# Some Aspects of the Oxidation of Deoxyhumulones to Humulones

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The synthesis and comparative reactivity to oxygen of a series of substituted phloroglucinols is used to define the structural patterns associated with the reactivity of deoxyhumulones to oxygen under very mild conditions. The relative reactivity of phloroglucinols bearing unsaturated alkyl side chains as compared with those bearing alkyl groups is investigated by intermolecular and intramolecular competitive experiments with model compounds. The acyldialkyl- and trialkyl-phloroglucinols react readily with oxygen, and we suggest that oxidation of the aromatic ring precedes oxidation of side-chain double bonds in the reaction of the deoxyhumulones with air or oxygen.

RECENTLY [1-6] considerable interest has been shown towards oxidation products of the deoxyhumulones (1), humulones (2), and lupulones (3), all of which occur in the 'soft resin' fraction of mature hops. Deoxyhumulones (1) may be converted inefficiently [7] by air-oxidation *in vitro* into the (racemic) humulones (2);
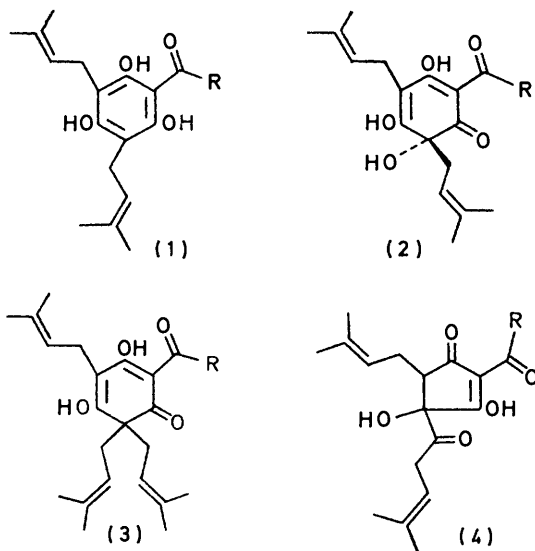
the latter are isomerised [8] to the bitter isohumulones (4) during traditional brewing processes. The lupulones [9] (3) are not involved to a major extent in this process, but they contribute indirectly to some of the bittering power of the hop.

This interest in oxidation stems from causes including: (i) a need to understand the chemical changes accompanying the ageing of stored hops, one important characteristic being a decrease in the humulone content of the hop which is not, however, accompanied by a similar decrease in its bittering power; (ii) the de-

sirability of finding a means of improving the transformation of the lupulones (3) into useful bitter oxidation products; and (iii) any potentially successful chemical synthetic approach to the humulones (2) and consequently the bitter isohumulones (4) requires a high-yield oxidative conversion from the synthetic deoxyhumulones [10] (1) into (2). Typically, the yield of this reaction under chemical conditions does not exceed 30% although it occurs very readily and presumably takes place enzymically in the growing hop cone, giving optically active (−)-humulone (2; R = Bu^i), and so *in vivo* and *in vitro* it is a reaction of central importance. It has however, received little or no systematic study, probably because the deoxyhumulones have proved, until recently,[10] very difficult to obtain in a pure condition.

The known oxidation products of the humulones include such compounds as (5) [1] and (6) [11] and it is significant that in each example oxidation or removal of the original unsaturated side chains has occurred in addition to the ready humulone ⟶ isohumulone ring contraction in (5). By comparison with the deoxyhumulones (1) the saturated analogues (7) and (8) oxidise equally readily in air, but in virtually quantitative yields, to the humulone analogues (9) [12,†] and (10).[13] It might therefore be assumed that reaction of the side-chain double bonds competes with direct oxidation of the aromatic nucleus in the natural products (1) and thus depletes the production of the humulones. This latter oxidation is not confined to the natural deoxyhumulones (1), *e.g.* the synthetic model compound (11) was transformed [14] into the ketone (12). Nonetheless the reaction appears to be very susceptible to the number and type of substituents in the aromatic ring since methylphloroglucinol, phloroacetophenone, and the acylalkylphloroglucinol (13) appear to be indefinitely stable under the same conditions.

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† Shaw and Smith [12] obtained the corresponding humulone analogue (9) by oxidation in the presence of lead(II) acetate as the lead(II) salt. Their yield was not quantitative, presumably owing to the partial solubility of the salt. We have found that slow oxidation in the absence of lead salts leads to quantitative conversion into (9).

[1] P. R. Ashurst and J. A. Elvidge, *J. Chem. Soc. (C),* 1966, 675.

[2] B. E. Connett and J. A. Elvidge, *J. Chem. Soc. (C),* 1968, 1193.

[3] D. M. Cahill and P. V. R. Shannon, *J. Chem. Soc. (C),* 1969, 938.

[4] E. Byrne, D. M. Cahill, and P. V. R. Shannon, *J. Chem. Soc. (C),* 1970, 1637.

[5] J. Coates, J. A. Elvidge, and D. R. J. Laws, *J.C.S. Perkin I,* 1974, 36.

[6] R. Van den Bossche, M. Anteunis, and M. Verzele, *Bull. Soc. chim. belges,* 1974, **83,** 77.

[7] W. Reidl, *Chem. Ber.,* 1952, **85,** 692.

[8] R. Stevens, *Chem. Rev.,* 1967, **67,** 1.

[9] R. Stevens and D. Wright, *J. Chem. Soc.,* 1963, 1763.

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

[11] S. J. Shaw and A. K. Mills, *Amer. Soc. Brewing Chemists Proc.,* 1967, 45.

[12] S. J. Shaw and P. Smith, *J. Chem. Soc. (C),* 1968, 1882.

[13] E. Byrne and S. J. Shaw, *J. Chem. Soc. (C),* 1971, 2810.

[14] W. J. G. Donnelly and P. V. R. Shannon, *J. Chem. Soc. (C),* 1970, 524.

In this paper we describe the effects of changing the benzenoid substituents of deoxyhumulone model compounds on their rates of air-oxidation and also determine the effect of unsaturation in alkyl substituents. Apart from the relevance to a feasible synthesis of bitter isohumulones (4) it is of interest that the orientation of oxygen and alkyl or acyl functions in the latter compounds, after removal of the 2-acyl group, would resemble that in the prostaglandin nucleus, and in the pyrethrin alcohols allethrolone and cinerolone.

In principle, either a radical process, or the intermediacy of singlet oxygen is possible in the *in vitro* oxidation of (1) to (2). For the reasons below it appears likely that, as with other reactive phenols under

(5)   (6)
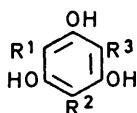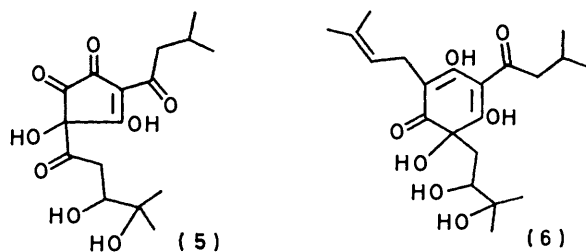
(7) R¹ = R² = Et, R³ = COMe
(8) R¹ = R² = [CH₂]₂CHMe₂, R³ = COCHMe₂
(11) R¹ = R² = [CH₂]₂CHMe₂, R³ = H
(13) R¹ = [CH₂]₂CHMe₂, R² = H, R³ = COMe
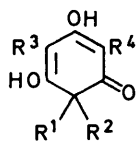
(9) R¹ = OH, R² = R³ = Et, R⁴ = COMe
(10) R¹ = OH, R² = R³ = [CH₂]₂CHMe₂, R⁴ = COCHMe₂
(12) R¹ = OH, R² = R⁴ = [CH₂]₂CHMe₂, R³ = H
(14) R¹ = OOH, R² = R³ = CH₂CH:CMe₂, R⁴ = COR

alkaline conditions,[15] radical species are involved. For the reaction *in vivo*, the presence of light and chlorophyll may implicate a singlet oxygen mechanism, but in either case the reaction probably proceeds *via* a hydroperoxide of type (14). This type of intermediate has never been isolated amongst the naturally occurring compounds although the hydroperoxide (15) was obtained by low temperature oxidation [16] of 2,4-di-t-butylresorcinol and the hydroperoxide (16) of hexahydrocolupulone has been isolated [9] by treatment with

[15] (a) M. S. Karasch and B. S. Joshi, *J. Org. Chem.*, 1957, 22, 1439; (b) J. K. Becconsall, S. Clough, and G. Scott, *Proc. Chem. Soc.*, 1959, 308; (c) F. R. Hewgill and S. L. Lee, *J. Chem. Soc. (C)*, 1968, 1549.
[16] H. Musso and D. Maassen, *Annalen*, 1965, 689, 93.

oxygen at room temperature. Since dialkyl- and acyl-dialkyl-phloroglucinols (*i.e.* deoxyhumulones) are known


(15)   (16)
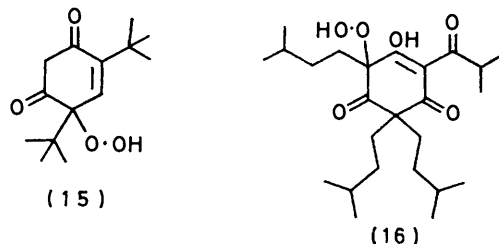
to undergo autoxidation, these compounds were selected for initial examination, and two series, I and II, were prepared.

Deoxyacetohumulone (18) was available from our earlier work [10] and di-isopentenylphloroglucinol (21) was prepared by a similar isopentylation of phloroglucinol. The tetrahydro-compounds (19) and (22) were obtained by catalytic hydrogenation of (18) and (21) respectively. Compounds (17) and (20) were synthesised from phloroglucinol by the route shown in Scheme 1.

These phloroglucinols were tested in pairs; each pair was allowed to compete for oxygen and the relative amounts of each compound were monitored throughout the reaction as follows: (22) *vs.* (20) and (17) *vs.* (19) to investigate the effect of length of hydrocarbon side chain; (21) *vs.* (22) and (18) *vs.* (19) to investigate the effect of unsaturation in the hydrocarbon side chain; and (17) *vs.* (20), (18) *vs.* (21), and (19) *vs.* (22) to compare the susceptibility to oxidation of dialkyl- and acyl-dialkyl-phloroglucinols.

Because autoxidations can be markedly dependent upon solvent impurities and other effects all competitive oxidations were carried out in the same solution: the phenols were distinguished by g.l.c. of their trimethylsilyl ethers. The decrease in peak height relative to an inert
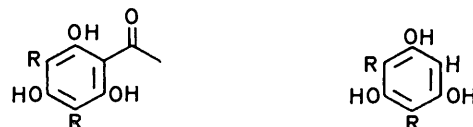
Series I
(17) R = Et
(18) R = CH₂CH:CMe₂
(19) R = [CH₂]₂CHMe₂

Series II
(20) R = Et
(21) R = CH₂CH:CMe₂
(22) R = [CH₂]₂CHMe₂

(23)
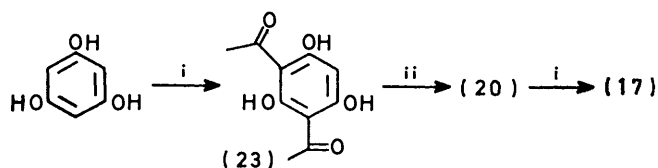
SCHEME 1
Reagents: i, CH₃COCl–AlCl₃; ii Zn–Hg–HCl

internal standard was taken as a measure of the degree of oxidation. In the case of the acyldialkyl-phloroglucinols trimethylsilylation invariably gave rise to

two peaks on g.l.c. It has been suggested [17] that in addition to the expected derivative (24), one involving
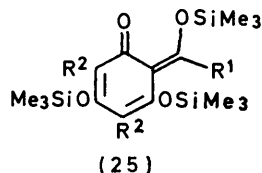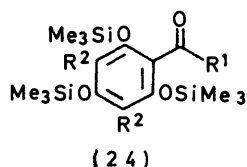
enolisation of the acyl side chain (25) may also be present. The sum of the two peaks was used in our calculations.
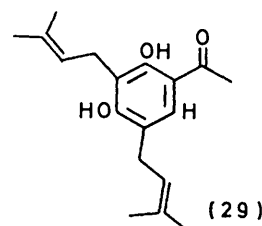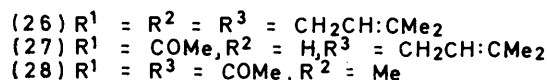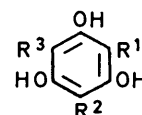
The oxidations took place under normal laboratory lighting conditions, *i.e.* a mixture of diffuse daylight and artificial light. Identical experiments were performed in complete darkness to obtain a semi-quantitative measurement of the effect of light. The results of the first two comparative experiments, compounds (22) *vs.* (20) and (17) *vs.* (19), showed that rate of oxidation was independent of chain length of alkyl substituents. In the next two comparisons a slightly faster oxidation rate was observed for the compound bearing the saturated side chains (22) over the unsaturated analogue (21) in the dialkylphloroglucinols whilst for (18) *vs.* (19), the model deoxyhumulones, the reverse was true. It was concluded therefore that neither the length nor degree of unsaturation of the alkyl side chains had any major effect on the rate of oxidation, but it is noteworthy that in compounds (18) and (19), which most resemble the natural products, the compounds containing unsaturated side chains reacted slightly faster.

The rate of oxidation of the two classes of phloroglucinols (series I or II), when measured independently of the other, differed considerably. The dialkyl compounds (series II) took *ca.* 50 h to oxidise to the extent of 50% whereas the acyldialkyl compounds (series I) (deoxyhumulones) reached this stage in less than 3 h. However, in the inter-series comparisons (20) *vs.* (17), (21) *vs.* (18), and (22) *vs.* (19) the difference in rate was less dramatic. Deoxyhumulone-type compounds were still oxidised faster, but at a rate approximately only twice that of the dialkyl compounds and the time taken for the latter to reach 50% oxidation was *ca.* 7 h. It is apparent, therefore, that deoxyhumulone-type compounds can act as sensitisers in the oxidation of dialkyl-phloroglucinols. This fact was clearer from the experiments in total darkness which showed that the oxidation rates of the deoxyhumulone analogues drop by *ca.* one half. Dialkylphloroglucinols were not oxidised at all during periods of up to 100 h in the dark, but in the presence of deoxyhumulone-type compounds slow oxidation occurred.

These inter-series comparative experiments demonstrate that the introduction of an acyl group into a dialkylphloroglucinol considerably enhances its susceptibility to oxidation under these mild conditions.

[17] C. E. Dalgliesh, A. K. Mills, and S. J. Shaw, *Amer. Soc. Brewing Chemists Proc.*, 1967, 53.

It was therefore of chemical interest to determine the effect of a third hydrocarbon group. Tri-isopentenyl-phloroglucinol (26), isolated in minor yield from the alkenylation of phloroglucinol, was compared with the di-isopentenyl compound (21), and was found to undergo oxidation much faster. In a further comparison, (26) *vs.* deoxyacetohumulone (18), the tri-isopentenyl compound (26) again showed the greater oxidation rate. Both (21) and (18) showed enhanced rates in the presence of the more reactive (26). These results suggest that a hydrocarbon group is more effective in activating the the phloroglucinol system than an acyl group. This conclusion received further support when the relative oxidation rates of di-isopentenylphloroglucinol (21), isopentenylphloroacetophenone (27), and diacetyl-(methyl)phloroglucinol (28) were measured. Only (21) was significantly oxidised. The observed decrease in concentrations of the phenols was due only to an oxidative process since when deoxyacetohumulone (18) was subjected to the same conditions, but in the absence of oxygen, no change in its concentration was evident after 24 h. More than 90% reaction had occurred under an oxygen atmosphere.

(26) R^1 = R^2 = R^3 = $CH_2CH:CMe_2$
(27) R^1 = $COMe, R^2$ = H, R^3 = $CH_2CH:CMe_2$
(28) R^1 = R^3 = $COMe, R^2$ = Me

(29)

Finally the effect of phenolic hydroxy-groups was examined. Deoxyacetohumulone (18) was compared with 3,5-di-isopentenyl-β-resacetophenone [18] (29). Like the compounds (27) and (28), (29) was not oxidised under our conditions whilst the deoxyhumulone (18) was consumed as previously. For the above experiment, g.l.c. analysis was not possible since the trimethylsilyl ethers of compounds (18) and (29) were inseparable. Instead we used high pressure liquid chromatography (h.p.l.c.) [19] of the phenol mixture and detection of the components by their u.v. absorption at 280 nm, using as an internal standard an inert phenol which had previously been tested on g.l.c. against the original internal standard.

The following tentative conclusions can be drawn

[18] A. C. Jain, P. Lal, and T. R. Seshadri, *Tetrahedron*, 1970, **26**, 2631.

[19] J. N. Done, G. J. Kennedy, and J. H. Knox, *Nature*, 1972, **237**, 77.

from the above experiments: (i) Three nuclear substitution patterns of the phloroglucinol ring render molecules susceptible to ready air-oxidation under the conditions of the deoxyhumulone–humulone conversion, *viz.* type A three hydrocarbon groups, type B two hydrocarbon and one acyl group, and type C two hydrocarbon groups. (ii) The rate of oxidation is type A > type B > type C. This, and other evidence shows that introduction of an acyl group enhances the rate of oxidation as does a hydrocarbon group, but the latter more effectively. (iii) Oxidation of type B compounds can proceed in the dark although at a slower rate than when illuminated. (iv) The presence of type A compounds accelerates the oxidation of types B and C. Type B compounds have a similar effect on type C compounds. (v) The chain-length and unsaturation (β to the ring) of hydrocarbon substituents does not greatly affect the oxidation rate although there is a relatively slight preference for attack at an alkenyl substituent in the acyldialkylphloroglucinols. Secondary or tertiary alkyl substituents were not investigated.

Although triplet oxygen is generally regarded [20,21] as too unreactive to initiate an autoxidative process, we believe that this may occur in the case of the deoxyhumulones. The initial removal of a phenolic hydrogen would produce a highly resonance-stabilised phenoxyl radical which could lead to a hydroperoxyl radical, *e.g.* from (14). In support of this are the observations (*a*) that the deoxyhumulones react with oxygen in the dark, (*b*) that the reactions are catalysed by light, and (*c*) that a solution of deoxyhumulone in ether gave a broad weak e.s.r. signal * ($g = 2$) which faded rapidly before more informative measurements could be made. However, ionic mechanisms cannot be excluded.†

Oxidation of the deoxyhumulone-type molecules was accelerated by light. These compounds exhibit absorbtion maxima at *ca.* 290 (ε 15,000—20,000) and 330—370 nm (3000—5000) and the longer wavelength absorbtion overlaps the emission spectrum of the light source used ($\geqslant$350 nm) in the experiments; accordingly the enhanced oxidation rate is understandable. The dialkylphloroglucinols which exhibit $\lambda_{max.}$ *ca.* 280 nm (ε *ca.* 800) would not normally be expected to absorb light but their enhanced reactivity may be due to trace amounts of tautomers such as (30) (calculated [22] $\lambda_{max.}$ 390 nm).

Two further experiments were carried out to determine the influence of saturated and unsaturated side chains on the oxidation rate of the acyldialkylphloroglucinols. A deoxyhumulone-type compound with non-identical side chains, isopentyl(methyl)phloroacetophenone (31) was synthesised as outlined in Scheme 2. Two humulone-type compounds (32) and (33) are derivable by nuclear oxidation of (31), corresponding to

* We are indebted to Dr. J. C. Evans for running the e.s.r. spectrum.

† We thank a referee for emphasising this point.

[20] J. March, 'Advanced Organic Chemistry: Reaction Mechanisms and Structure,' McGraw-Hill Book Company, New York, p. 544.

oxidation at the two non-equivalent ring sites. If the conclusion (v) above is correct, compounds (32) and (33) should be *initially* formed in approximately equal amounts. Oxidation was carried out by passing a stream of oxygen through a methanolic solution of the freshly crystallised phenol (31) containing lead(II) acetate. The purpose of the latter was to precipitate the 'humulones' (32) and (33) rapidly and selectively as their lead salts and thus to avoid complications resulting from their further oxidation, in particular at the double bonds in the side chains. It was anticipated that the ratio of (32) to (33) could be determined from the n.m.r. spectrum of the mixture obtained by regeneration from the lead salts, thus eliminating errors incurred by physical separation. This was the case
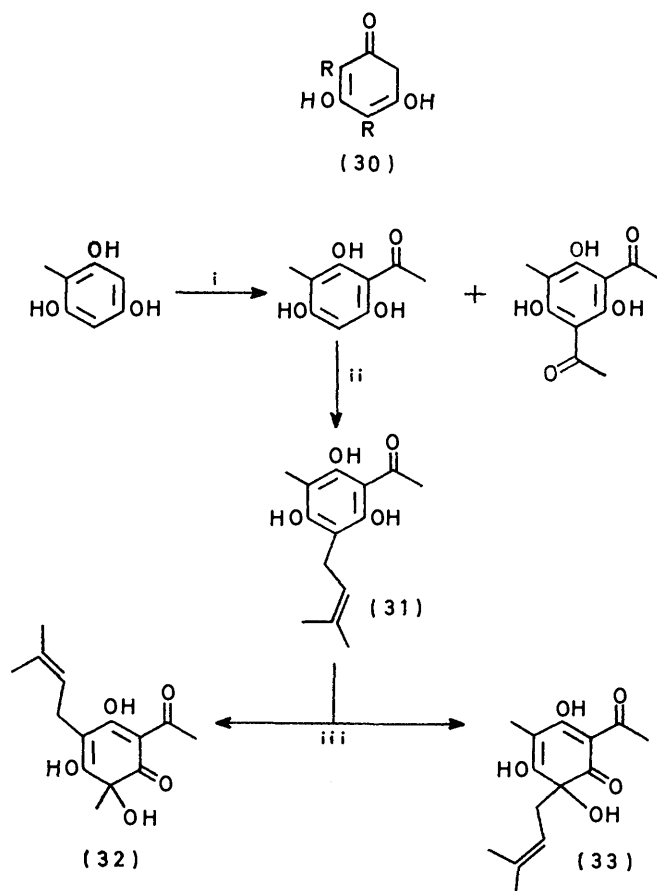
SCHEME 2

Reagents: i, CH_3COCl; ii, $CH_2{:}CH{\cdot}CMe_2OH{-}BF_3,Et_2O$;
iii, $O_2{-}MeOH{-}Pb(OAc)_2$

as shown in the Figure where salient regions of the spectrum of (32) and (33) are reproduced. The assignments were largely predictable by analogy with known compounds, but were confirmed by the subsequent isolation of substantially pure specimens of each isomer by preparative t.l.c. The proportions of (32) and

[21] P. Sykes, 'The Search for Organic Reaction Pathways,' Longman, London, 1972, p. 92.

[22] A. I. Scott, 'Interpretation of the Ultraviolet Spectra of Natural Products,' Pergamon Press, Oxford, 1964, p. 58.

(33) were best estimated by comparing the areas of the low-field hydroxy-signals, but the results were also confirmed by estimation of the high-field signals. The ratio of (32) to (33) was 75 : 100. The experiment was repeated with a second synthetic sample of (31) when the ratio of ' humulones ' was found to be 73 : 100. These figures are consistent with the earlier finding based on intermolecular competition and again indicate a slight preference for attack by oxygen at the point of attachment of an alkenyl rather than an alkyl side chain.

The most unexpected of the conclusions from these preliminary experiments was the relative independence of the oxidation rates on the nature of the primary hydrocarbon substituents. We had anticipated that the deoxyhumulone-type phenols bearing isopentenyl side chains might undergo two distinct, simultaneous oxidative processes: (a) at the six membered ring
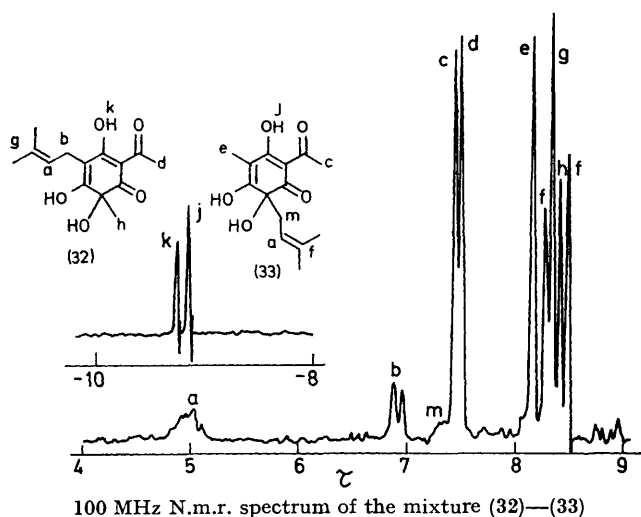
100 MHz N.m.r. spectrum of the mixture (32)—(33)

nucleus; and (b) at the unsaturated linkages in the side-chain. Since the second process is precluded in compounds with saturated side chains, their rate of oxidation was expected to be slower. The failure to detect a major difference suggests that ring oxidation in the natural deoxyhumulones is the faster of the two processes so that ' humulone ' formation effectively precedes any extensive epoxidation leading only to compounds of types (5) and (6) which have first lost the aromatic ring system.

The demonstration by intramolecular competition that the relative yield of ' humulones ' (32) and (33) from the model deoxyhumulone (31) follows the relative rates established by intramolecular competition supports this view. The more general criteria for reactivity which have emerged from this work suggest that the acyldialkyl trisubstituted phloroglucinol system has a rather selective reactivity to oxygen at room temperature which enables the deoxyhumulone —→ humulone reaction to take place under the mild conditions observed.

²³ E. Collins and P. V. R. Shannon, *J.C.S. Perkin I*, 1974, 944.
²⁴ F. M. Dean and A. Robertson, *J. Chem. Soc.*, 1953, 1241.

EXPERIMENTAL

For general experimental conditions see the previous paper [23] in this series. Diacetylphloroglucinol, m.p. 168° (lit.,[24] 168°), triacetylphloroglucinol, m.p. 155—156° (lit.,[24] 156°), diethylphloroglucinol, m.p. 110—112° (lit.,[25] 110—112°), diacetyl(methyl)phloroglucinol, m.p. 168—170° (lit.,[26] 170°), and methylphloroacetophenone, m.p. 207° (lit.,[27] 207°) were synthesised by standard methods.

Diethylphloroacetophenone (17).—Aluminium chloride (1·1 g) was dissolved in portions in a solution of diethylphloroglucinol (1·21 g) in nitrobenzene (25 ml), and then acetyl chloride (0·48 ml) was added. After 3 days the reaction was stopped, and a similar work-up to that described previously for diacetylphloroglucinol and chromatography on silicic acid (35 × 2·5 cm), eluting with ether–light petroleum (1 : 9) gave diethylphloroacetophenone (17) (410 mg) which on recrystallisation from chloroform–light petroleum had m.p. 106—109° (lit.,[12] 102—105°) (this m.p. was determined on a Kofler hot-stage apparatus, which gave erratic results. Some oxidation to a humulone was evident immediately after the m.p. determination), $\lambda_{max.}$ 293 (ε 17,400) and 340 nm (3000), $\lambda_{max.}$ (alkaline EtOH) 350 nm, τ 8·85 (6H, t, J 7·5 Hz, 2 × CH₂CH_3), 7·42 (partially obscured q, J 7·5 Hz, 2 × ArCH_2), 7·32 (s, COCH_3), 4·50 (1H, s, OH), 0·35br (2H, s, 2 × chelated OH), m/e 224 (M^+, 30%), 209 (100), and 191 (15).

Bis- (21) *and Tris-*(3-*methylbut-2-enyl*)*phloroglucinol* (26). —Dried phloroglucinol (6·3 g) was dissolved in dry dioxan (250 ml). Boron trifluoride–ether complex (5·0 ml) was added dropwise with stirring, followed by 2-methylbut-3-en-2-ol (8·6 g). The solution was maintained at 50° for 6 h, and then cooled to 20° and ether (500 ml) was added. After washing with water (4 × 300 ml) the ethereal solution was dried (MgSO₄) and the solvent removed under reduced pressure to give an oil which was chromatographed on silicic acid (40 × 3·5 cm).

Elution with ether–light petroleum (2 : 8) gave bis-(3-methylbut-2-enyl)phloroglucinol (21) (3·5 g), $\lambda_{max.}$ 280 nm, $\lambda_{max.}$ (alkaline EtOH) 267, 289, and 366 nm, τ 8·28, 8·22 (12H, 2s, 4 × CH₃), 6·69 (4H, d, J 7 Hz, 2 × CH₂), 4·81 (5H; t, J 7 Hz, 2 × CH₂=CH, and br s, 3 × OH), and 4·10 (1H, s, ArH). The *triacetate*, prepared by treatment of (21) (250 mg) with acetic anhydride (0·66 ml) in dry pyridine (3·5 ml) for 3 days, had m.p. 63° (Found: C, 67·9; H, 7·3. C₂₂H₂₈O₆ requires C, 68·0; H, 7·3%).

Ether–light petroleum (1 : 9) eluted tris-(3-methylbut-2-enyl)phloroglucinol (26) (1·51 g), τ 8·25, 8·18 (18H, 2s, 6 × Me), 6·65 (6H, d, J 7 Hz, 3 × CH₂), 4·77 (6H; t, J 7 Hz, 3 × =CH, and br s, 3 × OH). Its instability precluded analysis; the triacetate was an oil.

Tetrahydrodeoxyacetohumulone (19).—Deoxyacetohumulone (18) (1·5 g), m.p. 78—79°, prepared as described above, was hydrogenated over palladium on charcoal (10%; 250 mg) in ethanol (75 ml). After uptake of hydrogen had ceased, filtration, followed by evaporation of the solvent, afforded tetrahydrodeoxyacetohumulone (2',4',6'-trihydroxy-3',5'-di-isopentylacetophenone) (19), $\lambda_{max.}$ 294 (ε 15,400) and 341 nm (3800), $\lambda_{max.}$ (alkaline EtOH) 337 nm (ε 14,800), τ 9·03 (12H, d, J 6 Hz, 2 × CHMe₂), 8·2—8·9 (6H, m, 2 × CH_2CHMe₂), 7·45 (partially obscured t, J 8 Hz,

²⁵ W. Gruber and F. Traub, *Monatsh.*, 1947, **77**, 414.
²⁶ F. M. Dean, C. A. Evans, T. Francis, and A. Robertson, *J. Chem. Soc.*, 1957, 1577.
²⁷ W. Riedl, J. Nickl, K. H. Risse, and R. Mitteldorf, *Chem. Ber.*, 1956, **89**, 1849.

2 × ArCH$_2$), 7·32 (s, COCH$_3$), 4·55br (1H, s, non-chelated OH), and 0·35br (2H, s, 2 × chelated OH), m/e 308 (M^+, 21%), 265 (8), 251 (100), 195 (16), and 193 (10) (Found: M^+, 308·1987. C$_{18}$H$_{28}$O$_4$ requires M, 308·1987).

Di-isopentylphloroglucinol (22).—Bis-(3-methylbut-2-enyl)phloroglucinol (21) was hydrogenated over palladium on charcoal, as described for the preparation of (19) above, and gave di-isopentylphloroglucinol as an oil (lit.,[14] oil), $\lambda_{max.}$ 277 nm, τ 9·07 (12H, d, J 6 Hz, 4 × CH$_3$), 8·25—8·8 (6H, m, 2 × CH_2CHMe$_2$), 7·48 (4H, t, J 8 Hz, 2 × ArCH_2), 5·25br (2—3H, s, OH), and 4·15 (1H, s, ArH).

2′,4′,6′-Trihydroxy-3′-methyl-5′-(3-methylbut-2-enyl)acetophenone (31).—A stirred solution of methylphloroacetophenone (5·46 g) in dry dioxan (300 ml) was treated, dropwise, with boron trifluoride–ether complex (6·0 ml) and 2-methylbut-3-en-2-ol (2·6 g). After 9 h, ether (700 ml) was added, and the solution was washed with water (3 × 500 ml). The ether layer was dried (MgSO$_4$) and removal of the solvent under reduced pressure gave an oil which was chromatographed on silicic acid (40 × 3·5 cm). Elution with ether–light petroleum (1 : 2) gave crude (31) (2·2 g) which on crystallisation from chloroform–light petroleum gave the pure *phloroacetophenone* (31) (1·2 g), m.p. 115—117°, $\lambda_{max.}$ 293 (ε 17,500) and 340 nm (ε 3300), $\lambda_{max.}$ (alkaline EtOH) 338 nm, τ 8·17, 8·22 (6H, 2s, =CMe$_2$), 7·96 (3H, s, ArCH$_3$), 7·33 (3H, s, COCH$_3$), 6·63 (2H, d, J 6·5 Hz, CH$_2$), 4·80 (1H, t, J 6·5 Hz, CH$_2$CH=), 4·00 (1H, s, OH), and 0·15br and 0·05br (2H, 2s, 2 × chelated OH), m/e 250 (M^+, 49%), 235 (18), 209 (14), 207 (19), 195 (100), 179 (36), and 167 (13) (Found: C, 67·2; H, 7·25; C$_{14}$H$_{18}$O$_4$ requires C, 67·2; H, 7·25%).

Oxidations.—General procedure for comparative oxidations. The compounds to be tested were weighed into a cylindrical glass vial (15 ml; 7·5 × 1·6 cm); 15—20 mg of deoxyhumulone-type compounds and tri-isopentenylphloroglucinol was taken, and 10—15 mg of other phloroglucinols. A hydrocarbon (6 mg) which was resolved on g.l.c. from the trimethylsilyl ethers of the compounds being tested was then added. In the majority of cases nonadecane was suitable but eicosane was sometimes preferable. The mixture was dissolved in ether–light petroleum 1 : 1 (6 ml) and 0·5 ml was immediately taken for trimethylsilylation and g.l.c. Half the remaining sample was transferred to a second similar vial, a glass-covered magnet was added to each, the headspaces above the solutions were flushed with oxygen, and the vials were stopped with a polythene cap. The solutions in both vials were then stirred magnetically at a rate which gave as smooth a vortex as possible which reached the bottom of the solution. One vial was illuminated throughout by daylight and also by a desk lamp (the bulb in the lamp had maximum emission at 925 nm and no significant emission below 350 nm *). The second vial was kept in complete darkness. Aliquot portions (0·5 ml) were withdrawn from each vial at suitable intervals into a small vial and the solvent was evaporated under a jet of nitrogen. Trimethylsilylation was achieved by dissolving the residue in dimethylformamide (0·25 ml), adding hexamethyldisilazane (0·25 ml), and incubating at 50° for 30 min. A 1 μl sample was then taken for g.l.c. Quantitative estimation of the progress of the oxidation was made by measuring the peak heights

* Data kindly supplied by Crompton Parkinson Ltd., Guiseley, Leeds.

† For details of Supplementary Publications, see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1973, Index issue.

of the substrates relative to the unaffected hydrocarbon standard. With deoxyhumulone-type compounds the sum of the peak heights of the two peaks obtained was taken, and the quantities of phenols present were estimated from previously obtained calibration curves, and were of such a magnitude as to make quantitative estimation corresponding to more than 80% oxidation unreliable (with the amounts taken).

Results. The results of the comparative oxidations mentioned in the Discussion section are tabulated in Supplementary Publication No. SUP 21161 (5 pp.).†

Acyldialkylphloroglucinol vs. *acyldialkylresorcinol*. This comparison was carried out with freshly crystallised 4-deoxyacetohumulone (18) (6·4 mg) and 3,5-bis-(3-methylbut-2-enyl)-β-resacetophenone (29) (5·1 mg), m.p. 108° (lit.,[18] 109—110°) and 5-(3-methylbut-2-enyl)resacetophenone as an internal standard (previously shown to be unchanged relative to the g.l.c. standard over an oxygenation period of 22 h) in ether–light petroleum (b.p. 40—60°) (1 : 1; 5 ml). The reaction mixture was treated in the same way as for the g.l.c. monitored runs except that samples (several μl), taken at regular intervals, were injected directly onto a 6 ft × ⅛ in stainless steel column packed with Corasil II (silica 37—50 nm) and eluted with 10% ethyl acetate–light petoleum at 1 ml min^{-1} delivered by a Waters Associates chromatography pump.

The eluate was monitored by a Cecil Instruments CE 272 linear read-out u.v. spectrophotometer set at 280 nm, and the results are in Supplementary Publication No. SUP 21161.

Oxidation of 3′-Methyl-5′-(3-methylbut-2-enyl)phloroacetophenone (31).—(a) The phloroacetophenone (31) (1·00 g, 4·0 mmol) and lead(II) acetate (1·06 g, 4·0 × 0·7 mmol) were dissolved in methanol (20 ml), and a slow stream of oxygen was passed through the solution. After 2 days the precipitate was collected by centrifugation, washed with a little methanol, and dried under reduced pressure at 20° (740 mg). The supernatant liquid was oxygenated for a further 5 days, during which time additional precipitation (60 mg) occurred. Quantitative t.l.c. on the supernatant liquid at this stage indicated that *ca.* 70 mg starting material and *ca.* 110 mg unprecipitated 'humulones' were present.

The salt (150 mg) was shaken with hydrochloric acid (50 ml; 0·5M) and ether (60 ml). The ether layer was separated, washed with saturated brine, and dried (MgSO$_4$). After evaporation of the solvent an oil was obtained (110 mg) which gave the n.m.r. spectrum shown in the Figure. The ratio of the 'humulones' (32) : (33) was 75 : 100.

(b) The experiment was repeated with a second sample of the phloroacetophenone (31) (170 mg) in methanol (3·5 ml) containing lead(II) acetate trihydrate (200 mg); a slow stream of air was bubbled through the solution for 42 h. The solvent level was maintained throughout this period at the end of which the precipitate was collected as in (a) and washed (× 3) with a little cold methanol. Regeneration of the humulones from the salt as in (a) gave a mixture of (32) and (33) as a yellow gum (64 mg) which gave an n.m.r. spectrum nearly identical with that in the Figure. The ratio of humulones (32) : (33) was estimated as 73 : 100.