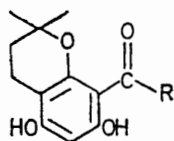


Chemistry of Hop Constituents. Part XXXIX.¹ A Novel Alkenylation Reaction giving Hop Constituents and Related Compounds

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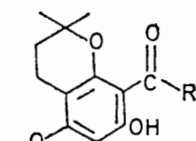
2-Acylcyclohexane-1,3,5-triones (acylphloroglucinols) can be alkenylated by bromides in the presence of ion-exchange resins to give deoxyhumulones (I), hop β -acids (II), lupones (III), and their analogues. The lupones are conveniently obtained in enhanced yields by using strongly basic resins; the deoxyhumulones are formed by using weakly basic resins. When 2-acylcyclohexane-1,3,5-triones are treated with 2-methylbut-3-en-2-ol in the presence of an acidic resin, mixtures of dihydrobenzopyrans (VII) and tetrahydrobenzodipyrans (VIII) are obtained.

In a preliminary communication² we described a new method for the isoprenylation of 2-acylcyclohexane-1,3,5-triones with 1-bromo-3-methylbut-2-ene, in the presence of ion-exchange resins. We now describe full details and extensions of the method to give compounds (I)—(VIII).



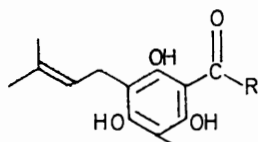
(VII)

R
a; Me
b; Et
c; Prⁿ
d; Prⁱ

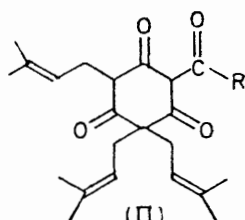


(VIII)

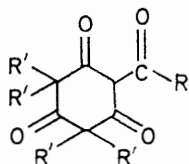
R
e; Buⁿ
f; Buⁱ
g; Bu^s
h; Ph



(I)



(II)



(III) R' = Me₂C:CH:CH₂

(V) R' = CH₂:CH:CH₂

(IV) R' = MeCH:CH:CH₂

(VI) R' = PhCH₂

Deoxyhumulones,³ lupulones,⁴ and lupones⁵ have been synthesized previously by treating the appropriate 2-acylcyclohexane-1,3,5-triones with 1-bromo-3-methyl-

but-2-ene in the presence of sodium ethoxide. The extent of the alkenylation depends on the molar proportions of the reactants. The resultant mixtures are difficult to separate, and the yields are low (5–30%). More recently hop β -acids⁶ (lupulones), free from other alkenylation products, have been obtained in 50–73% yields through the use of liquid ammonia. Deoxyhumulones have also been obtained satisfactorily, although in only 10–20% yields, by treating the appropriate triones with 2-methylbut-3-en-2-ol in the presence of a Lewis acid.⁷

Although basic ion-exchange resins have been used to effect Michael condensations⁸ and in the synthesis of benzyl ethers of phenols,⁹ they have not apparently been used in the C-alkenylation or -alkylation of phenols. We find that isoprenylation of 2-acylcyclohexane-1,3,5-triones with 1-bromo-3-methylbut-2-ene and ion-exchange resins proceeds well. The extent of the alkenylation is governed by the basicity of the resin, and the yields improve as the particle size of the resin is diminished.

Tetra-alkenylation of 2-acylcyclohexane-1,3,5-triones took place in the presence of strongly basic resins. The highest yields of lupones (30–40%) (Table I) resulted from use of DeAcidite FF-IP (OH⁻ form) in boiling benzene and an excess of the alkenyl bromide. Not only was the yield superior to that from the earlier synthesis of lupones⁵ but the isolation was simpler. Extension of the new method to alkenylation with 1-bromobut-2-ene and 1-bromoprop-2-ene gave compounds (IVa and h) and (Va) in 25–35% yield. Even the less reactive benzyl bromide afforded a low yield of the tetrasubstituted compound (VIa) from phloroacetophenone, in contrast to its failure to react by the liquid ammonia procedure. However, simple alkyl bromides did not react by either procedure.

Other strongly basic resins were tried but were less satisfactory, as also was percolation of the reagents in methanol through a column of the resin at ambient temperature.

When the weakly basic resin DeAcidite H-IP (OH⁻ form) in boiling dry benzene was used, with 3 molecular

¹ Part XXXVIII, M. Collins, D. R. J. Laws, J. D. McGuinness, and J. A. Elvidge, *J. Chem. Soc. (C)*, 1971, 3814.

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⁵ D. R. J. Laws, *J. Chem. Soc.*, 1965, 6542.

⁶ K. G. Drewett and D. R. J. Laws, *J. Inst. Brewing*, 1970, **76**, 188.

⁷ E. Collins, W. J. C. Donnelly, and P. V. R. Shannon, *Chem. and Ind.*, 1972, 120.

⁸ E. Bergman and R. Corett, *J. Org. Chem.*, 1956, **21**, 107.

⁹ E. J. Row, K. L. Kaufman, and C. Piantadosi, *J. Org. Chem.*, 1958, **23**, 1622.

proportions of 1-bromo-3-methylbut-2-ene, dialkenylation was the main reaction. A number of deoxyhumulones (Ia—g) were thus prepared (Table 2), and isolated by column chromatography on silicic acid. The yields were similar to those obtained by using 2-methylbut-3-en-2-ol and a Lewis acid but the isolation was simpler.

When 4 molecular proportions of alkenyl bromide were used (or a large excess), with the weakly basic resin, the hop β -acids and analogues (IIa, c, d, and g) were formed in 2–5% yields but their isolation from the accompanying deoxyhumulones (up to 10%) was tedious. No

Dialkenylation of 2-Acylcyclohexane-1,3,5-triones.—A mixture of phloroacetophenone (0.84 g, 0.005 mol), DeAcidite H-IP resin (OH⁻ form; 30 g) and 1-bromo-3-methylbut-2-ene (1.5 g, 0.01 mol) in dry benzene (200 ml) was refluxed with stirring for 16 h, cooled, and filtered; the resin was washed with acetone (30 ml), and the combined filtrate evaporated to give a viscous oil (0.62 g). This was chromatographed on a column of silicic acid (36 × 2.5 cm) in ether-hexane (1:9), and 25 ml fractions were collected. Fractions 2–8 afforded a pale yellow oil which soon crystallized. Recrystallization from light petroleum (b.p. 30–40°) gave 2-acetyl-4,6-bis-(3-methylbut-2-enyl)benzene-

TABLE 1
Synthetic lupones

Compound	C(%)		H(%)		λ_{\max}/nm (ϵ) (acidic EtOH)		λ_{\max}/nm (ϵ) (alkaline EtOH)	M.p. (°C)	Yield (%)
	Found	Required	Found	Required					
(IIIb)	76.3	76.6	9.0	9.2	233 (10,500)	283 (12,000)	280 (16,300)	43	32.8
(IIIc)	76.8	77.0	9.3	9.4	232 (10,700)	283 (13,800)	280 (17,500)	47	40.2
(IIIe)	77.0	77.2	9.2	9.5	230 (10,300)	283 (13,850)	281 (16,650)	45	36.8
(IIIh)	78.4	78.8	8.1	8.4	247 (9,750)	282 (10,580)	{ 251 (11,800) 277 (12,500)	49	38.5

specific trialkenylation, as with liquid ammonia,⁶ was achieved.

These reactions presumably proceed⁶ in stages of anion formation and C-alkenylation, so that, when the strongly basic resin is used, tetra-C-alkenylation occurs. With the weakly basic resin anion formation is such that di-C-alkenylation is favoured, and further anion formation from the less acidic dialkenylated product hardly occurs, so that very little trialkenylated product is formed.

Since methylbut-3-en-2-ol reacts with 2-acylcyclohexane-1,3,5-triones in the presence of Lewis acids to give deoxyhumulones⁷ (I) it seemed that similar alkenylation might be effected in the presence of an acidic ion-exchange resin. A mixture of the dihydrobenzopyran (VIIa) and the tetrahydrobenzodipyran (VIIIa) was formed when a mixture of phloroacetophenone, 2-methylbut-3-en-2-ol and Amberlite IR120 resin (H⁺ form) was heated under reflux in dioxan. The products were readily separated by column chromatography on silica gel.

The monopyrans (VIIId and e) and dipyrans (VIIId and e) were obtained in a similar way using phloroisobutyrophenone and phlorovalerophenone. Presumably both mono- and di-alkenylation of the 2-acylcyclohexane-1,3,5-trione initially occurred to give the corresponding isopentenyl compounds, which then cyclised under the acidic conditions to form the pyrans. Similar mixtures of dihydrobenzopyrans and tetrahydrobenzodipyran have been obtained previously by treating acylcyclohexanetriones with 1-bromo-3-methylbut-2-ene in the presence of powdered sodium¹ and then acidifying.

EXPERIMENTAL

U.v. and i.r. (Nujol mull) spectra were measured with a Pye-Unicam SP 1800 and a Perkin-Elmer 157G spectrophotometer, respectively. The resins used in these studies had a particle size of 200 mesh.

1,3,5-triol (Ia) (216 mg, 14.3%), m.p. 78° (lit.,⁷ 78–79°) (Found: C, 69.8; H, 7.8. Calc. for C₁₈H₂₄O₄: C, 71.0; H, 7.9%). The analogues (Ib—g) were prepared in a similar way (Table 2).

TABLE 2
Synthetic deoxyhumulones

Compound	C(%)		H(%)		M.p. (°C)	Yield (%)
	Found	Calc.	Found	Calc.		
(Ib)	71.7	71.8	8.0	8.2	83	11.6
(Ic)	72.0	72.4	8.1	8.4	(Oil)	12.6
(Id)	72.2	72.4	8.3	8.4	89	13.8
(Ie)	72.8	72.9	8.6	8.7	86	12.1
(If)	72.6	72.9	8.4	8.7	82	14.0
(Ig)	72.5	72.9	8.5	8.7	(Oil)	9.8

The triol (Ia) (72 mg) was also obtained from a similar reaction in which the DeAcidite H-IP resin was replaced by DeAcidite FF-IP resin (formate form; 40 g).

Trialkenylation of 2-Acylcyclohexane-1,3,5-triones.—A mixture of phloroacetophenone (0.84 g, 0.005 mol), DeAcidite H-IP resin (OH⁻ form; 43 g) and 1-bromo-3-methylbut-2-ene (3.0 g, 0.02 mol) in dry benzene (200 ml) was refluxed with stirring for 20 h, cooled, and filtered; the resin was washed with concentrated hydrochloric acid-methanol (1:10; 30 ml). The combined filtrate and washings were evaporated to 30 ml, water was added (100 ml) and the mixture was extracted with ether (3 × 100 ml). The extracts were washed successively with water (50 ml), saturated aqueous sodium hydrogen carbonate (40 ml), water (50 ml), and saturated aqueous sodium chloride (40 ml), dried (MgSO₄), and evaporated. The resulting viscous oil was extracted with boiling light petroleum (b.p. 40–60°; 5 × 100 ml). Concentration of the filtered extract (to 20 ml) and cooling afforded 2-acetyl-4,4,6-tris-(3-methylbut-2-enyl)cyclohexane-1,3,5-trione (IIa) (83 mg, 4.3%), m.p. 123° [from light petroleum (b.p. 60–80°)] (lit.,¹ 123°) (Found: C, 74.0; H, 8.6. Calc. for C₂₃H₃₂O₄: C, 74.2; H, 8.6%).

Similarly from phloropropiophenone, 2,4,4-tris-(3-methylbut-2-enyl)-6-propionylcyclohexane-1,3,5-trione (IIb) was obtained (2.4%); m.p. 103° (lit.,¹ 102°) (Found: C, 74.5;

H, 8.7. Calc. for $C_{24}H_{34}O_4$: C, 74.6; H, 8.8%. From phloroisobutyrophenone, 2-isobutyryl-4,4,6-tris-(3-methylbut-2-enyl)cyclohexane-1,3,5-trione (colupulone) (IIId) was obtained (3.8%), m.p. 94° (lit.,¹ 92°) (Found: C, 74.6; H, 8.9. Calc. for $C_{25}H_{36}O_4$: C, 75.0; H, 9.0%); and phlorisovalerophenone gave 2-isovaleryl-4,4,6-tris-(3-methylbut-2-enyl)cyclohexane-1,3,5-trione (lupulone) (IIIf) (5.6%), m.p. 93° (lit.,¹ 92°) (Found: C, 75.4; H, 9.1. Calc. for $C_{28}H_{38}O_4$: C, 75.4; H, 9.2%).

Tetra-alkenylation of 2-Acylcyclohexane-1,3,5-triones.—(i) A mixture of phloroacetophenone (0.84 g, 0.005 mol), DeAcidite FF-IP resin (OH⁻ form; 40 g) and 1-bromo-3-methylbut-2-ene (7.5 g, 0.05 mol) in dry benzene (200 ml) was refluxed with stirring for 16 h, cooled, and filtered; the resin was washed with acetone (50 ml) and the combined filtrate was evaporated to give a viscous oil (1.4 g). This was chromatographed on a column of silica gel (60 × 2.5 cm) in hexane-ethyl acetate (95 : 5) and 25 ml fractions were collected. Fractions 5—9 afforded a pale yellow oil which on distillation gave 6-acetyl-2,2,4,4-tetrakis-(3-methylbut-2-enyl)cyclohexane-1,3,5-trione (IIIa), b.p. 135—140° (bath) at 2×10^{-4} mmHg, as an oil which slowly crystallized (37.4%), m.p. 36° (Found: C, 76.2; H, 8.9. $C_{28}H_{40}O_4$ requires C, 76.4; H, 9.1%); λ_{max} . (acidic EtOH)¹⁰ 233 (ε 11,050) and 283 nm (9700), λ_{max} . (alkaline EtOH)¹⁰ 278 nm (ε 17,600); ν_{max} . 2980, 2920, 1715, 1675, 1570, 1450, 1380, 1160, 1115, 1070, 1030, 990, 910, and 830 cm^{-1} . The analogues (IIIb, c, e, and h) were prepared similarly (Table 1).

(ii) A mixture of phloroacetophenone (0.84 g, 0.005 mol), DeAcidite FF-IP resin (OH⁻ form; 40 g), and crotyl bromide (5.5 g, 0.04 mol) was refluxed in dry benzene (200 ml) with stirring for 22 h, cooled, and filtered; the resin was washed with acetone (50 ml) and the combined filtrate and washings were evaporated to give a dark brown oil which was dissolved in ether (20 ml) and treated with decolorising charcoal (1 g). The ether was evaporated off and the resulting oil chromatographed on a column of silicic acid (35 × 1.4 cm) in hexane-ethyl acetate (95 : 5); 2 ml fractions were collected. Fractions 19—35 afforded a yellow oil which on distillation gave 2-acetyl-4,4,6,6-tetra(but-2-enyl)cyclohexane-1,3,5-trione (IVa) (0.48 g, 25.1%), b.p. 110—115° (bath) at 1×10^{-3} mmHg (Found: C, 74.7; H, 8.5. $C_{24}H_{32}O_4$ requires C, 75.0; H, 9.3%), λ_{max} . (acidic EtOH) 237 (ε 7960) and 282 nm (ε 10,700), λ_{max} . (alkaline EtOH) 278 nm (ε 17,600); ν_{max} . 3030, 2970, 2920, 2860, 1715, 1670, 1565, 1440, 1380, 1210, and 970 cm^{-1} .

Similarly phlorobenzophenone gave 2-benzoyl-4,4,6,6-tetra(but-2-enyl)cyclohexane-1,3,5-trione (IVh) (28%), b.p. 135—140° (bath) at 4×10^{-4} mmHg (Found: C, 77.7; H, 7.4. $C_{29}H_{34}O_4$ requires C, 78.0; H, 7.6%), λ_{max} . (acidic EtOH) 254 (ε 11,300) and 284 nm (13,200), λ_{max} . (alkaline EtOH) 254 (ε 13,200) and 280 nm (ε 17,100); ν_{max} . 3080, 3030, 2970, 1930, 1860, 1715, 1675, 1570, 1445, 1380, 1340, 1240, 1185, 1075, 1030, 970, 925, 840, and 700 cm^{-1} .

(iii) Treatment of phloroacetophenone as in (ii) but using allyl bromide gave an oil after column chromatography

¹⁰ J. A. Elvidge and D. R. J. Laws, *J. Chem. Soc. (C)*, 1967, 1839.

¹¹ P. M. Brown, J. S. Burton, and R. Stevens, *Tetrahedron Letters*, 1963, 289.

which was distilled to give 2-acetyl-4,4,6,6-tetra(prop-2-enyl)cyclohexane-1,3,5-trione (Va) (35%), b.p. 15—80° (bath) and 2×10^{-4} mmHg (Found: C, 72.7; H, 7.3. $C_{20}H_{24}O_4$ requires C, 73.1; H, 7.3%), λ_{max} . (acidic EtOH) 282 nm (ε 10,700), λ_{max} . (alkaline EtOH) 278 nm (ε 17,600); ν_{max} . 3080, 3010, 2980, 2930, 1715, 1670, 1640, 1565, 1440, 1365, 1345, 1260, 1030, 1000, and 925 cm^{-1} .

(iv) A similar reaction to (iii), but with benzyl bromide gave a product which was chromatographed on a column of silicic acid (50 × 1.4 cm) in hexane-ethyl acetate (95 : 5); 2.0 ml fractions were collected. Fractions 22—36 afforded an oil which slowly crystallized. Recrystallization from aqueous methanol gave 2-acetyl-4,4,6,6-tetrabenzylcyclohexane-1,3,5-trione (VIa) (5.0%), m.p. 72° (Found: C, 81.4; H, 6.2. $C_{36}H_{32}O_4$ requires C, 81.8; H, 6.1%), λ_{max} . (acidic EtOH) 288 nm (ε 7050), λ_{max} . (alkaline EtOH) 279 nm (ε 12,000); ν_{max} . 3080, 3060, 3030, 1940, 1710, 1670, 1600, 1560, 1490, 1455, 1360, 1275, 1205, 1095, 1075, 1030, 1010, 950, 920, 750, and 705 cm^{-1} .

Alkylation of 2-Acylcyclohexane-1,3,5-triones in the Presence of Acidic Resins.—2-Methylbut-2-en-1-ol (0.86 g, 0.01 mol) in dioxan (100 ml) was added to a stirred mixture of phloroacetophenone (0.84 g, 0.005 mol), Amberlite IR-120 resin (H⁺ form; 20 g), and dioxan (100 ml) at 20° during 0.5 h. The mixture was stirred, refluxed for 24 h, cooled, and filtered, and the resin was washed with acetone (20 ml). The combined filtrate was evaporated to give a brown oil (1.4 g). This was chromatographed on a column of silica gel (75 × 2.5 cm) eluted with hexane-ethyl acetate (9 : 1); 50 ml fractions were collected. Fractions 7—10 afforded pale yellow crystals of 6-acetyl-3,4,9,10-tetrahydro-2,2,8,8-tetramethyl-2H,8H-benzo[1,2-b;3,4-b']dipyrans-5-ol (VIIIa) (95 mg), m.p. 117° (lit.,¹¹ 117—118°) (Found: C, 71.0; H, 8.2. Calc. for $C_{18}H_{24}O_4$: C, 71.1; H, 7.9%). Fractions 27—30 afforded crystalline 8-acetyl-2,2-dimethylchroman-5,7-diol (VIIa) (62 mg), m.p. 151° (lit.,¹² 150°) (Found: C, 66.0; H, 6.4. Calc. for $C_{13}H_{16}O_4$: C, 66.1; H, 6.8%).

Similarly phloroacetophenone (0.005 mol) gave 3,4,9,10-tetrahydro-2,2,8,8-tetramethyl-6-valeryl-2H,8H-benzo[1,2-b;3,4-b']dipyrans-5-ol (VIIIe) (58 mg), m.p. 56° (lit.,¹ 57°) (Found: C, 72.6; H, 8.6. Calc. for $C_{21}H_{30}O_4$: C, 72.9; H, 8.7%), together with 2,2-dimethyl-8-valerylchroman-5,7-diol (VIIe) (46 mg), m.p. 102° (lit.,¹ 102°) (Found: C, 68.7; H, 7.7. Calc. for $C_{16}H_{22}O_4$: C, 69.0; H, 7.9%).

Phloroisobutyrophenone (0.005 mole) gave 3,4,9,10-tetrahydro-6-isobutyryl-2,2,8,8-tetramethyl-2H,8H-benzo[1,2-b;3,4-b']dipyrans-5-ol (VIIId) (103 mg), m.p. 85° (lit.,¹³ 84°) (Found: C, 72.1; H, 8.2. Calc. for $C_{20}H_{28}O_4$: C, 72.4; H, 8.4%), together with 8-isobutyryl-2,2-dimethylchroman-5,7-diol (VIIId) (68 mg), m.p. 147° (lit.,¹⁴ 145°) (Found: C, 67.5; H, 7.6. Calc. for $C_{15}H_{20}O_4$: C, 67.8; H, 7.5%).

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¹⁴ T. Meikle and R. Stevens, *J.C.S. Chem. Comm.*, 1972, 123.