1205. *Chemistry of Hop Constituents. Part XXVII.*[1] *Further Model Compounds of Hulupone and Humulinic Acid*

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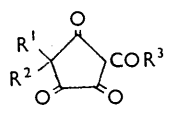
Oxidation of 2-acetyl-4,4,6-trimethylcyclohexane-1,3,5-trione (IV) with lead tetra-acetate gave the hydroxy-compound (V) and the bis-structure (VIII). Further treatment of (V) afforded the model hulupone, 3-acetyl-5,5-dimethylcyclopentane-1,2,4-trione (I). Two forms of the model humulinic acid, 2-acetyl-4-hydroxy-5-methylcyclopentane-1,3-dione (IX) have also been obtained, but both were shown to be mixtures of *cis*- and *trans*-isomers by proton magnetic resonance spectroscopy.

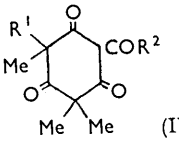
Model compounds of humulone,[2] isohumulone,[3] and lupulone [4] have been prepared in which the acyl group is acetyl and the alkyl groups methyl (although all these compounds are enolic, structures are written here in the keto forms). It was of interest to prepare

[1] Part XXVI, D. R. J. Laws, preceding Paper.
[2] T. W. Campbell and G. M. Coppinger, *J. Amer. Chem. Soc.*, 1951, **73**, 1849.
[3] P. M. Brown and G. A. Howard, *J.*, 1960, 164.
[4] W. Riedl and K. H. Risse, *Annalen*, 1953, **585**, 209.

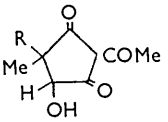
3-acetyl-5,5-dimethylcyclopentane-1,2,4-trione (I), the corresponding simple analogue of hulupone (II). Attempts to prepare this compound by oxidation of 2-acetyl-4,4-dimethylcyclopentane-1,3-dione [5] were unsuccessful, as were routes analogous to those used in preparing the parent compounds.[6,7] Thus, all attempts to methylate the trione (III) to give (I) failed, as did treatment of the lupulone analogue (IV) with oxygen in the presence of sodium sulphite or with sodium persulphate. Similarly, attempts to autoxidise the model (IV), as hexahydrocolupulone,[8] were unsuccessful. The reaction of the lupulone analogue (IV) with lead tetra-acetate, however, gave *inter alia* the hydroxy-compound (V). Alkaline hydrolysis of (V) then gave the humulinic acid analogue (VI) which was oxidised with bismuth oxide, or more successfully with manganese dioxide in chloroform, to the hulupone analogue (I). Its structure is supported by the proton magnetic resonance spectrum, in which the enol signal is in the same position as that given by cohulupone.[9]



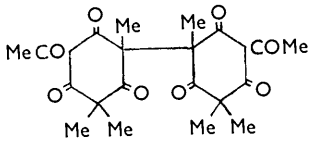
(I : $R^1 = R^2 = R^3 = Me$)
(II : $R^1 = R^2 = Me_2C{:}CH{\cdot}CH_2$, $R^3 = Bu^i$)
(III : $R^1 = R^3 = Me$, $R^2 = H$)



(IV : $R^1 = H$, $R^2 = Me$)
(V : $R^1 = OH$, $R^2 = Me$)
(VII : $R^1 = Me$, $R^2 = Bu^i$)



(VI : R = Me)
(IX : R = H)



(VIII)

The major product of the reaction of (IV) with lead tetra-acetate had analytical data in close agreement with those of the starting material, but the ultraviolet absorption ($\lambda_{max.}$ 280 mμ in either acid or alkaline ethanol) was similar to that of tetrasubstituted derivatives of acylphloroglucinols such as leptospermone (VII).[10] The product was therefore regarded as having the bis-structure (VIII), presumably formed by an oxidative coupling. Some confirmation of this structure was provided by the molecular weight from ebullioscopy. The p.m.r. spectra of the product and the starting material showed no signal attributable to a proton attached directly to the ring, indicating that both compounds were fully enolised. For the product (VIII) the intensity ratio of the enol and acetyl signal was 1 : 3, consistent with the bis-structure. From the starting material, there were two enol signals (see Table). Furthermore, the line from the 6-methyl group in (IV) was at a lower field than the corresponding signal from the product (VIII). This is expected if the 6-Me group is attached to a doubly-bonded carbon atom as required by the additional enolisation in (IV). It seems possible that similar oxidative couplings may take place with the hop β-acids (lupulones) either during storage or in the brewing processes.

In Part XIV [3] we described the preparation of a simple analogue (IX) of humulinic acid. With the demonstration that humulinic acid exists in two stereochemical forms, A and B,[11,12] it became of interest to see if two stereochemical forms of the model compound (IX) could be obtained.

[5] F. Merenyi and M. Nilsson, *Acta Chem. Scand.*, 1964, **18** (6), 1368.
[6] D. Wright, *J.*, 1963, 1769.
[7] P. M. Brown, J. S. Burton, and R. Stevens, *J.*, 1964, 4774.
[8] R. Stevens and D. Wright, *J.*, 1963, 1763.
[9] S. Forsen, M. Nilsson, J. A. Elvidge, J. S. Burton, and R. Stevens, *Acta Chem. Scand.*, 1964, **18**, 513.
[10] W. R. Chan and C. H. Hassall, *J.*, 1956, 3495.
[11] J. S. Burton, J. A. Elvidge, and R. Stevens, *J.*, 1964, 3816.
[12] A. Lepoivre, F. Alderweireldt, M. Anteunis, and M. Verzele, *Bull. Soc. chim. belges*, 1964, **73**, 275; F. Alderweireldt and M. Anteunis, *ibid.*, p. 285.

Proton magnetic resonance results for 5—10% solutions in $CDCl_3$ and containing 0·2% $SiMe_4$

(IX) *trans*	(IX) *cis*	τ-Values (intensity) (I)	(IV)	(VIII)		Intensity splitting * *J* (c./sec.)	Assignment
8·57	8·73					3d (7·0, 7·5) †	5-Me
		8·70	8·58			6s	*gem*-Me's
				8·42	8·30	6s, 6s	*gem*-Me's
			8·09	8·18		3s, 6s	6-Me's
7·47	7·47	7·28	7·39			3s	Ac groups
				7·53		6s	Ac groups
7·12	6·90					1m	5-H
5·98	5·58					1d (4·5, 7·5) †	4-H
0·83	0·83	−2·03				1b (0·3, 0·3, 0·3 p.p.m.) †	OH
			−9·08			1s	OH
				−8·25		1b (*ca.* 0·1 p.p.m.)	2 × OH

* s = Singlet, d = doublet, m = multiplet (not properly resolved), b = broadened.
† Respectively.

One form of this compound (IX), m. p. 112°, assumed to be the *trans*-isomer from its mode of preparation, was oxidised with bismuth oxide to 3-acetyl-5-methylcyclopentane-1,2,4-trione which exists as the dienol (III).[13] This compound was obtained earlier by autoxidation of (IX)[3] and more recently by synthesis.[14] We have also obtained (III) by autoxidation of model isohumulone, 2,4-diacetyl-4-hydroxy-5-methylcyclopentane-1,3-dione. Reduction of the trione with sodium borohydride then afforded a second form of the compound (IX) with m. p. 80°. This was assumed to be the *cis*-isomer, by analogy with the preparation of humulinic acid B.

However, proton magnetic resonance spectroscopy showed unambiguously that each form of compound (IX) was a mixture of the *cis*- and *trans*-isomers. This was an unexpected situation which could not otherwise have been revealed so easily. Each spectrum showed two doublets from the proton adjacent to the hydroxyl group, at positions and with splittings closely similar to those for the corresponding proton in humulinic acids A and B, and also two doublets, arising from the 5-methyl group. From the relative intensities of the paired signals it followed that the form of compound (IX) with m. p. 112° consisted of about two parts of the *trans*-isomer (with humulinic acid A stereochemistry) with one part of the *cis*-isomer. The form of compound (IX) with m. p. 81° consisted of about two parts of the *cis*-isomer (humulinic acid B stereochemistry) and one part of the *trans*. Attempts to separate the individual isomers by reversed-phase chromatography and by chromatography on an ion-exchange paper (Whatman DE20) failed.

Experimental

Light petroleum refers to the fraction of b. p. 40—60°. Molecular weights were determined ebullioscopically in ether. For the preparation of (IX), the starting material, 3,5-dimethylphloracetophenone, was more conveniently prepared from the commercially available 2,4,6-trihydroxytoluene, either through the 3-formyl compound,[15] characterised as its 2,4-*dinitrophenylhydrazone*, m. p. 285° (decomp.) (from ethanol–water) (Found: C, 47·9; H, 3·5; N, 15·9. $C_{14}H_{12}N_4O_7$ requires C, 48·3; H, 3·5; N, 16·1%), and then 3,5-dimethylphloroglucinol, or more conveniently[16] from the 3-methylphloracetophenone 2,4-*dinitrophenylhydrazone*, m. p. 266° (decomp.) (from ethanol and n-butanol) (Found: C, 49·7; H, 3·9; N, 15·1. $C_{15}H_{14}N_4O_7$ requires C, 49·7; H, 3·9; N, 15·5%), and thence 3-formyl-5-methylphloracetophenone. 2-Acetyl-4-hydroxy-5-methylcyclopentane-1,3-dione[3] (IX) had m. p. 111—112°. It was shown by proton magnetic resonance spectroscopy to consist of about two parts of the *trans*- with one of the *cis*-isomer.

[13] J. A. Elvidge and R. Stevens, *J.*, 1965, 2251.
[14] E. Leucht and W. Riedl, *Annalen*, 1963, **669**, 55.
[15] J. Herzig, F. Wenzel, and E. Kerenyi, *Monatsh.*, 1903, **24**, 876.
[16] A. Robertson and W. B. Whalley, *J.*, 1951, 3355.

2-*Acetyl*-4,4,6-*trimethylcyclohexane*-1,3,5-*trione* (IV).—This compound was made as described previously [17] except that the period of reflux was reduced to 0·5 hr. It had m. p. 161—162°, $\lambda_{max.}$ (in acid ethanol) 275 and 330 mμ (ε 5820 and 8500), (in alkaline ethanol) 355 mμ (ε 16,400).

Oxidation of 2-*Acetyl*-4,4,6-*trimethylcyclohexane*-1,3,5-*trione with Lead Tetra-acetate.*—The trione (IV) (6 g.) and lead tetra-acetate (12 g.) in acetic acid (250 ml.) were set aside overnight, diluted with water (500 ml.), and extracted with light petroleum. Washing, drying, and evaporation of the extract gave an oily residue which, on addition of ethanol, deposited 6,6′-*bis*-(2-*acetyl*-4,4,6-*trimethylcyclohexane*-1,3,5-*trione*) (VIII), m. p. 183° (from ethanol) (Found: C, 63·2; H, 6·4%; *M*, 462. $C_{22}H_{26}O_8$ requires C, 63·2; H, 6·2%; *M*, 418), $\lambda_{max.}$ (in ethanol) 240 and 275 mμ (ε 21,500 and 20,520), (in alkaline ethanol) 275 mμ (ε 31,510). With 2,4-dinitrophenylhydrazine it gave a *bis*(*anhydrohydrazone*), m. p. 296—297° (decomp.) (Found: C, 54·7; H, 3·8. $C_{34}H_{30}N_8O_{12}$ requires C, 55·0; H, 4·0%). Concentration of the mother-liquors from the parent compound gave a further crop of crystalline material, m. p. 136°, which was shown to be heterogeneous by proton magnetic resonance spectroscopy. When no further solid separated from the mother-liquors, they were concentrated and distilled, b. p. 130° (bath)4 × 10^{-3} mm., to give a yellow oil which crystallised. Recrystallisation from ethanol–water afforded 2-*acetyl*-6-*hydroxy*-4,4,6-*trimethylcyclohexane*-1,3,5-*trione*, m. p. 83° (Found: C, 58·6; H, 6·3. $C_{11}H_{14}O_5$ requires C, 58·4; H, 6·2%), $\lambda_{max.}$ (in ethanol) 237·5 and 275 mμ (ε 7563 and 10,370), (in alkaline ethanol) 270 mμ (ε 17,030).

2-*Acetyl*-4-*hydroxy*-5,5-*dimethylcyclopentane*-1,3-*dione* (VI).—The hydroxy-trione (VII) (0·72 g.) in ethanol (10 ml.) was heated under reflux with 2N-sodium hydroxide for 5 hr. By acidification at 0° and extraction with ether the *hydroxy-dione* (VI) was obtained, m. p. 105—106° (from ether) (Found: C, 59·0; H, 6·55. $C_9H_{12}O_4$ requires C, 58·7; H, 6·5%), $\lambda_{max.}$ (in ethanol) 225 and 267·5 mμ (ε 10,100 and 9700), (in alkaline ethanol) 250 and 270 mμ (ε 19,360 and 16,140).

3-*Acetyl*-5,5-*dimethylcyclopentane*-1,2,4-*trione* (I).—(*a*) The hydroxy-dione (VI) (0·8 g.) and manganese dioxide (4 g.) (B.D.H. Ltd.) in chloroform (30 ml.) were stirred for 0·5 hr. After filtration, the residue was extracted with hot methanol and the combined filtrates were evaporated, diluted with 2N-hydrochloric acid, and extracted with ether. The residue from the ethereal extract was then extracted with warm cyclohexane, to give the *trione*, m. p. 92—93° (from light petroleum) (Found: C, 59·5; H, 5·75. $C_9H_{10}O_4$ requires C, 59·3; H, 5·5%), $\lambda_{max.}$ (in ethanol) 282·5 mμ (ε 10,220), (in alkaline ethanol) 250 and 322·5 mμ (ε 13,720 and 10,300).

(*b*) The hydroxy-dione (355 mg.) and bismuth oxide (710 mg.) in acetic acid (25 ml.) were heated under reflux for 24 hr. Dilution and acidification afforded an oil which, after distillation, b. p. 135° (bath)/1·2 × 10^{-4} mm., solidified to give the trione, m. p. 87° undepressed on admixture with the sample obtained in (*a*).

3-*Acetyl*-5-*methylcyclopentane*-1,2,4-*trione* (III).—(*a*) A solution of 2,4-diacetyl-4-hydroxy-5-methylcyclopentane-1,3-dione [3] (512 mg.) in methanol (50 ml.), when set aside with lead acetate (2 g.) and access to the air, became deep orange and deposited a precipitate. After 2 days the lead salt was collected (629 mg.), suspended in methanol, and decomposed with hydrogen sulphide. Evaporation of the solvent gave the trione, m p. 216° (decomp.) after recrystallisation from water and sublimation (Found: C, 57·4; H, 5·0. Calc. for $C_8H_8O_4$: C, 57·2; H, 4·8%).

(*b*) 2-Acetyl-4-hydroxy-5-methylcyclopentane-1,3-dione (1·84 g.) in acetic acid (80 ml.) was heated under reflux with bismuth oxide (3 g.) for 2 hr. After dilution with 2N-hydrochloric acid (160 ml.) and saturated brine, the filtered solution was extracted with ethyl acetate. Evaporation of the extract afforded the trione as golden crystals (691 mg.), m. p. 216—217° (sealed tube) (from aqueous methanol).

Reduction of 3-*Acetyl*-5-*methylcyclopentane*-1,2,4-*trione with Sodium Borohydride.*—A solution of the trione (III) (1·06 g.) in methanol (60 ml.) was added dropwise to a stirred solution of sodium borohydride (1·06 g.) in water (30 ml.) at 0°. When the addition was complete, the mixture was stirred for a further 2 hr., acidified with 2N-hydrochloric acid, and extracted with ether. Evaporation of the washed and dried ethereal extract afforded a residue which was extracted with boiling cyclohexane. Cooling of the cyclohexane extract gave the second form of the *analogue* (IX), m. p. 80—81° after two recrystallisations from cyclohexane (Found: C, 56·5; H, 5·7. $C_8H_{10}O_4$ requires C, 56·4; H, 5·8%), $\lambda_{max.}$ (in ethanol) 225, 255, and 265sh mμ (ε 10,370, 9950, and 9560), (in alkaline ethanol) 250 and 270sh mμ (ε 21,300 and 16,400). This

[17] A. C. Jain and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 1955, **42** *A*, 279.

compound was shown to consist of about two parts of the *cis*- and one part of the *trans*-isomer by proton magnetic resonance spectroscopy.

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