Dimethylallylation Products of Phloroacetophenone; a Convenient One-stage Synthesis of Deoxyhumulones

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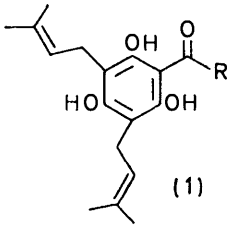
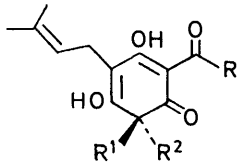
The structures of seven products of the reaction between 2-methylbut-3-en-2-ol and phloroacetophenone, catalysed by boron trifluoride–ether complex, are described; they include the important 2,4,6-trihydroxy-3,5-bis-(3-methylbut-2-enyl)acetophenone (4-deoxyacetohumulone). By a similar reaction the natural hop compounds 4-deoxyhumulone, 4-deoxycohumulone, and 4-deoxyadhumulone are readily synthesised. No 4-deoxyacetohumulone was obtained by reaction of 6-acetyl-2,2,8,8-tetramethyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b*']dipyran-5-ol with lithium in liquid ammonia.

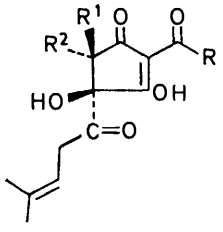
THE deoxyhumulones (I) were first isolated from hops in 1957.[1] Their subsequent association with the lupulones (2) and the more important humulones (3) in growing hops [2] suggested that they might be biogenetic precursors of the latter two series of compounds. Indeed *in vitro* conversions of the compounds are possible, *e.g.* photolysis of colupulone [3] (2; R = Pr^i) affords deoxycohumulone (1; R = Pr^i), and oxidation of



(1)



(2) $R^1 = R^2 = Me_2C{:}CH{\cdot}CH_2$
(3) $R^1 = Me_2C{:}CH{\cdot}CH_2$, $R^2 = OH$



(4) a; $R^1 = Me_2C{:}CH{\cdot}CH_2$, $R^2 = H$
b; $R^1 = H$, $R^2 = Me_2C{:}CH{\cdot}CH_2$

deoxyhumulones (1) by air gives the (racemic) humulones (3), although in relatively low yield.[4] The humulones (3) may be easily rearranged in high yield under laboratory conditions [5,6] (or much less efficiently during brewing) to the intensely bitter isohumulones (4a and b); consequently the deoxyhumulones are key intermediates in the potential production of synthetic humulones and isohumulones.

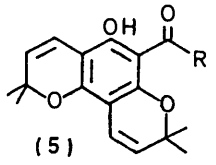
Much attention has been focused on the oxidative reactions of lupulones and humulones since in many cases they have been shown [7–16] to be the origins of new products, several of which are formed during the brewing process or during storage of old hops,[16–19] and some of which are demonstrably bitter.[10,12,15] For these chemical investigations colupulone (2; R = Pr^i) can be obtained relatively easily as a pure crystalline homologue from certain hops [20] but the natural humulones (3) can only be isolated as individual homologues in limited amounts and with difficulty; this fact hinders chemical investigation and analysis of their oxidation products. Similar but greater difficulties apply to the natural deoxyhumulones (1), of which the chemical instability is predictable; oxidation of the aromatic ring [21] and of the dimethylallyl side chains [12] and acid-catalysed or oxidative cyclisation of the latter [13,14] are all reactions which are likely to take place under mild conditions, and since these compounds are only relatively minor constituents of hops their isolation in useful quantities from this source is not a practical possibility. The original synthesis of deoxyhumulones [1,21] (condensation of an acylphloroglucinol with dimethylallyl bromide under basic conditions) gave products of almost completely indiscriminate alkenylation. Consequently the yields of the deoxy-compounds were very low [*e.g.* 2·7% [1c] for deoxycohumulone (1; R = Pr^i)]; moreover their intermediate polarity necessitates tedious separation from the other reaction products.

For the foregoing reasons, a rapid convenient synthesis of the pure deoxyhumulones is highly desirable. Three

[1] W. Riedl and H. Hubner, (*a*) *Chem. Ber.*, 1957, **90**, 2870; (*b*) *Angew Chem.*, 1958, **70**, 343; (*c*) H. Hubner, J. Maier, and W. Riedl, *Z. physiol. Chem.*, 1961, **325**, 224.
[2] (*a*) R. O. V. Lloyd, P. V. R. Shannon, and S. J. Shaw, *J. Inst. Brewing*, 1969, **75**, 32; (*b*) P. V. R. Shannon, R. O. V. Lloyd, and D. M. Cahill, *ibid.*, p. 376.
[3] C. M. Fernandez, *Chem. Comm.*, 1967, 1212.
[4] W. Riedl, *Brauwissenschaft*, 1951, **81**, 85.
[5] L. O. Spetsig, *Acta Chem. Scand.*, 1958, **12**, 592.
[6] D. R. J. Laws and J. A. Elvidge, *J. Chem. Soc.* (*C*), 1971, 2412.
[7] A. H. Cook and G. Harris, *J. Chem. Soc.*, 1950, 1873.
[8] G. A. Howard and J. R. A. Pollock, *J. Chem. Soc.*, 1952, 1902.
[9] G. A. Howard, J. R. A. Pollock, and A. R. Tatchell, *J. Chem. Soc.*, 1955, 174.
[10] D. Wright, *Proc. Chem. Soc.*, 1961, 315; *J. Chem. Soc.*, 1963, 1769.
[11] J. S. Burton, R. Stevens, and J. A. Elvidge, *J. Chem. Soc.*, 1964, 952.
[12] P. R. Ashurst and J. A. Elvidge, *J. Chem. Soc.* (*C*), 1966, 675.
[13] D. M. Cahill and P. V. R. Shannon, *J. Chem. Soc.* (*C*), 1969, 938.
[14] E. Byrne, D. M. Cahill, and P. V. R. Shannon, *J. Chem. Soc.* (*C*), 1970, 1637.
[15] J. P. Regan and J. A. Elvidge, *J. Inst. Brewing*, 1969, **75**, 10.
[16] B. E. Connett and J. A. Elvidge, *J. Chem. Soc.* (*C*), 1968, 1193.
[17] J. S. Burton and R. Stevens, *J. Inst. Brewing*, 1965, **71**, 51.
[18] L. O. Spetsig, M. Steninger, and S. Brohult, European Brewery Conv., Proc. 6th Congr., Copenhagen, 1957, p. 22.
[19] R. O. V. Lloyd, European Brewery Conv., Proc. 8th Congr., Vienna, 1961, p. 112.
[20] R. Stevens, *Chem. Rev.*, 1967, **67**, 1.
[21] W. Riedl, *Chem. Ber.*, 1952, **85**, 692.

synthetic routes were envisaged at the outset of this work: (A) reductive ring-opening of an acylbenzodipyran, (B) direct alkenylation of an acyl phloroglucinol with 2-methylbut-3-en-2-ol, and (C) double Claisen rearrangement of a bis-(1,1-dimethylallyl) ether of an acyl phloroglucinol. We describe here the results of the first two approaches.

The first of these was attractive because the requisite benzodipyran (5), and its linear isomer, were in principle obtainable from the lupulones by acid-catalysed cyclisation [9] and oxidation (*cf.* ref. 22). Birch [23] has shown that reduction of chromens by metal–ammonia can produce *o*-dimethylallyl phenols. However, attempted ring-opening of the synthetic [24] benzodipyran (5; R = Me) with lithium in liquid ammonia affected only one of the



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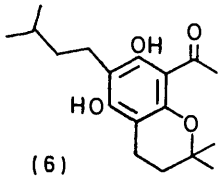

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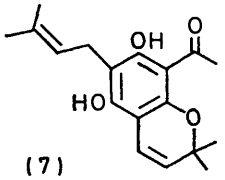


(7)

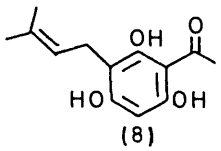
chromen rings, the isopentylchroman (6) with free *para*-hydroxy group (alkaline $\lambda_{max.}$ shift 39·5 nm) being obtained as the major product after hydrogenation as we have reported briefly previously.[25] Repeated attempts at this reaction gave no trace of the deoxyhumulone (I; R = Me) for which a sensitive analysis was possible by g.l.c. comparison with the trimethylsilyl ether [2a] of authentic material. The result was not affected by the use of ethanol as a more powerful proton source, but ultimately we were able to isolate with difficulty a very small amount of the highly unstable primary product, the dimethylallylchromen (7), which was characterised from its n.m.r. spectrum, thus confirming our earlier work.[25] It is possible that the chromen is resistant to further reduction because of its presence as a dianion. However, when the reaction was repeated with the acetate of the benzodipyran (5; R = Me) the products, which were isolated in low yield, still showed no trace, on t.l.c., of the deoxy-compound. The n.m.r. spectra of these products indicated in each case that cleavage of the *O*-acetyl group had taken place besides, as before, single chromen ring-opening; in one instance loss of the acyl side-chain occurred. The use of base-stable, acid-labile, hydroxy-protection (*e.g. O*-methoxymethylation) was not investigated because of the ease of chroman formation.

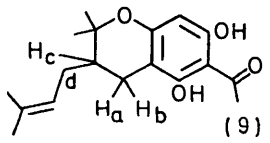
The second, completely synthetic, procedure (B) has the advantage that only one step is required, since the alkylating agent 2-methylbut-3-en-2-ol is commercially available. Precedents exist for its application to mono- and di-hydric phenols [26-29] although the initially formed *ortho*-dimethylallylphenols readily cyclise to chromans.[30] Our preliminary experiments were carried out with phloroacetophenone in dry dioxan at 20° with 2% boron trifluoride–ether complex as catalyst. Under these mild conditions, sequential formation of several compounds was observed during the first 2—3 h and optimum yields of dialkenyl components were achieved after *ca.* 8 h. The products could be rapidly fractionated by sodium carbonate extraction; the carbonate-insoluble materials contained the known [1a] dimethylallylphloroacetophenone (8) and larger quantities of the required 4-deoxyacetohumulone [1a] (I; R = Me), obtained as crystalline specimens only after column chromatography. The less polar 4-deoxyhumulones are the first major products eluted and hence the convenience of the synthesis is enhanced by their relatively easy isolation.

Two barely separated minor products were also separated from this fraction. The u.v. spectrum of the first indicated a blocked *para*-hydroxy-group of the phloroacetophenone nucleus (alkaline $\lambda_{max.}$ shift 9 nm). The 100 MHz n.m.r. spectrum showed two phenolic hydroxy-groups and a dimethylallyl chain *not* directly substituted into the aromatic ring [two singlets at τ 8·28 (3H) and 8·40 (3H) and a triplet at 4·82 (1H) but *no* doublet at τ 6·7]. Two singlets at τ 8·59 (3H) and 8·81 (3H) together with complex multiplets from τ 7·6—8·4 suggested a substituted dihydropyran ring system, and an aromatic proton singlet at τ 4·22 (1H) implied that the dimethylallyl chain was a substituent of the dihydropyran ring. The mass spectrum (M^+ 304) confirmed this by the absence of any ion at $M - 55$ [31] and the presence of intense ions at $M - 69$ and *m/e* 69. Furthermore, the base peak at $M - 123$ suggested that the position of substitution is as shown in (9) since analogous fragmentations of the dihydropyran ring have been demonstrated for closely related compounds.[31] Protons a, b, c, and d were not clearly assignable in the 100 MHz n.m.r. spectrum but deacylation of (9) with aqueous alkali gave the chroman (11) in whose spectrum the absence of of the acetyl signal revealed a double doublet at τ 7·33 (1H, *J* 16 and 5 Hz) which could be assigned to H_a. In the 220 MHz spectrum of (9) (see Figure) a second related double doublet τ 7·84 (1H, *J* 16 and 10 Hz)

[22] G. Cardillo, R. Cricchio, and L. Merlini, *Tetrahedron*, 1968, **24**, 4825.
[23] A. J. Birch, M. Maung, and A. Pelter, *Austral. J. Chem.*, 1969, **22**, 1923.
[24] W. J. G. Donnelly and P. V. R. Shannon, *J.C.S. Perkin I*, 1972, 25.
[25] E. Collins, W. J. G. Donnelly, and P. V. R. Shannon, *Chem. and Ind.*, 1972, 120.
[26] L. Jurd, K. Stevens, and G. Manners, *Tetrahedron Letters*, 1971, **25**, 2275.
[27] F. Bohlmann and K. M. Kleine, *Chem. Ber.*, 1966, **99**, 885.
[28] A. C. Jain and M. K. Zutshi, *Tetrahedron Letters*, 1971, 3179.
[29] A. C. Jain, P. Lal, and T. R. Seshadri, *Tetrahedron*, 1970, **26**, 2631.
[30] R. J. Molyneux and L. Jurd, *Tetrahedron*, 1970, **26**, 4743.
[31] S. J. Shaw and P. V. R. Shannon, *Org. Mass Spectrometry*, 1970, **3**, 941.

assignable to H_b was clearly resolved together with a multiplet (τ 7·71, 2 × H_d). Finally, a partially obscured multiplet centred at τ 8·12 could be assigned to H_c.


(8)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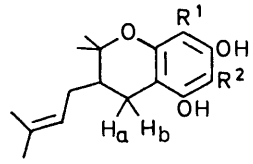
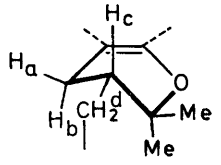

(10) R^1 = Ac, R^2 = H
(11) R^1 = R^2 = H
(12) R^1 = Ac, R^2 = $Me_2C{:}CH{\cdot}CH_2$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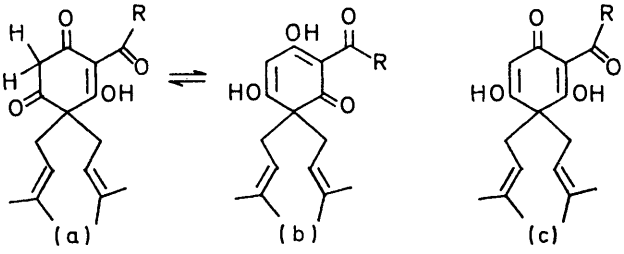
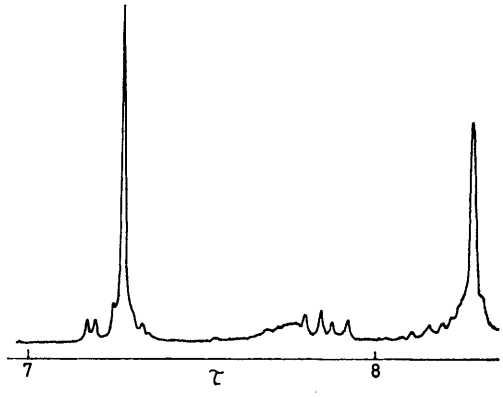

(14)

The spectrum was in accord with the half-chair conformation shown in (13) in which the dimethylallyl chain is equatorial; the pseudo-axial H_b is more shielded and



220 MHz N.m.r. spectrum of the chroman (9)

more strongly coupled to H_c than the pseudo-equatorial H_a.

Structure (9) was the key to the characterisation of other by-products. Thus the isomer (10), separable from (9) by careful chromatography, showed a much stronger $\lambda_{max.}$ shift in alkaline solution (38 nm), and its n.m.r. spectrum contained a sharper and lower field chelated hydroxy-signal. Its spectroscopic properties, which otherwise were very similar to those of (9), were in agreement only with structure (10). We also isolated by chromatography a component of lower polarity showing typical phloroacetophenone u.v. absorption, with an alkaline $\lambda_{max.}$ shift corresponding to a free *para*-hydroxy-group. The compound was unstable, as shown by its recovery in very low yield from chromatographic separations, and showed evidence in its mass spectrum of reaction with oxygen (see later) typical of polyalkylated phloroglucinols. The n.m.r. spectrum was very similar to that of (10) except that additional signals corresponding to a nuclear dimethylallyl group were superimposed; in particular the characteristic doublet at τ 6·7 (2H) corresponding to the benzylic–allylic CH_2 group was evident, as was the absence of any aromatic proton. A sharp low-field singlet τ −5 confirmed structure (12). The mass spectrum showed analogous fragmentations to those for (10) but in addition an abundant ion occurred at M − 55, typical of a nuclear dimethylallyl group.[31] A minor impurity with M^+ 372 + 16 was evident, and explainable by analogy with the ability of 4-deoxyhumulone [4] and colupulone [13] to react readily with air to form products with one extra atom of oxygen; subsequently g.l.c.–mass spectrometry confirmed that this ion was derived from an artefact produced by oxidation in air. Assignment of structure (12) was supported chemically by treating the chroman (10) with an excess of 2-methylbut-3-en-2-ol in the presence of warm aqueous formic acid. T.l.c. showed the conversion (10) ⟶ (12); the latter, however, then reacted further.

The formation of these dimethylallyl chromans under acidic conditions may be rationalised as shown in the Scheme. No evidence for the formation of trisdimethylallylation products had been found on work-up of the reaction mixture, but t.l.c. examination of the crystalline samples of 4-deoxyacetohumulone (1; R = Me) indicated traces of a component whose u.v. spectrum and chromatographic properties were those expected from acetolupulone [32] (2; R = Me). T.l.c. and u.v. comparison with an authentic sample of (2; R = Me) provided by Dr. D. R. J. Laws indicated identity; therefore it seems that very small amounts of acetolupulone are formed in the reaction and cocrystallise with 4-deoxyacetohumulone.

One main product (14; R = Me) was obtained from the sodium carbonate extract. Its n.m.r. spectrum showed evidence of two dimethylallyl side chains attached to the same nuclear carbon atom, a fact confirmed by a predominant loss of 69 a.m.u. from the molecular ion (*m/e* 304) in its mass spectrum. Hydrogenolysis (*cf.* ref. 13) of (14; R = Me) gave the phenol (15), identical with the hydrogenation product from (8), and treatment of (14; R = Me) with refluxing methanolic hydrochloric acid afforded the expected chromans (16; R = Me) and (17; R = Me) [25,33] and the tricyclic dipyran (18; R = Me) [25,34] as the major products. The

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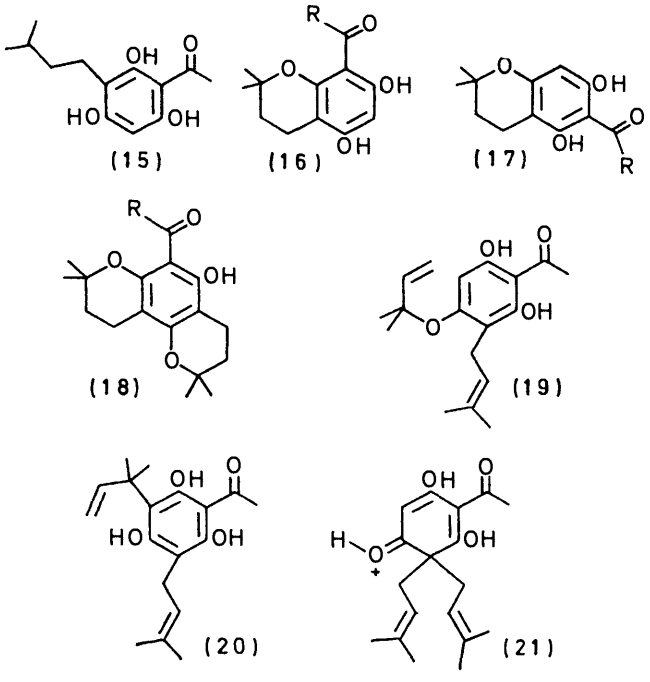
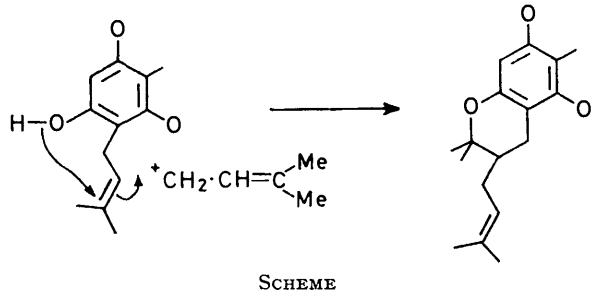
[33] T. Backhouse and A. Robertson, *J. Chem. Soc.*, 1939, 1257.
[34] P. M. Brown, J. S. Burton, and R. Stevens, *Tetrahedron Letters*, 1963, 289.

formation of the benzodipyran (18; R = Me) is interesting because it implies a reverse Claisen rearrangement of (14; R = Me) to the ether (19), which would then



undergo a normal rearrangement to the deoxyhumulone (1; R = Me) before cyclisation to (18). The rearrangement of (19) would be expected to be particularly ready under acidic conditions.[35] Normally, rearrangement of (14; R = Me) should lead to the inverted product (20), which would then cyclise.[36]



SCHEME

The n.m.r. spectrum of (14; R = Me) ($CDCl_3$) showed two broad singlets at τ 6·57 and 4·31, removed by deuterium oxide, whose relative intensity varied with conditions and which can be assigned to the nuclear methylene group of tautomer (14a; R = Me) and the nuclear proton of (14b; R = Me) or (14c; R = Me), respectively; this tautomerism parallels that previously noted [37] for 2,2,4,4-tetramethylcyclohexane-1,3,5-trione.

An alternative dienone tautomer in which the acyl side-chain is flanked by two enolic hydroxy-groups may be excluded for reasons already discussed.[32] The very low field chelated hydroxy-signals of (14; R = Me) showed the expected two sharp peaks of the correct relative intensity for (14a; R = Me) and the dienone form (14b or c; R = Me). A distinction between the latter two forms is not possible but, by analogy with colupulone,[38] (14b; R = Me) would be expected to predominate.

The formation of compound (14; R = Me) is unusual under Friedel–Crafts conditions; no analogous products were reported in the accounts of dimethylallylation of *para*-cresol, resorcinol, pyrogallol,[26] β-resacetophenone,[29] *ortho*-methoxyphloroacetophenone,[28] or hydroquinone.[26,27] The proportions of (1; R = Me) and (14; R = Me) are approximately equal throughout the reaction and so presumably (8) undergoes attack by the dimethylallyl cation at the two possible nuclear positions with equal ease. In the formation of (14; R = Me) the intermediate (21) can (exceptionally) be stabilised by loss of a proton from the *ortho*-hydroxy-group. The latter reaction has similarities to the first stage of electrophilic substitution of 3-alkylindoles under *mildly* acidic conditions in which 3,3-disubstituted 3*H*-indole salts are the intermediates.[39]

The dimethylallylation products for phloroacetophenone are paralleled by its other homologues. Thus the three major homologues of the natural mixture of hop compounds 4-deoxyhumulone [1a] (1; R = Bu^i), 4-deoxycohumulone [1c] (1; R = Pr^i), and 4-deoxyadhumulone [1c] (1; R = Bu^s) were synthesised in *ca.* 20% yields. The reaction in each instance gave an analogous range of by-products to that for 4-deoxyacetohumulone, *e.g.* the trione (14; R = Bu^i), degradation of which gave the chromans (16 and 17; R = Bu^i). The spectroscopic properties of the deoxyhumulones (1; R = Bu^i, Pr^i, or Bu^s) were completely in accord with their structures; the only previous report known to us of the n.m.r. spectrum of any of these compounds, that for deoxycohumulone prepared by photolysis of colupulone,[3] has signals not observed in our spectrum.

We have confirmed that dioxan may be replaced by a variety of solvents including mixed organic–aqueous single phase media, *e.g.* acetone–water, bis-(2-methoxyethyl ether)–water, tetrahydrofuran–water, in which formic acid may be used as the catalyst without significant changes in the products. Higher temperatures are necessary under aqueous conditions. The method has already advantages in yield, speed, and convenience compared with the former synthesis, but may well be developed to optimise the deoxyhumulone yield. Since our results were first briefly published,[25] higher yields have been achieved [40] than those reported here.

[35] U. Svanholm and V. D. Parker, *Chem. Comm.*, 1972, 645.
[36] M. M. Ballantyne, P. H. McCabe, and R. D. H. Murray, *Tetrahedron*, 1971, **27**, 871.
[37] I. R. C. Bick and D. H. S. Horn, *Austral. J. Chem.*, 1965, **18**, 1405.
[38] B. E. Connett and J. A. Elvidge, *J. Chem. Soc.* (*C*), 1969, 340.
[39] A. H. Jackson, B. Naidoo, and P. Smith, *Tetrahedron*, 1968, **24**, 6119.
[40] Dr. J. D. McGuinness, Brewing Industry Research Foundation, personal communication.

EXPERIMENTAL

M.p.s are corrected; n.m.r. spectra were measured for solutions in [^{2}H]chloroform with a Perkin-Elmer R14 instrument at 100 MHz. U.v. spectra were measured for solutions in ethanol (spectroscopic grade) with a Unicam SP 800 spectrophotometer and calibrated with a holmium filter. Silica gel for t.l.c. was Merck Kieselgel G and plates were sprayed with 3% w/v iron(III) chloride in methanol. Column chromatography was carried out on Mallinckrodt silicic acid (100 mesh). Light petroleum refers to a fraction of b.p. 40—60°. G.l.c. was carried out on a 7 ft. 1% F.60 column with a Pye series 104 chromatograph unless stated otherwise. Trimethylsilylation was carried out as previously described.[13]

Routine n.m.r. and mass spectral data for products are given in Supplementary Publication No. SUP 20615 (12 pp.).*

Reduction by Lithium in Liquid Ammonia of the Benzodipyran (5; R = Me).—The benzodipyran (5; R = Me) (300 mg) in liquid ammonia (300 ml; dried by distillation from sodium) was treated in portions, with stirring, with lithium (35 mg). After the disappearance of the blue colour (*ca.* 5 min) ammonium chloride was added, the ammonia was removed by evaporation, and water was added. Acidification followed by extraction with ethyl acetate and drying (Na_2SO_4) gave a brown oil (270 mg).

Hydrogenation.—The oil, which was unstable on silicic acid, was hydrogenated in methanol over palladised charcoal until uptake of hydrogen ceased. G.l.c. of the crude product after trimethylsilylation showed one major peak. A minor peak (*ca.* 5%) was coincident with a trimethylsilylated sample of the chroman (18; R = Me). An authentic sample of 4-deoxyacetohumulone (1; R = Me) was similarly hydrogenated and after trimethylsilylation showed one major peak on g.l.c. which was resolved from the peaks shown by the crude hydrogenation product.

8-*Acetyl*-6-*isopentyl*-2,2-*dimethylchroman*-5,7-*diol* (with W. J. G. Donnelly) (6).—The foregoing crude hydrogenation product was chromatographed on silicic acid. Elution with ether–light petroleum (3 : 7) gave the *chroman* (6) (160 mg), m.p. 137—137·5° (from hexane), $\lambda_{max.}$ 294·5 and 340 nm, $\lambda_{max.}$ (alkaline EtOH) 335 nm (Found: C, 70·1; H, 8·2. $C_{18}H_{26}O_4$ requires C, 70·6; H, 8·6%).

In another experiment the metal–ammonia reduction was carried out on one tenth of the scale and the crude product was submitted to a repeated reduction cycle. G.l.c. of the crude products, after trimethylsilylation but without hydrogenation, showed the absence of 4-deoxyacetohumulone (comparison with trimethylsilylated authentic specimen).

In a third experiment, addition of ethanol (25 mg) to the liquid ammonia likewise showed no change in the g.l.c. of the reaction products.

8-*Acetyl*-2,2-*dimethyl*-6-(3-*methylbut*-2-*enyl*)*chromen*-5,7-*diol* (7).—The benzodipyran (5; R = Me) (30 mg) was reduced as described in the first experiment. Isolation with ether gave an oil (23 mg) which was chromatographed on silicic acid. Elution with ether–light petroleum (*ca.* 2 : 8) afforded the chromendiol (2 mg), which t.l.c. indicated to be pure, $\lambda_{max.}$ 286 nm, $\lambda_{max.}$ (alkaline EtOH) 294 and 342 nm.

Reduction with Lithium in Ammonia of the Acetate of the Benzodipyran (5; R = Me).—The benzodipyran (300 mg) was kept in acetic anhydride (0·66 ml) and dry pyridine (3·5 ml) for 2 days. Normal work-up with ether afforded the acetate as an oil (315 mg). The product (300 mg) in ethanol (5 ml) and liquid ammonia (150 ml) was treated with lithium (40 mg). Work-up as before gave an oil which, on p.l.c. [light petroleum–ethyl acetate (9 : 1)] gave, apart from starting material (4 mg), two isolable fractions: (*a*), 11 mg, $\lambda_{max.}$ 285 nm, $\lambda_{max.}$ (alkaline EtOH) 295 and 340 nm [from spectra, this fraction appeared to be mainly compound (7)], and (*b*), 9 mg, $\lambda_{max.}$ 290 nm, $\lambda_{max.}$ (alkaline EtOH) 300 nm.

Dimethylallylation of Phloroacetophenone.—To a stirred solution of phloroacetophenone (8·4 g) in anhydrous dioxan (120 ml), boron trifluoride–ether complex (freshly distilled; 5 ml) was added dropwise, followed by 2-methylbut-3-en-2-ol (8·6 g) in anhydrous dioxan (120 ml). After stirring at 20° for 9 h, ether (500 ml) was added and the solution was washed with water (3 × 250 ml) and sodium carbonate solution (1%; 2 × 250 ml). The ether layer was dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography of the residual oil on silicic acid (150 g; 36 × 3·5 cm column) gave the crude deoxyacetohumulone, eluted in ether–light petroleum (1 : 9) as an oil (3·2 g) which solidified at 0° overnight. Crystallisation (× 2) from light petroleum (b.p. 30—40°) at 0° gave pure 4-deoxyacetohumulone (1; R = Me) as pale yellow crystals, m.p. 78—79° (lit.,[1a] 78—79°), $\lambda_{max.}$ 292 nm (ε 15,800), $\lambda_{max.}$ (alkaline EtOH) 333 nm (ε 15,000) (Found: C, 71·1; H, 8·35. Calc. for $C_{18}H_{24}O_4$: C, 71·0; H, 7·95).

Elution with ether–light petroleum (70 : 30) gave 2′,4′,6′-*trihydroxy*-3′-(3-*methylbut*-2-*enyl*)*acetophenone* (1·23 g), which after repeated crystallisation from chloroform–light petroleum gave pale yellow crystals, m.p. 171—173° (lit.,[41] 172°), $\lambda_{max.}$ 292 (ε 17,100) nm, $\lambda_{max.}$ (alkaline EtOH) 326 nm. Elution with ether–light petroleum (1 : 2) afforded a fraction (1·3 g) which contained a mixture of the substituted chromans (9) and (10). Rechromatography on silicic acid (50 g) and careful gradient elution with ether gave 6-*acetyl*-2,2-*dimethyl*-3-(3-*methylbut*-2-*enyl*)*chroman*-5,7-*diol* (9) (250 mg); recrystallisation (× 5) gave colourless crystals, m.p. 91—93° (softening at 87°), $\lambda_{max.}$ 292 (ε 19,200) nm, $\lambda_{max.}$ (alkaline EtOH) 302 and 377 nm (Found: C, 71·0; H, 7·9%; *M*, 304·1674. $C_{18}H_{24}O_4$ requires C, 71·0; H, 7·95%: *M*, 304·1674).

The following fractions, after removal of solvent gave the impure isomer (10). Recrystallisation gave 8-*acetyl*-2,2-*dimethyl*-3-(3-*methylbut*-2-*enyl*)*chroman*-5,7-*diol* (10) (150 mg), m.p. 119—120° $\lambda_{max.}$ 292 (ε 17,200) nm, $\lambda_{max.}$ (alkaline EtOH) 330 nm (Found: C, 70·7; H, 7·8%; *M*, 304·1674).

Deacylation of the Chroman (9).—The chroman (9) (75 mg) in aqueous 5% potassium hydroxide (25 ml) was heated under reflux in an atmosphere of nitrogen for 6 h. After cooling and acidification, the mixture was extracted into ether, washed with water, and dried (sodium sulphate). Removal of solvent gave the crude chroman (50 mg). Chromatography on silicic acid [elution with ether–light petroleum (1 : 1)] afforded an oil (33 mg) which on crystallisation from chloroform–light petroleum gave 2,2-*dimethyl*-3-(3-*methylbut*-2-*enyl*)*chroman*-5,7-*diol* (11), m.p. 127—128°, $\lambda_{max.}$ 271 (ε 730) nm, $\lambda_{max.}$ (alkaline EtOH) 334 nm (Found: C, 73·0; H, 8·7. $C_{16}H_{22}O_3$ requires C, 73·25; H, 8·45%).

From the earliest fractions of the main chromatogram was obtained a high R_F component. Removal of solvent afforded 8-*acetyl*-2,2-*dimethyl*-3,6-*bis*-(3-*methylbut*-2-*enyl*)-*chroman*-5,7-*diol* (12) as a yellow oil (130 mg), $\lambda_{max.}$ 294 nm,

* For details of Supplementary Publications see Notice to Authors No. 7 in *J. Chem. Soc.* (*A*), 1970, Issue No. 20.

[41] W. Reidl, J. Nickl, R. H. Risse, and R. Mitteldorf, *Chem. Ber.*, 1956, **89**, 1849.

$\lambda_{max.}$ (alkaline EtOH) 338 nm (Found: *M*, 372·2285. $C_{23}H_{32}O_4$ requires *M*, 372·2300).

The chroman (10) (4·5 mg) in a solution (0·4 ml) of formic acid (0·5 ml), water (0·5 ml), acetone (1 ml), and 2-methylbut-3-en-2-ol (400 mg) was kept at 90°. After 20 min, t.l.c. (3% ethyl acetate in light petroleum) showed a major spot (blue-black with ferric chloride) of the same R_F (0·45) as (12). The reaction mixture, when enriched with (12), gave one main spot. A second spot (R_F 0·4) became the major product in the later stages of the reaction.

2-*Acetyl*-4,4-*bis*-(3-*methylbut*-2-*enyl*)*cyclohexane*-1,3,5-*trione* (14; R = Me).—The sodium carbonate-soluble fraction from the main alkylation reaction, after acidification (2N-hydrochloric acid) and extraction into ether, was chromatographed on silicic acid (150 g). Elution with light petroleum–ether (7 : 3) gave an oil (2·16 g) which solidified on treatment with light petroleum. Recrystallisation from chloroform–light petroleum gave the *trione* (14; R = Me) as crystals (1·6 g), m.p. 104—105°, $\lambda_{max.}$ 273 (ε 6700) and 338 (8000) nm, $\lambda_{max.}$ (alkaline EtOH) 245 and 327 nm (Found: C, 71·0; H, 7·9. $C_{18}H_{24}O_4$ requires C, 71·0; H, 7·95%).

Later fractions gave unchanged phloroacetophenone (1·4 g).

Treatment of the Trione (14; R = Me) *with Acid*.—The trione (600 mg) was heated under reflux in methanol (20 ml) and conc. hydrochloric acid (10 ml) for 1 h. The solution was diluted with water (100 ml) and extracted with ether; the extract was dried (Na_2SO_4) and chromatographed on silicic acid. Gradient elution with ether–light petroleum gave (*a*) 6-acetyl-3,4,9,10-tetrahydro-2,2,8,8-tetramethyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b*']dipyran-5-ol (18; R = Me) (98 mg), m.p. 117—118·5° (lit.,[34] 117—118°; lit.,[24] 118—119°); (*b*) 6-acetyl-2,2-dimethylchroman-5,7-diol (17; R = Me) (104 mg), m.p. 229° (lit.,[24] 230°), $\lambda_{max.}$ 291 (ε 19,100) nm, $\lambda_{max.}$ (alkaline EtOH) 301 and 363 nm; and (*c*) 8-acetyl-2,2-dimethylchroman-5,7-diol (16; R = Me) (98 mg), m.p. 149° (lit.,[24] 150°), $\lambda_{max.}$ 292 (ε 16,100) nm, $\lambda_{max.}$ (alkaline EtOH) 330 nm.

Hydrogenolysis of the Trione (14; R = Me).—The trione (125 mg) was hydrogenated in ethanol (3 ml) over 10% palladised charcoal (70 mg) at atmospheric pressure. After the uptake of 3 mol. equiv. of hydrogen, filtration and removal of solvent afforded the crude phenol (15) (91 mg), which was recrystallised from chloroform–light petroleum to give 2′,4′,6′-trihydroxy-3′-isopentylacetophenone, m.p. 184—185·5° (lit.,[41] 185°), $\lambda_{max.}$ 292 (ε 17,700) nm, $\lambda_{max.}$ (alkaline EtOH) 362 nm. The spectra and m.p. (mixed m.p. 184—185°) were identical with those of the sample (m.p. 184—185°) prepared by hydrogenation of the phenol (8).

2-*Isovaleryl*-4,4-*bis*-(3-*methylbut*-2-*enyl*)*cyclohexane*-1,3,5-*trione* (14; R = Bu^i).—Similar dimethylallylation of phloroisovalerophenone (10 g) and the same work-up procedure as used in the acetyl series afforded (*a*) 4-deoxyhumulone (1; R = Bu^i) (3·97 g), recrystallised from light petroleum (b.p. <40°) to give material (2·17 g), m.p. 83—85° (lit.,[1a] 81—83°), $\lambda_{max.}$ 292 (ε 16,400) nm, $\lambda_{max.}$ (alkaline EtOH) 340 nm (Found: C, 72·4; H, 8·9%; *M*, 346·2144. Calc. for $C_{21}H_{30}O_4$: C, 72·8; H, 8·7%; *M*, 346·2144); (*b*) the *trione* (14; R = Bu^i) (1·82 g), m.p. 105—106° (from chloroform–light petroleum), $\lambda_{max.}$ 273 (ε 6200) and 325 (9300) nm, $\lambda_{max.}$ (alkaline EtOH) 348 nm (Found: C, 72·9; H, 8·7. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%).

Degradation of Compound (14; R = Bu^i) *with Acid*.—Acid degradation of (14; R = Bu^i) (750 mg) as described for (14; R = Me) gave (*a*) 6-isovaleryl-2,2-dimethylchroman-5,7-diol (17; R = Bu^i) (142 mg), m.p. 142° (lit.,[42] 144—145°), $\lambda_{max.}$ 293 (ε 19,500) nm, $\lambda_{max.}$ (alkaline EtOH) 303 nm (Found: C, 69·3; H, 7·9. Calc. for $C_{16}H_{22}O_4$: C, 69·0; H, 8·0%); (*b*) 8-isovaleryl-2,2-dimethylchroman-5,7-diol (16; R = Bu^i) (172 mg), m.p. 136° (lit.,[42] 138°), $\lambda_{max.}$ 293 (ε 17,000) nm, $\lambda_{max.}$ (alkaline EtOH) 333 nm (Found: C, 69·1; H, 7·8%); and (*c*) 6-isovaleryl-3,4,9,10-tetrahydro-2,2,8,8-tetramethyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b*']-dipyran-5-ol (18; R = Bu^i) as an oil [9] (184 mg), $\lambda_{max.}$ 297 nm, $\lambda_{max.}$ (alkaline EtOH) 297 nm.

4-*Deoxycohumulone* (1; R = Pr^i) *and* 4-*Deoxyadhumulone* 1; R = Bu^s).—Dimethylallylation of (*a*) phloroisobutyrophenone (4·9 g) and (*b*) 2,4,6-trihydroxyphenyl-s-butyl ketone (6·1 g) essentially as described for phloroacetophenone gave, respectively, (a) 2,4,6-trihydroxy-3,5-bis-(3-methylbut-2-enyl)phenyl isopropyl ketone (1; R = Pr^i) (1·2 g) as a solid which crystallised from chloroform–light petroleum as pale yellow crystals (900 mg), m.p. 88—90° (lit.,[1c] 88—89°), $\lambda_{max.}$ 293 (ε 16,300) nm, $\lambda_{max.}$ (alkaline EtOH) 336 nm (Found: C, 72·1; H, 8·5. Calc. for $C_{20}H_{28}O_4$: C, 72·25; H, 8·5%), and (*b*) 2,4,6-trihydroxy-3,5-bis-(3-methylbut-2-enyl)phenyl s-butyl ketone (1; R = Bu^s) (1·27 g) as an oil, $\lambda_{max.}$ 294 (ε 13,800) nm, $\lambda_{max.}$ (alkaline EtOH) 335 nm. Treatment of the latter ketone (177 mg) in dry pyridine (2 ml) with benzoyl chloride (redistilled; 2 ml) at 20° gave (after chromatography) the tribenzoate (202 mg), m.p. 127° (lit.,[1c] 127°) (Found: C, 76·4; H, 6·3. Calc. for $C_{42}H_{42}O_7$: C, 76·6; H, 6·4%).

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