Oxidation Products of Hop Bitter Acids. Part VI.[1] Five-membered Ring Products from the Oxidation of Colupulone

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Oxidation of colupulone (I) produces a complex mixture, separation of which by counter-current distribution gives the cyclopenta[*b*]furan (III) and the cyclopenta[*b*]pyran (IV). Support for these structures comes mainly from n.m.r. and mass spectral data.

BUBBLING oxygen through a solution of colupulone (I) in iso-octane produced a very complex oxidation mixture. Isolation of the products was achieved by counter-current distribution (CCD) with a buffer of pH 1·9 as lower phase and iso-octane as the upper phase. After 1225 transfers two bands with $K = 0{\cdot}60$ [(III); 1·25% yield)] and $K = 0{\cdot}88$ [(IV); 3·75% yield)] were obtained. A similar procedure but with buffer pH 4·5 and after 390 transfers gave cohulupone,[2] the main five-membered ring oxidation product of colupulone. Table 1 gives some physical data for the products (III) and (IV), while Tables 2 and 3 detail the n.m.r. spectra of compounds (III) and (IV), respectively.

TABLE 1

Compound	M.p. (°C)	*M*	pK_a (MeOH)	$\lambda_{max.}$/nm [a]	$10^{-3}\varepsilon$ [a]	$\lambda_{max.}$/nm [b]	$10^{-3}\varepsilon$ [b]
(III)	*c*	352	3·35	230	5·6	254	12·35
				272	5·4	267	sh [d]
(IV)	80	352	3·05	227	9·8	253	18·5
				265	8·9	268	sh [d]

[a] In acid. [b] In base. [c] An oil. [d] sh = Shoulder.

TABLE 2

N.m.r. spectrum of compound (III) [a]

Proton	δ/p.p.m.	Multiplicity	Integration	*J*/Hz	
a	1·14	2	6H	5·5	
b	3·45	7	1H	5·5	
c	1·57	1			
c′	1·62	1	6H		
d	5·08	3	1H		
e	2·45	4	2H	^3J 6	
f	1·05—1·18		6H		
H_A	2·30	8	2H	^3J 6·5	^2J(AB) 13·4
H_B	1·92			^3J 7·5	Σ^3J 14
H_X	4·24	4	1H		
g	7—8	1	2H		

[a] As a 10% solution in CCl_4.

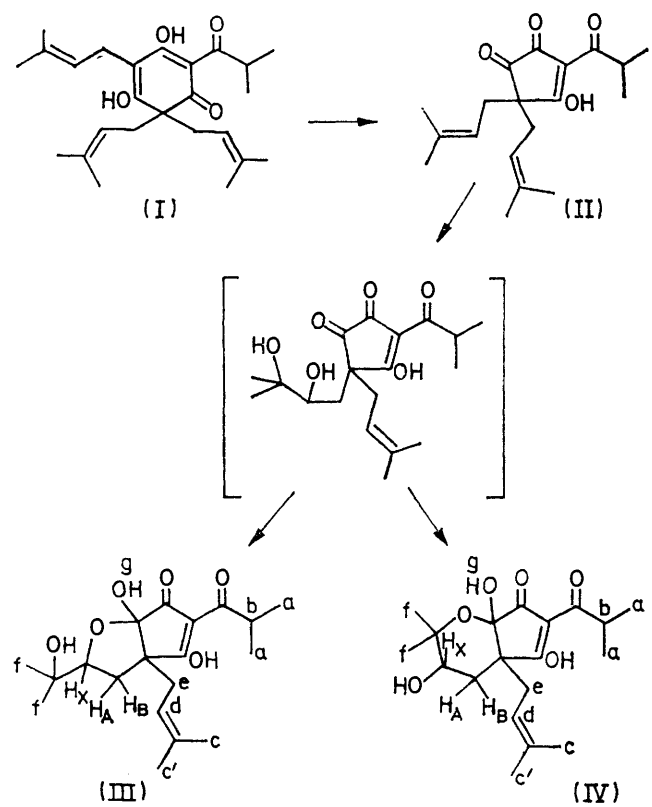
TABLE 3

N.m.r. spectrum of compound (IV) [a]

Proton	δ/p.p.m.	Multiplicity	Integration	*J*/Hz	
a	1·16	2	6H	6·5	
b	3·35	7	1H	6·5	
c	1·54	1	6H		
c′	1·60	1			
d	5	3	1H		
e_A	2·55	4	2H	^3J 8·5	
e_B	2·10			^3J 5	
f	1·05	1	6H		
f	1·20	1			
H_X	3·65	4	1H		
H_A	2·18	(8)[b]	2H	^3J 6·5	^2J(AB) 13·0
H_B				^3J 10·5	Σ^3J 17
g	7—8	1	1H		

[a] As a 10% solution in CCl_4. [b] Partially obscured.

The five-membered carbocyclic ring in compounds (III) and (IV) was indicated by the similarity between the p*K* values and the u.v. spectra of the new substances and those of other five-membered ring, hop derived, substances (iso-α-acids, humulinic acids, *etc.*).[3] While all six-membered ring hop bitter acids produce a very low field n.m.r. signal (δ *ca.* 19 p.p.m.), the five-membered ring derivatives do not. The latter situation obtained for the new substances. They are possibly formed by epoxidation of a double bond in cohulupone (II), subsequent opening of the oxiran ring with water (from undried solvent), and intramolecular acetalization (see Scheme 1); thus giving the dihydroxycyclopentafuranone (III) and the dihydroxycyclopentapyranone

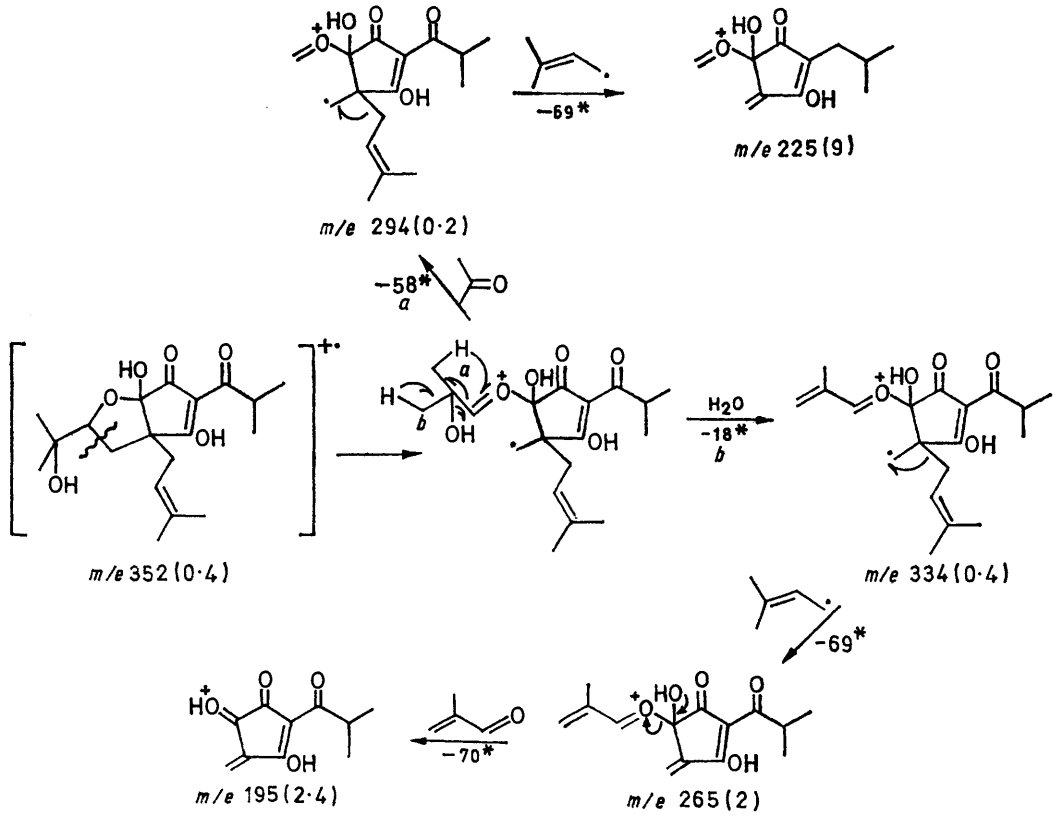


SCHEME 1

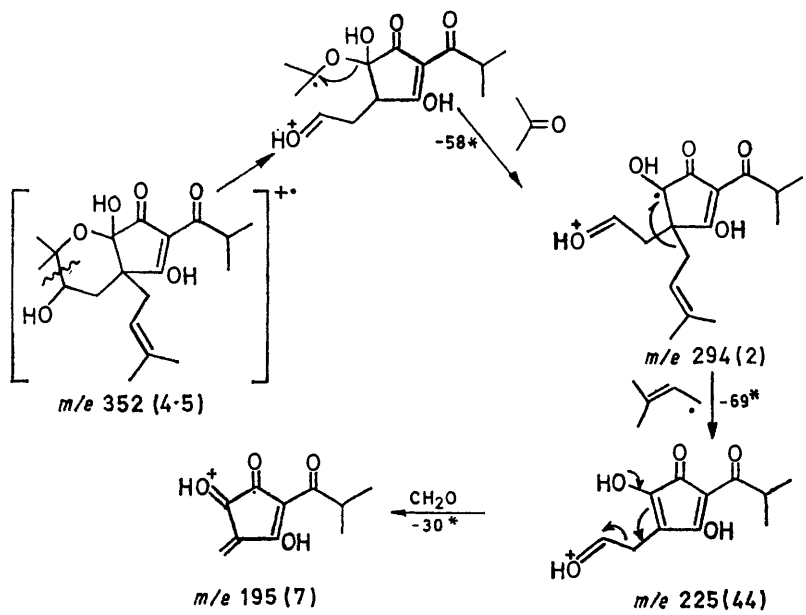
[1] Part V, M. Vanhoey, M. Vandewalle, and M. Verzele, *Bull. Soc. chim. belges*, 1970, **79**, 499.

[2] L. Spetsig, M. Steniger, and S. Brohult, European Brew. Convention Copenhagen, 1967, p. 22.

[3] F. Alderweireldt and M. Verzele, *Bull. Soc. chim. belges.*, 1957, **66**, 391.



SCHEME 2



SCHEME 3

(IV). Another supporting feature in the n.m.r. spectrum is the shift of proton b. This is a function of the ring size and degree of hydroxylation of the ring to which the acyl group is attached. Some examples

TABLE 4

Compound	δ Value of the b-proton/p.p.m. (10% solutions in CCl_4)
1. Cohulupone (II)	3·62
2. (III)	3·45
3. (IV)	3·50
4. *cis*-Isocohumulone	3·40
5. *trans*-Isocohumulone	3·38
6. Colupulone (I)	3·94
7. Cohumulone	3·65
8. Deoxytetrahydrocohumulone	3·82

showing this are presented in Table 4. All the five-membered ring compounds (1—5 in Table 4) have lower values for proton b than the three six-membered ring compounds (6—8). The difference between deoxytetrahydrocohumulone and cohumulone is an upfield shift of 0·17 p.p.m.; likewise the difference between cohulupone and products (III) and (IV) is an upfield shift of 0·17 and 0·12 p.p.m. respectively, for an equivalent difference but with one more hydroxy-group on the ring. Deoxytetrahydrocohumulone is the hydrogenation product of colupulone; hydrogenolysis removes a side chain and the structure is then that of tetrahydrohumulone less the tertiary hydroxy-group.

Attribution of the furanoid structure (III) to the compound with lower distribution coefficient and of the pyranoid structure (IV) to the compound with the higher distribution coefficient is only tentative. This is based on some of the coupling constants given in Tables 2 and 3.

The conformations of furanoid and pyranoid rings have been studied extensively. The spin coupling systems are well known and in our case the ABX systems, considering the conformational equilibria possible for the compounds, should produce a sum for J_{AX} and J_{BX} of 17 Hz for the six-membered ring and 15·2 Hz for the five-membered ring.[4,5] This sum of the coupling constants in compound (III) is 14·5 Hz and in (IV) it is 17 Hz. Accordingly the furanoid structure is attributed to (III) and the pyranoid structure to (IV).

Mass Spectra.—Determination of the molecular weight by high resolution mass spectrometry gave *M* 352·1897 and 352·1899 for (III) and (IV), respectively, leading to the molecular formula, $C_{19}H_{28}O_6$, for both.

The mass spectra also allow, with a fairly high probability, the assignment of the heterocyclic ring size for the compounds. The relevant degradation paths (see Schemes 2 and 3) are confirmed by high resolution measurements and by the metastable focusing technique.[6,7] In both spectra the peak *m/e* 225 is an important one. Its formation from the six-membered ring (Scheme 3) is highly favoured because the initial cleavage leading to this ion is both an alcohol and ether cleavage. The subsequent loss of acetone is also more plausible than for the five-membered ring compound (III).

The analogous fission for compound (III) (Scheme 2) is rendered plausible by the formation of ion *m/e* 195. A metastable transition shows that the latter ion arises from ion *m/e* 265 by the loss of methacrylaldehyde as a neutral fragment. The one step loss of methylacraldehyde can only be rationalized for a five-membered heterocyclic ring. In the spectra of compound (IV) (Scheme 3) ion *m/e* 195 is formed from the ion with *m/e* 225.

EXPERIMENTAL

N.m.r. spectra were determined with a Varian instrument at 100 MHz, and mass spectra on an AEI MS9 spectrometer.

Through a solution of colupulone (20 g) (m.p. 95·5 °C) in undried iso-octane (200 ml), undried oxygen was passed (7 l h^{-1}) during 7 h. The temperature was kept at 50° and daylight (or a 500 W light bulb) catalysed the reaction. More iso-octane was added whenever necessary to keep the volume constant. A yellow oil separated out. The solvent was removed and iso-octane (100 ml) and buffer of pH 1·9 [100 ml; 0·25M-citric acid (15 ml), 0·25M-NaOH (15 ml), and 0·25M-HCl (70 ml)] were added. The first ten tubes (20 ml each) of a counter-current distribution (CCD) system with 330 tubes were filled. CCD was now carried out with the phase system; iso-octane–buffer (pH 1·9). After 310 transfers and after 520 transfers (recycling) the results were analysed. All tubes not containing (III) and (IV) were emptied and refilled with fresh solvent. The distribution was continued for 1225 transfers.

The separated bands were removed, the lower layers were acidified and extracted with iso-octane. The iso-octane solutions were evaporated to complete dryness *in vacuo* leaving 2,3,3a,6a-tetrahydro-4,6a-dihydroxy-2-(1-hydroxy-1-methylethyl)-5-isobutyryl-3a-(3-methylbut-2-enyl)-6*H*-cyclopenta[*b*]furan-6-one (III) (0·19 g) and 2,3,4a,7a-tetrahydro-3,5,7a-trihydroxy-6-isobutyryl-2,2-dimethyl-4a-(3-methylbut-2-enyl)cyclopenta[*b*]pyran-7(4*H*)-one (IV) (0·65 g). The cyclopentafuranone (III) is an oil, while the cyclopentapyranone (IV) has m.p. 80° (from iso-octane).

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[4] R. Fahey, G. Graham, and R. Piccioni, *J. Amer. Chem. Soc.*, 1966, **12**, 193.

[5] H. Buys, 'Conformation Investigations in Five-membered Ring Compounds,' Bronder Offset, Rotterdam, 1968.

[6] J. Beynon, R. Sauners, and A. Williams, *Nature*, 1964, **204**, 67.

[7] K. Jennings, *J. Chem. Soc.*, 1965, **43**, 4176.