%), ν_{\max} (CCl₄) 2960, 2930, 2850, 1660w, 1465, 1453, 1380, 1375, 1360, 1170, 1130, 1105, 1050, 975, 920, 910, 900, and 870 cm⁻¹, τ (CCl₄) 4.8, 4.9, 4.95, and 5.05 (very small) (total 3H), 7.9 (2H, s), 8.40 (3H, d, *J* 2 Hz), and 8.90, 8.92, and 8.96 (9H, 3s).

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