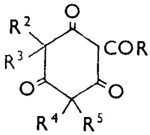
1204. *Chemistry of Hop Constituents. Part XXVI.*[1] *2-Acyl-4,4,6,6-tetra(3-methylbut-2-enyl)cyclohexane-1,3,5-triones (Lupones)*

By D. R. J. Laws

The synthesis of lupones by the isoprenylation of acylphloroglucinols is described. Lupones have been characterised as crystalline imines and nickel salts, but have not as yet been found in hops.

Hop resin constituents have structures consisting of acylphloroglucinol nuclei substituted with 3-methylbut-2-enyl (isoprenyl) groups. Thus, humulone (I; $R^1 = Bu^i$, $R^2 = R^5 = CH_2\cdot CH:CMe_2$, $R^3 = H$, $R^4 = OH$) and lupulone (I; $R^1 = Bu^i$, $R^2 = R^4 = R^5 = CH_2\cdot CH:CMe_2$, $R^3 = H$) contain, respectively, two and three isoprenyl groups, while the pigment xanthohumol contains only one such grouping [2] and is a monomethyl enol ether of (I; $R^1 = CH:CH\cdot C_6H_4\cdot OH$-*p*, $R^2 = R^4 = R^5 = H$, $R^3 = CH_2\cdot CH:CMe_2$). Tetrasubstituted derivatives (I; $R^2 = R^3 = R^4 = R^5 = CH_2\cdot CH:CMe_2$) have not been encountered, although leptospermone (I; $R^1 = Bu^i$, $R^2 = R^3 = R^4 = R^5 = Me$) is a well characterised component of the essential oil of *Leptospermum spp.*[3] An earlier examination of the steam-volatile fractions of hops by thin-layer chromatography [4] revealed bands which seemed consistent with the presence of such tetrasubstituted acylcyclohexane triones, and several such compounds have now been synthesised. The trivial name lupone is proposed for the compound (I; $R^1 = Bu^i$, $R^2 = R^3 = R^4 = R^5 = CH_2\cdot CH:CMe_2$), and colupone (I; $R^1 = Pr^i$, $R^2 = R^3 = R^4 = R^5 = CH_2\cdot CH:CMe_2$) and adlupone (I; $R^1 = Bu^s$, $R^2 = R^3 = R^4 = R^5 = CH_2\cdot CH:CMe_2$) for the analogues, in concordance with accepted nomenclature in hop chemistry.



(I)

Riedl [5] reports the preparation of lupone, m. p. 92—93°, by the isoprenylation of phloroisovalerophenone, but the melting point and analytical data suggest that this product was lupulone. Lupone was obtained as a high-boiling oil which slowly crystallised and then had m. p. 44°. Colupone and adlupone were similarly prepared. The light absorption of all the analogues was similar to that of leptospermone.[6] The lupones were characterised as crystalline imines and nickel salts. A copper salt, prepared from lupone, slowly decomposed on standing. The proton magnetic resonance spectrum of colupone [7] is consistent with structure (I; $R^1 = Pr^i$, $R^2 = R^3 = R^4 = R^5 = CH_2\cdot CH:CMe_2$). Hydrogenation of lupones using palladium chloride as catalyst resulted in the absorption of 4 moles of hydrogen; hydrogenolysis [8] did not occur.

The lupones were steam-volatile; after 24 hours, 70% of the lupone was recovered from the distillate. Several varieties of hops (1964 crop) were examined for lupones, and it soon became clear that the material originally thought to be lupones did not correspond to the synthetic compounds.

Experimental

Light petroleum refers to the fraction of b. p. 40—60°. All reactions were carried out under nitrogen.

2-Isobutyryl-4,4,6,6-tetra-(3-methylbut-2-enyl)cyclohexane-1,3,5-trione (*Colupone*).—Sodium (5·0 g.) was added to dry ethanol (80 ml.), the solution cooled to 0°, and phloroisobutyrophenone

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[1] Part XXV, P. R. Ashurst, D. R. J. Laws, and R. Stevens, *J. Inst. Brewing*, in the press.

[2] M. Verzele, J. Stockx, F. Fontijn, and M. Anteunis, *Bull. Soc. chim. belges*, 1957, **66**, 452.

[3] L. H. Briggs, A. R. Penfold, and W. F. Short, *J.*, 1938, 1193.

[4] P. Margaret Brown and D. R. Maule, unpublished results.

[5] W. Riedl, *Chem. Ber.*, 1952, **85**, 692.

[6] L. H. Briggs, C. H. Hassall, and W. F. Short, *J.*, 1945, 706.

[7] J. A. Elvidge, unpublished results.

[8] W. Riedl, " Recent Progress in the Chemistry of Natural and Synthetic Colouring Matters and Related Fields," ed. T. S. Gore, B. S. Joshi, S. V. Sunthanker, and B. D. Tilak, Academic Press, New York, 1962, p. 77.

(8·6 g.) in dry ether (60 ml.) added during 0·25 hr. The mixture was stirred at room temperature for 0·5 hr., 1-bromo-3-methylbut-2-ene (44·5 g.) in dry ether (20 ml.) was added dropwise, and the mixture stirred overnight. The reaction mixture was diluted with ether, filtered, and the filtrate washed successively with dilute hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate, and water, then dried ($MgSO_4$). After evaporation of the solvent the residue was extracted with light petroleum and the organic phase shaken with 2N-sodium hydroxide (2 × 100 ml.); oil formed at the interface. The oil and aqueous phase were combined, acidified, and extracted with chloroform. The chloroform layer was dried ($MgSO_4$) and evaporated, to afford crude colupone (13 g.) as a viscous oil. A portion of this material (2·0 g.) was chromatographed on silica gel (140 g.) using ethyl acetate in hexane (5 : 95) as eluant, and 40 ml. fractions were collected. Fractions 5—7 were combined and evaporated, leaving a yellow viscous material which on distillation gave *colupone* as a colourless oil, b. p. 135—140° (bath)/ 2·2 × 10^{-3} mm. (0·9 g.). On standing, the distillate slowly crystallised, m. p. 42° (Found: C, 76·8; H, 9·5. $C_{30}H_{44}O_4$ requires C, 76·9; H, 9·4%), $\lambda_{max.}$ (acidic ethanol) 245sh, 285 mμ. (ε 9500), $\lambda_{max.}$ (alkaline ethanol) 240sh, 280 mμ (ε 19,600), $\nu_{max.}$ (film) 3400vw, 3000s, 2950vs, 1700m. 1660s, 1550s, 1440s, 1365m, 1320w, 1280w, 1100m, 1060m, 1040m, 825m cm.$^{-1}$. An *imine*, m. p. 112°, was prepared by treating a methanolic solution of colupone with ammonia (*d* 0·880) (Found: C, 76·9; H, 9·7; N, 3·1. $C_{30}H_{45}NO_3$ requires C, 77·1; H, 9·65; N, 3·0%). A *nickel salt*, m. p. 88°, was prepared from colupone (Found: C, 71·0; H, 9·1. $C_{60}H_{86}NiO_8,H_2O$ requires C, 71·2; H, 8·7%).

Lupone.—This *compound* was prepared by a similar procedure, m. p. 44°, b. p. 140—145° (bath)/2 × 10^{-4} mm. (Found: C, 77·0; H, 9·7. $C_{31}H_{46}O_4$ requires C, 77·2; H, 9·6%), and gave an *imine*, m. p. 72° (Found: C, 77·7; H, 10·0; N, 2·9. $C_{31}H_{47}NO_3$ requires C, 77·6; H, 9·9; N, 2·9%). A *nickel salt*, m. p. 121°, was prepared from lupone (Found: C, 71·2; H, 8·5. $C_{62}H_{90}NiO_8,H_2O$ requires C, 71·5; H, 8·8%), and an unstable copper salt, m. p. 75°, was also obtained.

Adlupone.—This *compound* had m. p. 45°, b. p. 150—155° (bath)/2 × 10^{-3} mm. (Found: C, 76·9; H, 9·5. $C_{31}H_{46}O_4$ requires C, 77·2; H, 9·6%); the corresponding *imine* had m. p. 101° (Found: C, 77·4; H, 9·8; N, 2·9. $C_{31}H_{47}NO_3$ requires C, 77·6; H, 9·9; N, 2·9%), and the *nickel salt* had m. p. 95° (Found: C, 71·1; H, 8·6. $C_{62}H_{90}NiO_8,H_2O$ requires C, 71·5; H, 8·8%). The infrared and ultraviolet spectra of both lupone and adlupone were almost identical with that of colupone.

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