Allyl and Prop-2-ynyl Ethers in the Phloroglucinol Series and their Thermal Rearrangements. An Alternative Synthesis of Deoxyhumulone and its Analogues

By **Edward Collins** and **Patrick V. R. Shannon,*** Department of Chemistry. University College, Cardiff

Treatment of phloroacetophenone (2',4',6'-trihydroxyacetophenone) with prop-2-ynyl bromide and potassium carbonate gave 2'-hydroxy-4',6'-bis(prop-2-ynyloxy)acetophenone (3; R = H). 2',4'-dihydroxy-6'-(prop-2-ynyloxy)acetophenone (4; $R^1 = CH_2C{:}CH$. R^2 = H). 8-acetyl-2,3,5,6-tetrahydro-2,5-dimethylenebenzo-[1,2-*b*:3,4-*b*']difuran-7-ol (5). and other minor products including 6'-hydroxy-5'-(prop-2-ynyl)-2',4'-bis(prop-2-ynyloxy)acetophenone (9).

Hydrogenation of (3; R = H) with quinoline–sulphur-poisoned palladium was only partially selective giving 2',4'-bis(allyloxy)-6'-hydroxyacetophenone (2; R^1 = Me. R^2 = H) as the predominant product. Thermal rearrangement of (2; R^1 = Me, R^2 = H) in refluxing *N*-methylpiperazine under nitrogen gave 3'-allyl-4'-allyloxy-2',6'-dihydroxyacetophenone (12) in 55% yield whilst rearrangement in refluxing *NN*-diethylaniline gave the deoxyhumulone analogue. 3',5'-diallyl-2',4',6'-trihydroxyacetophenone (1; R^1 = Me. R^2 = H) in 85% yield.

Attempted etherification of phloroacetophenone with 1,1-dimethylprop-2-ynyl chloride in dry acetone gave no reaction but in the presence of water the major product was 8-acetyl-2,2-dimethylchromen-5,7-diol (13; R = H). Amongst other products were 7-acetyl-2,3-dihydro-3,3-dimethyl-2-methylenebenzo[*b*]furan-4,6-diol (14; R = H). which was transformed by dilute acid to 7-acetyl-2,3-dihydro-2,3,3-trimethylbenzo[*b*]furan-2,4,6-triol (18). 6-acetyl-2,2,8,8-tetramethyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b*']dipyran-5-ol (7). and 8-acetyl-5-(1,1-dimethylprop-2-ynyloxy)-2,2-dimethylchromen-7-ol (20). Similar attempts to etherify 3',5'-diacetylphloroacetophenone gave 6,8-diacetyl-2,2-dimethylchromen-5,7-diol (13; R = Ac) and 5,7-diacetyl-2,3-dihydro-3,3-dimethyl-2-methylenebenzo[*b*]furan-4,6-diol (14; R = Ac).

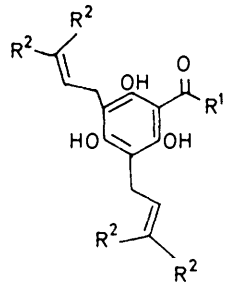
Thermal rearrangement of 2-isovaleryl-4,4-bis-(3-methylbut-2-enyl)cyclohexane-1,3,5-trione (26; R = Me_2CHCH_2) gave a complex mixture including 2,4,6-trihydroxy-3,5-bis-(3-methylbut-2-enyl)isovalerophenone (deoxyhumulone) (1; $R^1 = Me_2CHCH_2$. R^2 = Me) (10%) and 8-isovaleryl-2,2-dimethyl-6-(3-methylbut-2-enyl)chroman-5,7-diol (30).

In the preceding paper in this series [1] we outlined three separate possible approaches to the synthesis of deoxyhumulones (1; R^2 = Me) and described the results of the first two routes which included a convenient one-stage synthesis.

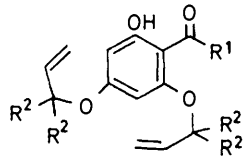
[1] E. Collins and P. V. R. Shannon, *J.C.S. Perkin I*, 1973, 419.

The third approach was *via* a possible double-Claisen rearrangement of appropriate phloroacylphenone bis-(1,1-dimethylallyl) ethers of general type (2; R^2 = Me). This reaction has been used recently [2] to give nuclear-substituted 3,3-dimethylallyl phenolic compounds, but we had no knowledge of its simultaneous double application in the same molecule or for the synthesis of phloroglucinols with three free hydroxy-groups; both these conditions were requirements in our case. The proposed synthesis thus necessitated (a) preparation of a bis-(1,1-methylprop-2-ynyl) ether of the acylphloroglucinol, (b) its partial hydrogenation to the corresponding bis-allylic ether (2; R^2 = Me), and (c) thermal rearrangement. Our first experiments were based on the model compound (2; R^1 = Me, R^2 = H) which was simpler, and which was obtainable, in principle, from commercially available materials.

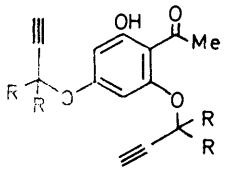
Phloroacetophenone and prop-2-ynyl bromide, heated under reflux in acetone in the presence of potassium



(1)



(2)



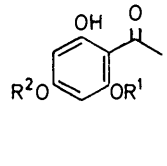
(3)

carbonate and potassium iodide, gave, after two days, a mixture separable by chromatography. The major product was the required 2',4'-bis(prop-2-ynyl ether) (3; R = H), identified from its spectroscopic properties which enabled its discrimination from the isomeric 2',6'-ether. Thus the n.m.r. spectrum contained a single, low-field, chelated hydroxy-signal (τ −3·8) and both the prop-2-ynyl methylene doublets (τ 5·34 and 5·30) and aromatic proton doublets (τ 3·98 and 3·88) showed non-equivalence. The overlapping multiplets of the two acetylenic protons were resolved from the acetyl methyl signal by pyridine, or better, [$^2H_6$]acetone.

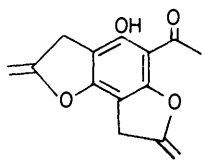
[2] (*a*) R. D. H. Murray, M. M. Ballantyne, and K. P. Mathai, *Tetrahedron*, 1971, **27**, 247; (*b*) R. D. H. Murray, T. C. Hogg, M. M. Ballantyne, and P. H. McCabe, *Tetrahedron Letters*, 1971, 3317; (*c*) J. Hlubucek, E. Ritchie, and W. C. Taylor, *Austral. J. Chem.*, 1971, **24**, 2355.

[3] W. J. G. Donnelly and P. V. R. Shannon, *J.C.S. Perkin I*, 1972, 25.

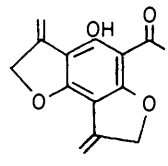
The mono-ether (4; $R^1 = CH_2C{:}CH$, R^2 = H) was obtained in lower yield. Here also the alternative structure (4; R^1 = H, $R^2 = CH_2C{:}CH$) could be ruled out since the n.m.r. spectrum of the product showed *two* distinct low-field hydroxy-signals at τ −3·8sh and 0·6br and an alkali-induced bathochromic shift of 38 nm in its u.v. maximum.



(4)



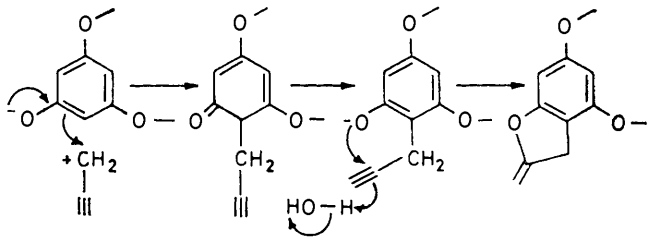
(5)



(6)

The tricyclic compound (5) (M^+ 244, 100%) was also isolated from the reaction mixture. N.m.r. signals due to aromatic and acetylenic protons were absent and the benzylic-allylic methylene signals were a multiplet at τ 6·26 whilst the *gem*-olefinic protons appeared as multiplets at 5·2 and 5·6. A chelated hydroxy-signal at τ −3·1 established the general orientation of the tricyclic system. Evidence for the position of the exocyclic methylene group was found in the chemical shift of the CH_2 groups and in the u.v. spectrum. For the alternative structure (6), derivable in theory by *O*-alkylation of phloroacetophenone followed by cyclisation, (a) the chemical shift of the CH_2 groups would be at lower field (*ca.* τ 5·2) and (b) the u.v. spectrum would not be that of a simple phloroacetophenone as was the case for (5) ($\lambda_{max.}$ 294 nm) but similar to that of the dichromen (7) [3] (see below).

Nucleophilic attack on the acetylenic bond is well known [4] and formation of the tricyclic dihydrofuran derivative (5) from phloroacetophenone can be explained by assuming initial *C*-alkylation of the ring followed by internal nucleophilic attack by the phenolate anion on the acetylenic linkage (see Scheme 1).



SCHEME 1

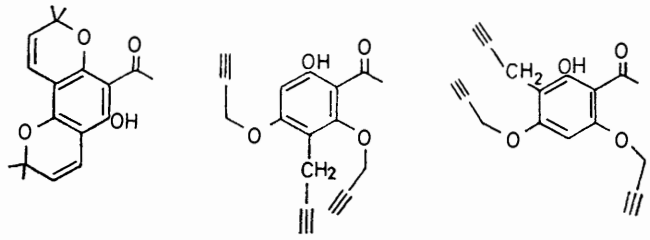
Analogous acid-catalysed [5] and thermal [6] cyclisation of 1,1-dimethylallyl side chains to give trimethyldihydrofuran rings have been reported. A compound (M^+

[4] (*a*) R. A. Raphael, 'Acetylenic Compounds in Organic Synthesis,' Butterworths, London, 1955, p. 37; (*b*) E. R. H. Jones, *Proc. Chem. Soc.*, 1960, 199; (*c*) Sir E. R. H. Jones, G. Lowe, and P. V. R. Shannon, *J. Chem. Soc.* (*C*), 1966, 139.

[5] (*a*) H. D. Locksley, I. Moore, and F. Scheinmann, *J. Chem. Soc.* (*C*), 1966, 2265; (*b*) H. D. Locksley and I. G. Murray, *J. Chem. Soc.* (*C*), 1971, 1332.

[6] M. M. Ballantyne, P. H. McCabe, and R. D. H. Murray, *Tetrahedron*, 1971, **27**, 871.

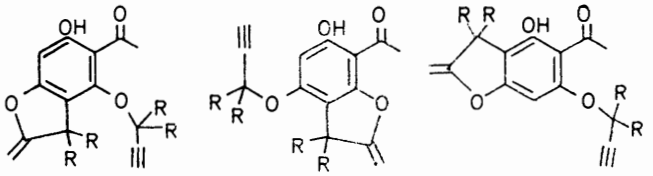
282) containing a *C*-prop-2-ynyl group was also isolated, this feature being recognised through its n.m.r. methylene signal at τ 6·5 (2H, d, J 2·5 Hz). Two *O*-prop-2-ynyl groups were also present and a single free hydroxy-group *ortho* to the acetyl substituent was obvious [τ −4·0 (s)].



(7) (8) (9)

Accordingly this product was either (8) or (9). Application of the modified Gibbs test [7] to this and closely related compounds was inconclusive. However, hydrogenation followed by acid-catalysed cleavage of the acetyl group gave a *C*-n-propyl-bis(n-propyl ether) whose n.m.r. spectrum (in C_6D_6) showed non-equivalence of the two aromatic protons (2d, J 2·2 Hz, at τ 3·79 and 4·06) and the two O·CH_2 groups (2 overlapping t, J 6 Hz, at τ 6·31 and 6·38) thus establishing the structure (9). An interesting feature of the n.m.r. spectrum of (9) was that the acetylenic proton of the *C*-prop-2-ynyl group resonated as a triplet at τ 8·12, almost 1 p.p.m. higher than that of the *O*-prop-2-ynyl groups.

Amongst the minor products from this reaction we isolated a compound whose mass spectrum (M^+ 244) implied the incorporation of two prop-2-ynyl groups. The n.m.r. spectrum indicated one *O*-prop-2-ynyl group and one free *ortho*-hydroxy-group (τ −3·2). By inference, the remaining *O*-prop-2-ynyl group had cyclised, and the occurrence of signals at τ 6·28 (2H, m) and two multiplets at 5·23 and 5·63 again suggested the 2-methylene-2,3-dihydrobenzofuran structure (10a; R = H) or



(a) (b) (c)

(10)

one of its two possible positional isomers (10b or c; R = H). Under mildly acidic conditions this product was converted into a new compound whose n.m.r. and u.v. spectra were in accord with the expected benzofuran (11) (or corresponding positional isomers). In particular the single proton of the furan ring resonated predictably [8] for the β-position at τ 3·61 providing additional confirmation of the orientation of the exocyclic methylene group in the original dihydrofuran.* The structure of this minor product (10a, b, or c; R = H) was not investigated further.

We hoped that partial hydrogenation of the main product (3; R = H) would proceed smoothly to the required di-allyl ether (2; R^1 = Me, R^2 = H) over poisoned catalyst, if not under normal conditions.[9] However, when partial hydrogenation of (3; R = H) was attempted no selective reduction was observed; on stopping the reaction after the uptake of 2 mol. equiv. of hydrogen the products appeared from n.m.r. analysis to contain equal proportions of saturated, allylic, and prop-2-ynyl ethers. The use of quinoline–sulphur-poisoned catalyst [10] resulted in complete inhibition of reduction; very much smaller quantities of poison were more successful but no clear distinction between complete and partial reduction was possible; in the most successful cases a mixture containing 50% of the desired allylic ether was obtained. However, it was assumed that in the projected reduction of the 1,1-dimethylprop-2-ynyl ethers (3; R = Me) the *gem*-dimethyl groups would, by steric effects, enhance the selectivity of the reaction (*cf.* ref. 2), and for our immediate requirements the diallyl ether (2; R^1 = Me, R^2 = H) was obtained more expeditiously from phloroacetophenone and allyl bromide. As with the preparation of the diprop-2-ynyl ether, the reaction gave a complex mixture of products, but in this instance we made no attempt to isolate or to elucidate the structures of the by-products.

For the thermal rearrangement of the ether (2; R^1 = Me, R^2 = H), obtained pure by chromatography, we used the lowest possible temperature, and at 130°, pyrolysis in a sealed tube gave one major product which reached a maximum concentration after 18 h and which, after chromatography, gave pale yellow crystals, M^+ 248. Its n.m.r. spectrum showed evidence of one nuclear *C*-allyl [τ 6·6 (2H, d, J 6 Hz)] and one unrearranged *O*-allyl group. The region τ 3·5—5·0 was a series of complex multiplets due to four olefinic and one aromatic protons whilst two, broad, one-proton singlets at τ −0·05 and −0·55 were consistent with the time-averaged but unequal chelation expected of two hydroxy-groups each *ortho* to the acetyl substituent. This last fact and the $\lambda_{max.}$ in alkaline ethanol (297 nm) led unambiguously to structure (12) and eliminated the two other possible isomeric mono-ether structures. The yield of (12) obtained by the foregoing procedure was 35% but was raised to 55% over a shorter time (5 h) by effecting the rearrangement under nitrogen in refluxing *N*-methylpiperazine. Under the latter conditions the reaction was particularly selective, there being no evidence of any other phenolic product. It was therefore apparent that the *ortho*-*O*-allyl group alone of (2;

* The signal from the remaining benzenoid aromatic proton in the benzofuran (τ 3·54) was not ambiguous in this respect.

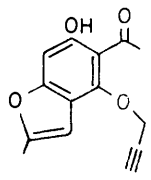
[7] L. Crombie and R. Peace, *J. Chem. Soc.*, 1961, 5445.

[8] J. H. Elvidge and R. G. Foster, *J. Chem. Soc.*, 1964, 981.

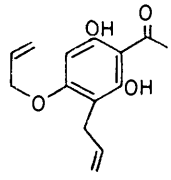
[9] *Cf.* L. Crombie and P. A. Jenkins, *Chem. Comm.*, 1969, 394.

[10] A. I. Vogel, 'Practical Organic Chemistry,' 3rd edn., Longmans, London, 1962, p. 700.

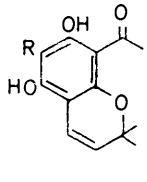
R^1 = Me, R^2 = H) rearranged and that higher temperatures were necessary to bring about rearrangement of both ether groups. In refluxing *NN*-dimethylaniline, or better, *NN*-diethylaniline, formation of (12) took place rapidly, but after only 30 min reaction, a single new product remained which was the desired deoxyhumulone analogue (1; R^1 = Me, R^2 = H). It is noteworthy that the yield of (1; R^1 = Me, R^2 = H)



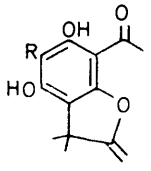
(11)



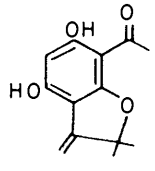
(12)



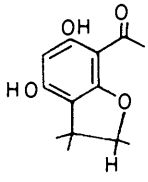
(13)



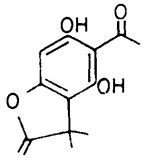
(14)



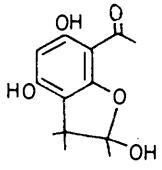
(15)



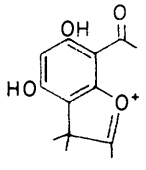
(16)



(17)



(18)



(19)

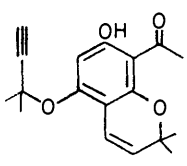
from (2; R^1 = Me, R^2 = H) was 85%, the product being obtained pure without the need for chromatography, but that the purity of the *NN*-diethylaniline very markedly affected the success of the reaction.

1,1-Dimethylprop-2-ynyl chloride was prepared from the corresponding alcohol and etherification of phloroacetophenone was attempted by the procedure described above. No reaction occurred, however, unless water was added when less polar compounds (t.l.c.) were formed. Careful chromatography afforded the major product as bright yellow crystals ($C_{13}H_{14}O_4$). An AB quartet (τ 3·44 and 4·55, J 10 Hz) and a six-proton singlet at τ 8·5 in the n.m.r. spectrum suggested the presence of a 2,2-dimethylchromen system, which was supported by an intense u.v. maximum [$\lambda_{max.}$ 277 nm (ε 23,000)]. Of the two isomeric chromens consistent with these data, structure (13; R = H) was correct as shown by the resonances of the hydroxy-groups in the n.m.r. spectrum and by the hydrogenation of (13; R = H) to the known [1] corresponding chroman.

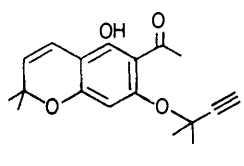
Material giving a second t.l.c. spot was also isolated and on closer examination proved to be a mixture of two structurally closely related compounds. The major (*ca.* 70%) component, obtained pure after fractional crystallisation, was shown to be (14; R = H) from its n.m.r. spectrum [chelated hydroxy-signal at τ −3·3, six-proton singlet at 8·5, and an AB quartet (τ 5·6 and 5·3, J 2·5 Hz) assignable to the exocyclic methylene group]. Although the inverted ring structure (15) is again consistent with the above data, the u.v. spectrum, $\lambda_{max.}$ (ethanol) 287, $\lambda_{max.}$ (alkaline ethanol) 327 nm, indicated that the $=CH_2$ unit was not in conjugation with the aromatic ketone. Additional proof of structure was provided by hydrogenation of (14; R = H) to a compound whose spectra were consistent only with the structural orientation (16); in particular the 2-methine proton appeared as a quartet at τ 5·49. The minor component in the mixture was very probably the isomer (17).

The 2-methylene-dihydrobenzofuran (14; R = H) presumably arises in an analogous way to that for compounds (5) and (10; R = H). Like the latter, (14; R = H) was labile under acid conditions. When an acidification step was used in the work-up, hydration under very mild conditions gave the triol (18), presumably as a result of the stability of the carbo-cation (19), and by analogy with the benzopyrylium system.[11]

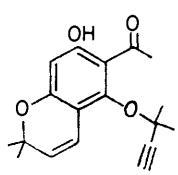
Besides the two main compounds (13 and 14; R = H) a number of minor components of low polarity were formed in the etherification reaction, and the two most prominent were isolated. The first, a yellow oil, proved to be a 1 : 1 mixture of two compounds, one of which was the dichromen (7). This was primarily evident from the n.m.r. spectrum of the mixture but was confirmed by identical mass spectral–g.l.c. correspondence with an authentic specimen.[3] The n.m.r. signals of the second component of this mixture were of the correct chemical shifts and intensities for a phloroacetophenone with one dihydrofuran ring [as in (14; R = H)], one *O*-(1,1-dimethylprop-2-ynyl) group, and one free *ortho*-hydroxy-group. The g.l.c.–mass spectrum confirmed that the molecular weight was 300. Thus only three isomeric structures, (10a, b, or c; R = Me) were possible



(20)



(21)

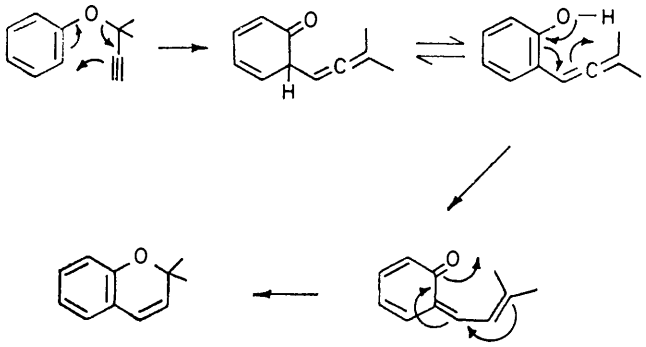


(22)

for this compound and as for the analogous isomers (10a, b, or c; R = H) we were unable to decide from the available evidence which was the correct orientation.

[11] J. A. Joule and S. F. Smith, ' Heterocyclic Chemistry,' Van Nostrand Reinhold Co., London, 1972, p. 167.

A third minor product, obtained as a pure crystalline compound, also exhibited M^+ at 300 a.m.u. Its n.m.r. spectrum contained signals corresponding to a phloroacetophenone derivative with one chelated hydroxy-group, one aromatic proton, a dimethylchromen ring, and an *O*-(1,1-dimethylprop-2-ynyl) group [the last group being evident from a six-proton singlet at τ 8·29,

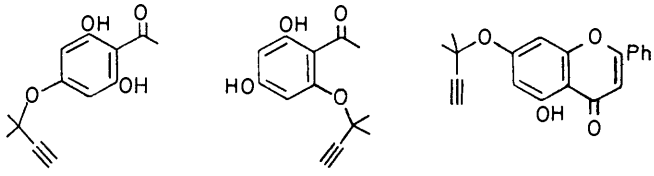


SCHEME 2

a one proton singlet which could be resolved for the acetyl methyl signal on the addition of pyridine, and from the i.r. spectrum $\nu_{max.}$ 3330sh and 2130 cm^{-1}]. As in the case of (10; R = Me), three structures [(20), (21), and (22)] are in agreement with the foregoing spectral data. As is discussed in more detail below 1,1-dimethylprop-2-ynyl ethers of phloroglucinol undergo ready thermal rearrangement yielding 2,2-dimethylchromens (see Scheme 2) and it is to be expected that both (20) and (21) but not (22) should be converted on heating into the dichromen (7). In fact the chromen was shown by t.l.c. to isomerise to (7), (a) on heating in the aqueous acetone etherification medium, or (b) on heating in a sealed vial at 100° and so two structures [(20) and (21)] remained possible. *O*-Acetylation of the chromen by the method of Arnone [12] gave a product with no significant shift in its α-chromen proton n.m.r. signals, thus ruling out structure (21). Further chemical evidence was adduced from the fact that when the previously isolated chromen (13; R = H) was submitted to the etherification reaction three products were detected, one of which corresponded by t.l.c. with the dichromen (7) and a second with the 'unknown' chromen for which structure (20) is therefore proposed with confidence.

The failure to isolate the required diether (3; R = Me) from the reaction in this series was disappointing in view of our success with the bis(prop-2-ynyl ether) (3; R = H) and of similar preparations of mono-(1,1-dimethylprop-2-ynyl) ethers described recently.[2] In our experiments addition of water led to the formation of the chromen (13; R = H) and the dihydrofuran (14; R = H) as the major products; the isolation of the former, and smaller quantities of (20) suggests that an *O*-(1,1-dimethylprop-2-ynyl) group was formed initially but that it then cyclised according to the pathway (Scheme 2) suggested by Zsindely and Schmid [13] and used in chromen synthesis by Ritchie.[14] Our chromen (13; R = H) could arise from either the 4- (23) or the 2- (24) ether of phloroacetophenone. Conditions for such cyclisations are typically to heat in refluxing *NN*-diethylaniline for 8 h.[14] The boiling point of the aqueous acetone reaction mixture was 64°, considerably lower than that of diethylaniline (215°), so that the rearrangement in our case proceeded unusually readily. Efforts to detect the intermediate ethers (23) or (24) during the early stages of the reaction were unsuccessful, no other products being observed before the appearance of (13 and 14; R = H). Ritchie *et al.*[14] have also observed two examples of very ready cyclisation under standard etherification conditions. In the case of the flavone chrysin, reaction at 65° gave 81% of a mixture of chromens and only 11% of the expected ether (25). An increase in yield to 60% for the ether was achieved when the reaction was carried out at 50°. This suggests that a lower temperature in our etherification reaction might result in the discrete formation of the ethers (23) and (24) although in view of the low yield of the chromen (13; R = H) it is unlikely to be a useful procedure for the preparation of the required diether (3; R = Me).

Chromens were not encountered in the preparation of the prop-2-ynyl ethers of phloroacetophenone, nor did cyclisation occur when the diether (3; R = H) was heated in the reaction medium for 48 h. The formation of the dihydrofuran (14; R = H) has already been



(23) (24) (25)

referred to as the probable result of cyclisation of a *C*-alkylated product. It is interesting that neither Murray *et al.*[2] nor Ritchie *et al.*[14] encountered analogous products.

An attempt to prepare a bis-(1,1-dimethylprop-2-ynyl ether) of 3',5'-diacetylphoroglucinol was also made. It was thought that the presence of a second deactivating group might reduce the tendency of any ether formed to cyclise. In the event two products (13 and 14; R = Ac) were isolated in low yield and were analogous to the main products from phloroacetophenone. Attempted etherification of triacetylphloroglucinol resulted only in its slow deacylation to diacetylphloroglucinol and the formation of trace quantities of (13 and 14; R = Ac).

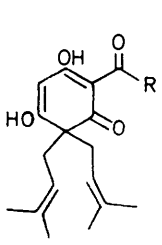
We previously reported [1] the results of heating the synthetic compound (26; R = Me) in methanol–hydrochloric acid; the tetrahydrodipyran (27) was one of the

[12] A. Arnone, G. Cardillo, L. Merlini, and R. Mondelli, *Tetrahedron Letters*, 1967, 4201.

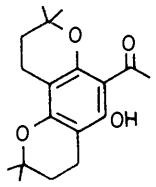
[13] J. Zsindely and H. Schmid, *Helv. Chim. Acta*, 1968, **51**, 1510.

[14] J. Hlubucek, E. Ritchie, and W. C. Taylor, *Austral. J. Chem.*, 1971, **24**, 2347.

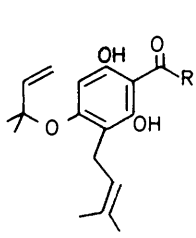
main products. We suggested that (27) was the final compound formed in a rearrangement which might involve as intermediates (a) the ether (28; R = Me) and (b) deoxyacetohumulone (1; $R^1 = R^2 = Me$), the latter having finally cyclised to (27) under the acidic conditions



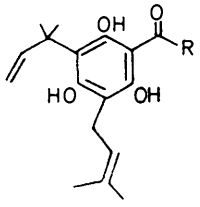
(26)



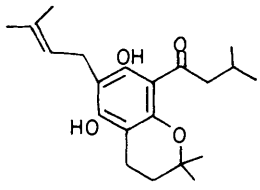
(27)



(28)



(29)



(30)

used. This hypothetical intermediate (28; R = Me) is, of course, entirely analogous to and homologous with the experimentally realised intermediate (12) which we described above, in the successful double Claisen conversion of (2; $R^1 = Me$, $R^2 = H$) into (1; $R^1 = Me$, $R^2 = H$). It was therefore promising to attempt the direct thermal conversion of homologues of type (26), which we had prepared as by-products of our previous synthesis,[1] into the desired natural deoxyhumulones (1; $R^2 = Me$), but under non-acidic conditions. Also, possible, of course, was a Cope rearrangement of (26) to compounds of type (29) and further rearrangement of the latter by the 'abnormal' Claisen pathway.[6,15] On heating (26; R = Bu^i) in a sealed vial at 180° at least six products were formed. One of these was shown, after isolation by preparative t.l.c. to be identical in t.l.c., g.l.c. of its trimethylsilyl ether, and u.v. and n.m.r. spectra with authentic deoxyhumulone (1; $R^1 = Bu^i$, $R^2 = Me$). Isolation of the other components was exceedingly difficult, but one was obtained in a substantially pure state. Its u.v. spectrum, $\lambda_{max.}$ 296, $\lambda_{max.}$ (alkaline ethanol) 342 nm, and n.m.r. spectrum (signals corresponding to one nuclear 3,3-dimethylallyl chain and one 2,2-dimethylchroman ring) together with its mass spectral data (M^+ 346) revealed its structure as (30). Although neither (28) nor (29) (R = Bu^i) were isolated they may have been present in the mixture.

‡ For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1972, Index issue.

The results of these experiments indicate that Claisen-type rearrangements are fruitful synthetic routes to certain deoxyhumulone analogues and that if the requisite 1,1-dimethylallyl ethers could be obtained in good yield the method would be applicable to the deoxyhumulones themselves. Our conditions for etherification of phloroacetophenone or for the thermal rearrangement of (26; R = Bu^i) are not necessarily the optimum ones.

EXPERIMENTAL

General experimental conditions were those described previously.[1] Relevant mass and n.m.r. spectral data were mentioned in the Discussion section; in this section the n.m.r. and mass spectral data of compounds marked with an asterisk (*) and the n.m.r. data of compounds marked with a dagger (†) are listed in Supplementary Publication No. SUP 20939 (15 pp., 1 microfiche).‡

Etherification of Phloroacetophenone with Prop-2-ynyl Bromide.—Anhydrous potassium carbonate (7·0 g) and potassium iodide (6·0 g) were added to dried phloroacetophenone (4·2 g) and prop-2-ynyl bromide (redistilled; 6·2 g) in AnalaR acetone (150 ml). The mixture was gently heated under reflux in an atmosphere of nitrogen, for 48 h. After cooling, the salts were filtered off, and washed with a little warm acetone. The combined filtrate and washings were evaporated to dryness under reduced pressure and the residual solid was chromatographed on silicic acid (150 g; column 38 × 3·5 cm). Ether–light petroleum (1 : 2) eluted *2′-hydroxy-4′,6′-bis(prop-2-ynyloxy)acetophenone* * (3; R = H) (970 mg) which was recrystallised from chloroform–light petroleum (750 mg), m.p. 111°, $\lambda_{max.}$ 282·5 (ε 17,700), 320sh (3400), and 224 (16,000) nm, $\lambda_{max.}$ (alkaline ethanol) 282·5 (9600), 335 (4400), and 233 (14,200) nm, $\nu_{max.}$ 3325, 2140, 1625, and 1602 cm^{-1} (Found: C, 69·0; H, 4·9. $C_{14}H_{12}O_4$ requires C, 68·8; H, 4·95%).

Ether–light petroleum (4 : 1) eluted *2′,4′-dihydroxy-6′-(prop-2-ynyloxy)acetophenone* * (4; $R^1 = CH_2C{:}CH$, $R^2 = H$) (380 mg) which gave crystals (250 mg), from chloroform–light petroleum, m.p. 142—143°, $\lambda_{max.}$ 287·5 (ε 15,500) and 222 (12,000) nm, $\lambda_{max.}$ (alkaline ethanol) 325 (25,000) and 246 (4600) nm (Found: C, 64·2; H, 4·9. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%).

Elution with ether–light petroleum (3 : 2) afforded *6′-hydroxy-5′-(prop-2-ynyl)-2′,4′-bis(prop-2-ynyloxy)acetophenone* * (9) (395 mg) which crystallised from chloroform–light petroleum as light fluffy crystals (255 mg), m.p. 150—151°, $\lambda_{max.}$ 285 (ε 18,200), 223 (16,400), and 320sh (2300) nm, $\lambda_{max.}$ (alkaline ethanol) 285 (9700), 235 (15,400), and 337 (3750) nm, $\nu_{max.}$ 3325, 2125, 1625, and 1603 cm^{-1} (Found: C, 72·6; H, 4·8. $C_{17}H_{14}O_4$ requires C, 72·3; H, 5·0%).

Hydrogenation and Deacetylation of (9).—The above diether (250 mg) was hydrogenated in ethanol (100 ml) over 10% Pd–C (100 mg). (Warming was necessary to dissolve the diether before the addition of catalyst.) The major product was isolated by chromatography on silicic acid as a white solid,† m.p. 78—80° (200 mg). The hydrogenated compound (200 mg) was heated under reflux with methanol–conc. hydrochloric acid (2 : 1). After 3 days a compound of lower R_F was formed which was isolated as an oil † (20 mg) from unchanged starting material (150 mg).

[15] E. N. Marvel, D. R. Anderson, and J. Ong, *J. Org. Chem.*, 1962, **27**, 1109.

The dihydrofuran (10a, b, or c; R = H) was eluted in ether–light petroleum (1 : 4). Recrystallisation of the crude product from chloroform–light petroleum gave the pure compound * (132 mg), m.p. 139·5—142°, $\lambda_{max.}$ 283 (ε 17,500), 340 (3330), 243sh (16,800), and 238 (18,100) nm, $\lambda_{max.}$ (alkaline ethanol) 284 (10,300), 362 (5200), 255sh (13,800), and 242 (16,100) nm, $\nu_{max.}$ 3330, 2140, and 1600—1650 cm^{-1} (Found: C, 68·9; H, 5·05. $C_{14}H_{12}O_4$ requires C, 68·8; H, 4·95%).

The early fractions from the column, eluted with ether–light petroleum (1 : 9), contained 8-*acetyl*-2,3,5,6-*tetrahydro*-2,5-*dimethylenebenzo*[1,2-b:3,4-b′]*difuran*-7-*ol* * (5) (15 mg), m.p. 106—120°. Crystallisation from petroleum ether at −78° gave 5 mg, m.p. 117—124°, $\lambda_{max.}$ 294, 338sh, and 248 nm, $\lambda_{max.}$ (alkaline ethanol) 293, 356, and 260 nm (Found: M^+, 244·0742. $C_{14}H_{12}O_4$ requires M, 244·0736).

Conversion of (10; R = H) *into a Benzofuran.*—Etherification of phloroacetophenone was carried out as described above. After removal of the inorganic material, the acetone solution was poured into N-hydrochloric acid (250 ml). After 10 min the mixture was extracted with ether (2 × 150 ml). T.l.c. examination of the ethereal extract revealed that the material corresponding to (10) was absent, and was replaced by a compound of slightly higher R_F. Column chromatography gave a benzofuran † [(11) or isomer] (200 mg) which on recrystallisation from chloroform–light petroleum had m.p. 163—164°, $\lambda_{max.}$ 240 (ε 24,200), 246sh, 289 (15,500), and 346 (5400) nm, $\lambda_{max.}$ (alkaline ethanol) 249 (21,000), 284 (12,400), and 362 (6600) nm (Found: C, 68·6; H, 4·7. $C_{14}H_{12}O_4$ requires C, 68·8; H, 4·95%).

Hydrogenation of the Bis(prop-2-ynyl Ether) (3; R = H).—*Over palladised charcoal.* (i) The foregoing diether (60 mg) in methanol (5 ml) was hydrogenated over palladised charcoal (30 mg; 10%). Steady uptake of hydrogen (25 ml; *ca.* 4 mol. equiv.) took place over 45 min, indicating complete hydrogenation.

(ii) A similar hydrogenation of (3; R = H) (60 mg) was carried out, but the reaction was stopped after the uptake of 11·5 ml of hydrogen (2 mol. equiv.). The solution was filtered and the solvent evaporated under reduced pressure. The resulting oil consisted of *ca.* equal amounts of prop-2-ynyl, allyl, and propyl ethers (by n.m.r.). In this and subsequent hydrogenation experiments, the proportion of fully, partially, and non-reduced ethers was estimated by means of the integrated n.m.r. signals at τ 5·95—6·15 (OCH_2CH_2-CH_3), 5·35—5·55 ($OCH_2CH{:}CH_2$), and 5·2—5·35 (OCH_2-$C{:}CH$) respectively.

Over poisoned catalysts. (a) The ether (20 mg) in methanol (5 ml) was hydrogenated over palladium on calcium carbonate (10 mg), ' poisoned ' by the addition of quinoline (0·1 ml). Uptake of 7·2 ml of hydrogen (*ca.* 4 mol. equiv.) took place steadily over 50 min, indicating no selectivity in reduction.

(b) With quinoline–sulphur poison. The catalyst poison was prepared as described by Vogel.[10] (i) Hydrogenation of the diether (20 mg) in ethyl acetate (10 ml) over palladium on barium sulphate (5%; 6 mg) poisoned by the addition of quinoline–sulphur (0·05 ml) was attempted. No uptake of hydrogen took place.

(ii) The catalyst poison was diluted 200-fold with ethyl acetate. Hydrogenation of the diether (22 mg) in ethyl acetate (10 ml) over palladium on barium sulphate (9·6 mg; 10%) poisoned by the addition of the diluted poison (0·40 ml) resulted in the uptake of hydrogen (4·0 ml, 2 mol. equiv.) over 35 min after which time the reaction was stopped. N.m.r. examination showed a mixture containing *ca.* 50% of diallyl ether.

(iii) In a similar hydrogenation to (ii), uptake of 4 mol. equiv. of hydrogen, *i.e.* complete hydrogenation, took place over 2 h.

Allylation of Phloroacetophenone.—Phloroacetophenone (4·2 g) was etherified as described above for the preparation of prop-2-ynyl ethers of phloroacetophenone, using allyl bromide (freshly distilled: 6·1 g) in place of prop-2-ynyl bromide. Following similar work-up and chromatographic procedures, the main product (900 mg) was eluted in ether–light petroleum (1 : 4), and gave on recrystallisation from pentane at 0°, crystals of 2′,4′-*bis*(*allyloxy*)-6′-*hydroxyacetophenone* * (2; R^1 = Me, R^2 = H) (600 mg), m.p. 62·5°, $\lambda_{max.}$ 286 (ε 17,900), 226 (15,000), and 320sh (3800) nm, $\lambda_{max.}$ (alkaline ethanol) 286 (10,300), 230, and 335 (3800) nm (Found: C, 67·5; H, 6·4. $C_{14}H_{16}O_4$ requires C, 67·7; H, 6·5%).

Thermal Rearrangement of (2; R^1 = Me, R^2 = H) *in* N-*Methylpiperazine.*—The diether (2; R^1 = Me, R^2 = H) (200 mg) was heated under reflux in *N*-methylpiperazine (10 ml) in an atmosphere of nitrogen for 5 h. On cooling, the solution was added to N-hydrochloric acid (400 ml) and extracted with ether (2 × 100 ml). After drying ($MgSO_4$) and removal of solvent under reduced pressure, an oil (150 mg) was obtained which was chromatographed on silicic acid (20 × 1·5 cm). Elution with ether–light petroleum (2 : 3) afforded 3′-*allyl*-4′-*allyloxy*-2′,6′-*dihydroxyacetophenone* * (12) which crystallised from chloroform–light petroleum as pale yellow crystals (105 mg), m.p. 102—103·5°, $\lambda_{max.}$ 287 (ε 19,200) and 227 (14,000) nm, $\lambda_{max.}$ (alkaline ethanol) 297 (15,800), 376 (4000), and 246 (13,000) nm (Found: C, 67·6; H, 6·3. $C_{14}H_{16}O_4$ requires C, 67·7; H, 6·5%). This product was also formed when (2; R^1 = Me, R^2 = H) (75 mg) was heated in a sealed vial for 13 h at 130°. After chromatography of the resulting dark red oil on silicic acid, (12) (25 mg) was isolated.

Thermal Rearrangement of (2; R^1 = Me, R^2 = H) *in* NN-*Diethylaniline.*—The foregoing diallyl ether (350 mg) was heated under reflux under nitrogen in *NN*-diethylaniline (20 ml; b.p. 215°), for 30 min. The solution was diluted with ether (40 ml) and extracted into sodium hydroxide (0·2M; 20 ml). The aqueous layer was washed with ether (2 × 20 ml), acidified, and extracted with ether (2 × 20 ml). The ether layer was dried ($MgSO_4$), and on evaporation of solvent, an oil (305 mg) was obtained which crystallised overnight at 0°. Recrystallisation from hexane afforded pure 3,5-*diallylphloroacetophenone* * (1; R^1 = Me, R^2 = H), m.p. 67—68°, $\lambda_{max.}$ 292 (ε 17,500), 229 (16,400), and 330 (3000) nm, $\lambda_{max.}$ (alkaline ethanol) 333 (18,000) and 245sh nm (Found: C, 67·75; H, 6·5. $C_{14}H_{16}O_4$ requires C, 67·7; H, 6·5%).

Attempted Etherification of Phloroacetophenone with 1,1-*Dimethylprop*-2-*ynyl Chloride.*—Phloroacetophenone (4·2 g), 1,1-dimethylprop-2-ynyl chloride (5·1 g), potassium carbonate (6 g), and potassium iodide (4 g) were added to a mixture of acetone (200 ml) and water (100 ml). After refluxing under an atmosphere of nitrogen for 20 h, the mixture was added to potassium carbonate solution (1%; 500 ml) and extracted continuously with ether for 10 h. Starting material remained in the aqueous layer. The ether extract was dried ($MgSO_4$) and the solvent evaporated under reduced pressure, affording an oil (4 g) which was chromatographed on silicic acid (125 g; 31 × 3·5 cm).

Ether–light petroleum (1 : 2) eluted 8-*acetyl*-2,2-*dimethyl*-

chromen-5,7-*diol* * (13; R = H) (850 mg), which on crystallisation from chloroform–light petroleum gave brilliant orange crystals, m.p. 135—138° (with extensive decomp.), $\lambda_{max.}$ 277 (ε 23,000), 287sh (20,500), and 269sh (19,000) nm, $\lambda_{max.}$ (alkaline ethanol) 290 (21,000) and 325 (21,000) nm (Found: C, 66·65; H, 6·0. $C_{13}H_{14}O_4$ requires C, 66·65; H, 6·0%).

Ether–light petroleum (1 : 4) eluted a mixture of the dihydrobenzofuran (14; R = H) and (17) (375 mg). Recrystallisation from chloroform–light petroleum afforded the major component 7-*acetyl*-2,3-*dihydro*-3,3-*dimethyl*-2-*methylenebenzo*[b]*furan*-4,6-*diol* * (14; R = H) (185 mg), as crystals, m.p. 196—198°, $\lambda_{max.}$ 287 (ε 18,200), 236 (19,400), and 331 (4800) nm, $\lambda_{max.}$ (alkaline ethanol) 327 (32,000), 240 (13,600), and 248 nm (Found: C, 66·6; H, 5·8. $C_{13}H_{14}O_4$ requires C, 66·65; H, 6·0%).

Ether–light petroleum (1 : 9) eluted 8-*acetyl*-5-(1,1-*dimethylprop*-2-*ynyloxy*)-2,2-*dimethylchromen*-7-*ol* * (20) (75 mg), which crystallised from pentane at −78°, m.p. 72—74°, $\lambda_{max.}$ 279 nm, $\lambda_{max.}$ (alkaline ethanol) 281 nm, $\nu_{max.}$ 3330, 2130, 1645, 1615, and 1590 cm^{-1} (Found: C, 71·8; H, 6·6. $C_{18}H_{20}O_4$ requires C, 72·0; H, 6·7%). Treatment of the chromen (22 mg) with acetic anhydride (0·15 ml) in dry pyridine (1·5 ml) gave after work-up and chromatography the mono-acetate † as an oil, (12 mg).

Ether–light petroleum (*ca.* 1 : 15) eluted an oil (120 mg) which gave one spot on t.l.c., but was a mixture of two components, (a) the benzodipyran (7) [the mass spectrum obtained by g.l.c.–mass spectrometry (3% OV1 column) of the mixture and the other spectroscopic data, were in agreement with those of an authentic [3] sample of (7)], and (b) (10a; R = Me).

Hydrogenation of (13; R = H).—The chromen (13; R = H) (25 mg) in ethanol (10 ml) was hydrogenated over palladised charcoal (10 mg; 10%). After uptake of hydrogen had ceased, the solution was filtered and evaporated under reduced pressure, affording a solid which agreed in t.l.c. behaviour, u.v. and n.m.r. spectra, and m.p. with an authentic sample [1] of 8-acetyl-2,2-dimethylchroman-5,7-diol.

Hydrogenation of (14; R = H).—A similar hydrogenation of (14; R = H) (50 mg) to that described above afforded 7-*acetyl*-2,3-*dihydro*-2,3,3-*trimethylbenzo*[b]*furan*-4,6-*diol* † (16), m.p. 176°, $\lambda_{max.}$ 286 nm, $\lambda_{max.}$ (alkaline ethanol) 327 nm (Found: C, 66·3; H, 6·3%; M^+, 236·1043. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%; M, 236·1049).

Hydration of the Methylenedihydrobenzofuran (14; R = H).—Etherification of phloroacetophenone (4 g) with 1,1-dimethylprop-2-ynyl chloride was carried out in a similar manner to that described above. After 20 h, the solution was cooled, added to water (300 ml), and acidified to pH 0—1 with hydrochloric acid. Following extraction with ether (2 × 150 ml), t.l.c. examination showed that the material corresponding to (14; R = H) had been almost completely transformed to a compound of lower polarity. After drying ($MgSO_4$) and evaporation of the ether, the residual gum (6 g) was submitted to column chromatography on silicic acid (38 × 3·5 cm).

Elution with ether–light petroleum (4 : 1) afforded a solid, which on crystallisation from chloroform–light petroleum gave crystals of 7-*acetyl*-2,3-*dihydro*-2,3,3-*trimethylbenzo*[b]*furan*-2,4,6-*triol* * (18) (200 mg), m.p. 218—220° (decomp.), $\lambda_{max.}$ 287 (ε 19,400), 230 (14,000), and 335 (3200) nm, $\lambda_{max.}$ (alkaline ethanol) 327 (*ca.* 26,000) and 243 (5000) nm (Found: M^+, 252·0998. $C_{13}H_{16}O_5$ requires M, 252·0998).

Cyclisation of (20) *to the Benzodipyran* (7).—The ether (20) (1 mg) was dissolved in the etherification medium [potassium carbonate (100 mg) and potassium iodide (67 mg) in water–acetone (5 ml; 1 : 2)] (0·25 ml), and the mixture was refluxed gently under nitrogen in a microflask (0·5 ml). After 6 h t.l.c. (5% ethyl acetate in light petroleum) showed a very faint spot corresponding to starting material (R_F 0·5), and a strong spot which agreed in R_F (0·75) with the benzodipyran (7).

Pyrolysis of (20) at 100° in a sealed m.p. tube for 40 min followed by t.l.c. also showed formation of (7).

Formation of (20) *from the Chromen* (13; R = H).—The chromen (13; R = H) (20 mg), potassium carbonate (15 mg), potassium iodide (13 mg), and 1,1-dimethylprop-2-ynyl chloride (9 mg) were heated under reflux in water–acetone (1 : 2; 1 ml). After 3 h, t.l.c. (5% ethyl acetate in light petroleum) examination of the reaction showed the production of three new compounds; (a) R_F 0·45, which agreed with authentic (20); (b) R_F 0·65, which agreed with authentic (7); and (c) R_F 0·75.

Attempted Etherification of Diacetylphloroglucinol with 1,1-*Dimethylprop*-2-*ynyl Chloride*.—Diacetylphloroglucinol (2·10 g), 1,1-dimethylprop-2-ynyl chloride (1·03 g), potassium carbonate (1·38 g), and potassium iodide (0·83 g) were heated to reflux in a mixture of acetone (35 ml) and water (15 ml), under an atmosphere of nitrogen. The reaction was monitored by t.l.c. which revealed the slow formation of two compounds of low polarity, both of which appeared to reach maximum concentration after about 3 days. The reaction was stopped after 7 days, and the solution was added to aqueous potassium carbonate solution (150 ml; 1%), followed by continuous extraction with ether for 15 h. The ether extract was dried ($MgSO_4$), evaporated under reduced pressure, and the residual oil was chromatographed on silicic acid (40 g; 18 × 2·5 cm). Elution with ether–light petroleum (1 : 9) first gave 5,7-*diacetyl*-2,3-*dihydro*-3,3-*dimethyl*-2-*methylenebenzo*[b]*furan*-4,6-*diol* * (14; R = Ac) which crystallised from pentane at 0° as bright yellow crystals (88 mg), m.p. 104°, $\lambda_{max.}$ 270 (ε 34,500), 292sh, and 341 (5500) nm, $\lambda_{max.}$ (alkaline ethanol) 293 (*ca.* 23,000), 325sh, and 382 (5000) nm (Found: C, 65·1; H, 5·7. $C_{15}H_{16}O_5$ requires C, 65·2; H, 5·8%).

Eluted in the following fractions was 6,7-diacetyl-5,7-dihydroxy-2,2-dimethylchromen * (13; R = Ac) which crystallised from pentane as yellow crystals (105 mg), m.p. 138° (lit.,[3] 138—139°), $\lambda_{max.}$ 270 (ε 42,000), 287sh, and 368 (4200) nm, $\lambda_{max.}$ (alkaline ethanol) 286 (24,000) nm (Found: C, 65·4; H, 5·8. Calc. for $C_{15}H_{16}O_5$: C, 65·2; H, 5·8%).

Attempted Etherification of Triacetylphloroglucinol with 1,1-*Dimethylprop*-2-*ynyl Chloride*.—Triacetylphloroglucinol (126 mg), 1,1-dimethylprop-2-ynyl chloride (105 mg), potassium carbonate (138 mg), and potassium iodide (83 mg) were heated under reflux in acetone–water (20 ml; 10 ml). After 4 days, t.l.c. showed that extensive deacylation to diacetylphloroglucinol had occurred, and that minor amounts of (13; R = Ac) and (14; R = Ac) had been produced. No spots were observed which might have corresponded to an ether of triacetylphloroglucinol.

Pyrolysis of the Trione (26; R = Bu^i).—(i) The trione (100 mg) was heated in a sealed vial at 170° for 4 h. The mixture was applied to three p.l.c. plates (20 × 20 cm) and developed in ethyl acetate–light petroleum (1 : 4). The band corresponding to deoxyhumulone (1; R^1 = Bu^i, R^2 = Me) in R_F (R_F 0·5) and in colour reaction to $FeCl_3$ spray gave an oil (10 mg), pure by t.l.c., which gave identical u.v. and

n.m.r. spectra with authentic deoxyhumulone (1; R^1 = Bu^i, R^2 = Me). Its trimethylsilyl ether derivatives had identical retention times with that of the authentic compound on g.l.c. (columns: F-60 and OV1).

(ii) After a similar pyrolysis of the trione (26; R = Bu^i) (400 mg), and chromatography on eight p.l.c. plates, two bands (a) R_F 0·4 and (b) R_F 0·7 were isolated; (a) afforded 8-isovaleryl-2,2-dimethyl-6-(3-methylbut-2-enyl)chroman-5,7-diol * (30) as an oil (16 mg), $\lambda_{max.}$ 296 nm, $\lambda_{max.}$ (alkaline ethanol) 342 nm; (b) afforded an impure oil (18 mg).

We thank A. Guinness, Son and Co. (Dublin) Ltd. for financial assistance, and the S.R.C. for assistance in the purchase of the mass spectrometer.

[3/2407 *Received*, 26*th November*, 1973