The Synthesis of Some Novel Deoxyhumulone Analogues. Observations on the Air-oxidation of 2',4',6'-Trihydroxy-3'-isopentyl-5'-(3-methylbut-2-enyl)isovalerophenone and its corresponding Humulone† Derivatives

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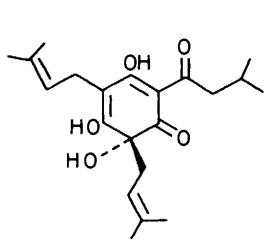
Two novel analogues of natural deoxyhumulone have been synthesised: (a) with the 3-methylbutanoyl side chain replaced by benzoyl, and (b) with the dimethylallyl substituents replaced by the cycloheptylidene analogues. Oxidation of these with air gave the corresponding humulones. Modification of these syntheses afford the two half-hydrogenated deoxyhumulone analogues, 2,4,6-trihydroxy-3-isopentyl-5-(3-methylbut-2-enyl)benzophenone and 2',4',6'-trihydroxy-3'-isopentyl-5'-(3-methylbut-2-enyl)isovalerophenone. Air-oxidation of the latter compounds gave in each case two isomeric humulones. Each pair of humulones was oxidised further, competitively, and the progress of the oxidation followed by ^{1}H n.m.r. spectroscopy. The results indicated a preferential oxidation rate for the isomers containing an unsaturated side chain at C-5 rather than at C-3.

Humulone (**1**) readily undergoes oxidation reactions in air and with chemical oxidants. Under the former conditions the reaction is responsible for the drastic diminution in the content of humulone and its natural analogues in stored hops. It has been claimed,[1] however, that hops in which the humulone content has been reduced by 70% on storage still retain 80% of their bittering power in brewing. Hence the humulone oxidation products must be transformed into compounds which are bitter or potentially bitter when boiled with wort.

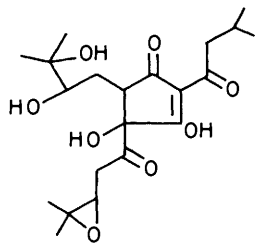
Chemical oxidations of humulone have enabled the characterisation and structural identification of several compounds which have subsequently been recognised as components formed by air-oxidation in stored hops. These include, for example, the glycol (**2**)[2] (from monoperphthalic acid) and the tricyclodehydroisohumulone (**3**)[3] (from lead tetra-acetate). The formation in air alone of others such as humulinone (**4**)[4] (from hydrogen peroxide) and the dihydrofuran (**5**)[5] (from *m*-chloroperbenzoic acid) is less certain.

Attempts to identify directly any products formed in air or oxygen have been less fruitful except for the example of the glycol (**6**).[6] Difficulties with this approach are (a) the complexity of the ^{1}H n.m.r. spectra of the natural humulone homologues and their analogues and derivatives; (b) their high polarity, which makes complete separation of the mixtures obtained very difficult; and (c) the reactivity towards air of many of the oxidation products. It was therefore decided to attempt to synthesise the phenyl derivatives (**12**) and (**24**) of deoxyhumulone and humulone, respectively, and the cycloheptylidene analogues (**13**) and (**25**). The benzoyl side chain in compounds (**12**) and (**24**) would undoubtedly simplify the ^{1}H n.m.r. spectra of the oxidation products, and the cycloheptylidene substituents should decrease their polarity.

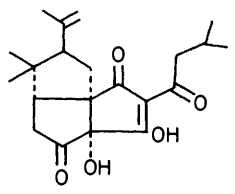
For the phenyl series, 2,4,6-trihydroxybenzophenone (**7**) was 'prenylated' with 2-methylbut-3-en-2-ol and boron trifluoride–ether in dioxane (Scheme) as described previously[7] for 2,4,6-trihydroxyacetophenone. The products were separated into the sodium carbonate soluble and insoluble fractions and the latter, on column chromatography, afforded the benzoyldeoxyhumulone (**12**) (11%) and the monoprenylated product (**9**) (4%) whose structures followed from their spectroscopic properties and by analogy with the earlier work.[7] In addition the chromans (**34**) (7%) and (**36**) (2%) were isolated; their isomeric orientations were distinguished by the shifts of their u.v. maxima in alkali. The sodium carbonate soluble products included the ketone (**19**) (4%). The two dimethylallyl groups were recognised in the ^{1}H n.m.r. spectrum from their corresponding methyl, methylene, and methine signals at τ 8.40 and 8.34, 7.30, and 5.06 respectively whilst the 5-H signal appeared as *two* singlets at τ 4.54 and 6.54 corresponding to the tautomers (**a**) and (**b**) respectively, of (**19**); other tautomeric forms may be envisaged for this compound and its analogues, but we have no evidence for their existence from our data. The facile loss of the dimethylallyl side chain was seen in the electron



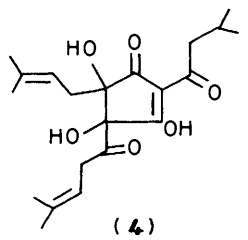
(**1**)



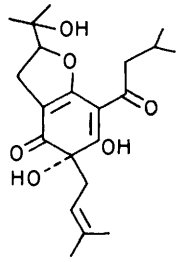
(**2**)



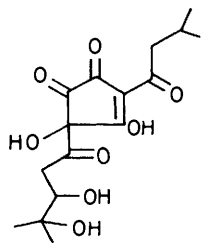
(**3**)



(**4**)

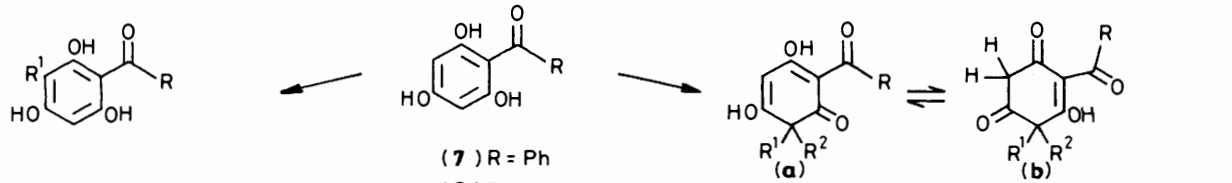


(**5**)



(**6**)

† Humulone is (*R*)-3,5,6-trihydroxy-2-isovaleryl-4,6-bis(3-methylbut-2-enyl)cyclohexa-2,4-dien-1-one.



(9) R = Ph, R^1 = $Me_2C{=}CHCH_2$
(10) R = Me_2CHCH_2, R^1 = cycloheptylidene–$CHCH_2$
(11) R = Me_2CHCH_2, R^1 = $Me_2C{=}CHCH_2$

(7) R = Ph
(8) R = Me_2CHCH_2

(19) R = Ph, R^1 = R^2 = $Me_2C{=}CHCH_2$
(20) R = Me_2CHCH_2, R^1 = R^2 = cycloheptylidene–$CHCH_2$
(21) R = Ph, R^1 = $Me_2C{=}CHCH_2$, R^2 = $Me_2CHCH_2CH_2$
(22) R = Me_2CHCH_2, R^1 = R^2 = $Me_2C{=}CHCH_2$
(23) R = Me_2CHCH_2, R^1 = $Me_2C{=}CHCH_2$, R^2 = $Me_2CHCH_2CH_2$

(12) R = Ph, R^1 = R^2 = $Me_2C{=}CHCH_2$
(13) R = Me_2CHCH_2, R^1 = R^2 = cycloheptylidene–$CHCH_2$
(14) R = Me_2CHCH_2, R^1 = R^2 = $Me_2C{=}CHCH_2$
(15) R = Ph, R^1 = $Me_2C{=}CHCH_2$, R^2 = $Me_2CHCH_2CH_2$
(16) R = Me_2CHCH_2, R^1 = $Me_2C{=}CHCH_2$, R^2 = $Me_2CHCH_2CH_2$
(17) R = Me, R^1 = $Me_2C{=}CHCH_2$, R^2 = $Me_2CHCH_2CH_2$
(18) R = Me, R^1 = R^2 = $Me_2C{=}CHCH_2$

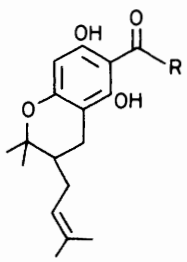
(24) R = Ph, R^1 = R^2 = $Me_2C{=}CHCH_2$
(25) R = Me_2CHCH_2, R^1 = R^2 = cycloheptylidene–$CHCH_2$
(26) R = Me, R^1 = $Me_2C{=}CHCH_2$, R^2 = $Me_2CHCH_2CH_2$
(27) R = Me, R^1 = $Me_2CHCH_2CH_2$, R^2 = $Me_2C{=}CHCH_2$
(28) R = Ph, R^1 = $Me_2C{=}CHCH_2$, R^2 = $Me_2CHCH_2CH_2$
(29) R = Ph, R^1 = $Me_2CHCH_2CH_2$, R^2 = $Me_2C{=}CHCH_2$
(30) R = Me_2CHCH_2, R^1 = $Me_2C{=}CHCH_2$, R^2 = $Me_2CHCH_2CH_2$
(31) R = Me_2CHCH_2, R^1 = $Me_2CHCH_2CH_2$, R^2 = $Me_2C{=}CHCH_2$

(32) R = Ph, R^1 = $Me_2CHCH_2CH_2$
(33) R = Me_2CHCH_2, R^1 = $Me_2CHCH_2CH_2$

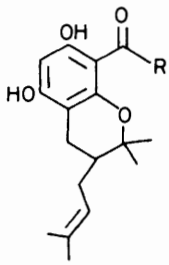
Scheme.

impact (e.i.) mass spectrum, which showed a weak molecular ion at *m/z* 366 and the base peak at *m/z* 297. Hydrogenolysis of the ketone (**19**) over palladium–charcoal gave the 2,4,6-trihydroxybenzophenone (**32**). Minor amounts of other compounds were formed in the prenylation reaction and, when the products of several reactions were combined, a colourless crystalline material with M^+ 434 [field desorption (f.d.) mass spectrometry] and elemental analysis consistent with a molecular formula $C_{28}H_{34}O_4$ was obtained. The ^1H n.m.r. spectrum showed the presence of three dimethylallyl side chains of which one contained a doubly allylic CH_2 group. Comparison of the spectroscopic properties with those in the literature[8] confirmed the structure as that of the benzoyllupulone (**37**) although the reported m.p.[8] is considerably higher than that found in the present work.

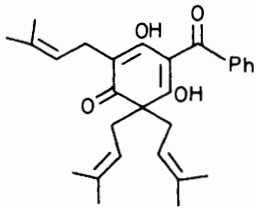
The benzoyldeoxyhumulone (**12**) in methanol and in the presence of lead(II) acetate trihydrate was treated with a stream of oxygen for three weeks. The insoluble yellow lead(II) salt of the corresponding humulone (**24**), in marked contrast to that of natural humulone (**1**) [from natural deoxyhumulone (**14**)], was formed very slowly. Decomposition of the lead(II) salt with dilute sulphuric acid gave the benzoylhumulone (**24**) as an oil (9%). The u.v. spectrum, $\lambda_{max.}$(acidic methanol) 350sh, 307, 251; $\lambda_{max.}$(alkaline methanol) 345 and 270 nm, showed the formation



(34) R = Ph
(35) R = Me_2CHCH_2



(36) R = Ph



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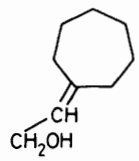
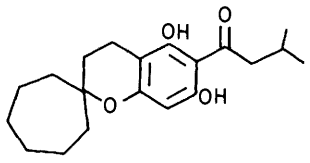


(38)

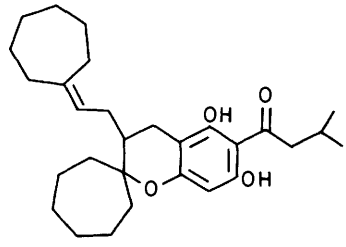
of the humulone ring system, but there was a slight bathochromic shift (16 nm) compared with the natural analogues. The e.i. mass spectrum showed a very small (0.4%) molecular ion peak at *m/z* 382.1772 ($C_{23}H_{26}O_5$) and fragment ions at *m/z* 105 and 77, and *m/z* 69, due to fragmentation of the benzoyl and dimethylallyl groups respectively. The ^{1}H n.m.r. spectrum also confirmed the structure and, in particular, the methylene doublet signals of the 3- and 5-dimethylallyl groups were at τ 7.35 and 6.90, respectively. The low-field signal from the chelated OH proton was (unusually) very broad at 35 °C, but at −25 °C it sharpened to a singlet (1 H) at τ −8.46. This effect is presumably a result of a somewhat weaker hydrogen bond in the chelate than in the analogues with aliphatic side chains. T.l.c. indicated that the compound was pure. In certain preparations of the benzoylhumulone (**24**), an impurity was detected from the ^{1}H n.m.r. spectrum which showed an extra doublet centred on τ 6.68. It became clear that when the humulone was heated at *ca.* 80 °C in a vacuum, benzoic acid was isolated by sublimation. The other decomposition products were evidently complex and were not investigated in detail.

For the synthesis of the cycloheptylidene analogue (**13**) of deoxyhumulone, cycloheptanone was converted *via* (a) a Reformatsky reaction with ethyl bromoacetate,[9] (b) base hydrolysis of the resultant ester and dehydration, and (c) reduction of the derived α,β-unsaturated acid with lithium aluminium hydride to the requisite alcohol (**38**). Treatment of 2′,4′,6′-trihydroxyisobutyrophenone (**8**) with this alcohol and boron trifluoride–ether, by analogy with the synthesis of the benzoyldeoxyhumulone (**12**), gave the monoalkenylated product (**10**) and the bis derivative (**20**). The latter compound showed a molecular ion at *m/z* 454 and intense fragment ions at *m/z* 331 and 223 corresponding to the loss of a cycloheptylidene-ethyl radical followed by loss of a cycloheptylidenemethyl group with hydrogen rearrangement. The ^{1}H n.m.r. spectrum showed complex signals confirming the existence of multiple tautomers. During the chromatography of these products, a major component was isolated with the expected R_F value and u.v. and ^{1}H n.m.r. spectra for the desired deoxyhumulone (**13**); however, it proved to be exceptionally unstable and was evidently transformed into compounds of much greater polarity. The R_F value and the colour on staining of one of these new products was strongly suggestive of the corresponding humulone (**25**), but it was also unusually unstable to air. It was, however, possible to trap a sample of the humulone (**25**) as its lead(II) salt by shaking the solution with lead(II) acetate trihydrate. Regeneration of the precipitate obtained gave an oil (20 mg) whose f.d. mass spectrum gave M^+ 470 and the u.v. spectrum was very similar to that of natural humulone (**1**). The ^{1}H n.m.r. spectrum showed a single sharp low-field signal at τ −8.82 and the high-field signals expected from structure (**25**). A single spot was obtained on t.l.c., of higher R_F than that for natural humulone (**1**).

Two further minor products were isolated as oils by chromatography and were clearly derived from the prenylation. After their separation by p.l.c., the first (1%) gave a u.v. spectrum typical of a 2′,4′,6′-trihydroxyisovalerophenone nucleus with a blocked *p*-hydroxy group. The f.d. mass spectrum (M^+ 332) showed that only one prenyl group had reacted, and accurate mass measurement of the molecular ion (e.i.) confirmed the molecular formula as $C_{20}H_{28}O_4$. That subsequent cyclisation to the chroman (**39**) had occurred was indicated by two triplet signals at τ 7.80 and 7.52 in the ^{1}H n.m.r. spectrum and the base peak in the e.i. mass spectrum (*m/z* 223), attributable to the loss of a cycloheptylidenemethyl radical by retro Diels–Alder-type fragmentation with hydrogen rearrangement.[10] The second compound, also obtained in 1% yield, had the molecular formula $C_{29}H_{42}O_4$ (f.d. mass spectrum, M^+ 454; e.i., M^+ 454.3086) showing the association of two prenyl groups



(**39**)



(**40**)

with the starting ketone (**8**). The u.v. and ^{1}H n.m.r. spectra confirmed the 2,4,6-trihydroxyacylphenone nucleus with a blocked *p*-hydroxy group, and in the n.m.r. spectrum the presence of both one aromatic and one olefinic proton (τ 4.27 and 4.87 respectively) but the absence of a methylene doublet at τ *ca.* 6.7 indicated that the remaining cycloheptylidene-ethyl group was not directly attached to the phloroglucinol ring. The full structure (**40**) followed by analogy with the chromans (**34**) and (**36**) and, as with the chroman (**39**), the base peak in the e.i. mass spectrum appeared at *m/z* 223 owing to the retro-Diels–Alder-type cleavage of the dihydropyran ring system.

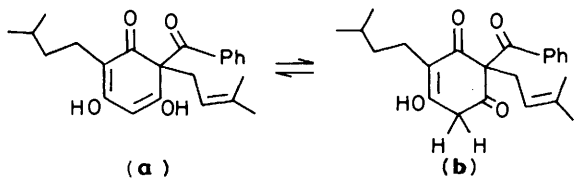
These synthetic schemes, directed towards model deoxyhumulones and humulones, led to the unexpected result that substitution of the acyl side chain in the natural compounds by the benzoyl group slowed up the oxidation of the deoxy compound to the humulone, whilst replacement of the dimethylallyl side chains by the more lipophilic cycloheptylidene groups had the opposite effect. The explanation of these effects is not clear, but they meant that the use of the deoxyhumulone (**13**) and the humulone (**25**) for model oxidation experiments was not practicable. The benzoyl analogues (**12**) and (**24**), however, although relatively insensitive to oxidation, were still useful for study of the oxidation of the dimethylallyl side chains also present in the natural products.

Compounds (**3**)—(**5**), all derived by oxidation of humulone (**1**), each show evidence, either from their structures or the probable mechanism for their formation,[3] of selective oxidation at the C-5 side chain rather than that at C-3 in humulone (**1**). There is circumstantial evidence[5] that this may also be true of the derivatives (**2**) and (**6**). Moreover, earlier work[11] on the competitive air-oxidation of the two isomeric synthetic model humulones (**26**) and (**27**) showed that the former isomer was oxidised more rapidly than the latter. This experiment also implied preferential attack by oxygen at the C-5 unsaturated side chain. It was desirable that this result should be confirmed both with the phenyl and, particularly, with the natural isobutyryl side chains to support the generality of the result.

Hydrogenolysis of the ketone (**19**) or hydrogenation of the ketone (**9**) gave 2,4,6-trihydroxy-3-isopentylbenzophenone (**32**) which was prenylated as previously described for 2,4,6-trihydroxybenzophenone (**7**). The dihydrodeoxybenzoyl-humulone (**15**) was obtained, after chromatography, as a relatively stable bright yellow solid (33%); its spectroscopic properties and elemental analysis fully supported its structure. The sodium carbonate soluble fraction of the products contained the analogue (**21**) of the bisphenyl compound (**19**); as with the latter, hydrogenolysis of (**21**) gave the phenol (**32**) in good yield.

A second component was isolated from this fraction by p.l.c.

It showed M^+ 368 and 368.1987 ($C_{23}H_{28}O_4$) by f.d. and e.i. mass spectrometry respectively and the u.v. spectrum [$\lambda_{max.}$ 254 (ε 5 600) and 356 (11 760) nm] indicated that the compound, although extensively conjugated, contained neither an acyl phoroglucinol nor a humulone nucleus. The ^{1}H n.m.r. spectrum showed no low-field chelate signal but confirmed the retention of the benzoyl and isopentyl groups, whilst methyl signals at τ 8.45 together with a methylene signal at τ 7.42 and an olefinic proton at τ 5.07 revealed the presence of a dimethylallyl group linked to a saturated carbon centre. Spin decoupling linked the last two signals. The spectrum also showed a singlet and a weak multiplet at τ 4.17 and 6.35, respectively, which were in accord with a tautomeric equilibrium involving structures of type (**41**) [(**a**) and (**b**)]. The basic structure was supported by ions at *m/z*



(41)

105 (82%) and 69 (71%) in the e.i. mass spectrum due to the expected fragmentations of the benzoyl and dimethylallyl groups, and by the f.d. spectrum which showed loss of the dimethylallyl group with hydrogen rearrangement (*m/z* 300) as the sole fragment ion.

The dihydrodeoxybenzoylhumulone (**15**) was oxidised to the corresponding mixture of humulones (**28**) and (**29**) *via* the lead(II) salts, as in the case of the analogue (**12**). After two weeks, the isomeric humulones (**28**) and (**29**) were regenerated with dilute acid. The ^{1}H n.m.r. spectrum of this mixture showed two sharp low-field signals from the chelated enol signals of the two isomers at τ −8.69 and −8.62 at −25 °C. The possibility that these low-field signals might be due to two alternative chelated forms of the same humulone could be ruled out since the benzoylhumulone (**24**) gave, as expected, only one low-field signal.

The humulone (**28**) showed a characteristic doublet signal at τ 6.88 due to the methylene of the C-5 side chain, whereas its isomer (**29**) gave a signal at τ 7.37 due to the methylene of its C-3 side chain. These two signals provided an approximate estimate of the ratio of the two humulones which enabled the correct assignment of the two sharp low-field signals from which the ratio was accurately measured. On regeneration of the mixture of lead salts, the ratio (**29**):(**28**) was 1.6:1. Whilst the solution of these compounds in deuteriochloroform was undisturbed, relatively little change took place, except that there was a slow selective disappearance of the isomer (**28**). Thus the ratio (**29**):(**28**) changed to 1.7:1 after 25 days and to 2:1 after 62 days (Table). This effect was accelerated however when air was bubbled through the solution; within 3 days the ratio had changed to 6.0:1 and after a further 5 days there was no significant amount of the isomer (**28**) remaining.

These results were concordant with the earlier ones obtained with the isomeric model humulones (**26**) and (**27**); they indicated that the C-5 dimethylallyl substituent is preferentially oxidised in the humulones. It was, however, desirable to ascertain finally that they were also true of the closest possible model for natural humulone, the isomers (**30**) and (**31**).

The necessary 'half-hydrogenated' deoxyhumulone (**16**) was synthesised *via* the ketone (**22**).[7] During the synthesis of the latter from 2,4,6-trihydroxyisobutyrophenone (**8**) and 2-methylbut-3-en-2-ol, the other expected products deoxyhumulone

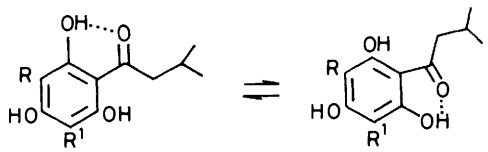
Table. Ratios of humulones (**28**) and (**29**) on standing, as determined by ^{1}H n.m.r. spectroscopy

Time (days)	Ratio (**29**):(**28**)
0	1.6:1
27	1.7:1
55	1.8:1
64	2.0:1
82*	2.05:1
85	6.0:1
90	9.0:1

* Air subsequently bubbled through the solution; $CDCl_3$ level maintained constant.

(**14**)[7] and the phenol (**11**)[12] were obtained as well as the chroman (**35**). The last compound showed M^+ 346.2125 ($C_{21}H_{30}O_4$) in its e.i. mass spectrum, and, in the ^{1}H n.m.r. spectrum, signals due to two OH groups, one moderately strongly chelated [τ −3.36 (s, 1 H)] and the other free [τ 2.95 (br s, 1 H)], and a single aromatic proton [τ 4.27 (s, 1 H)]. In the high-field region, besides the signals of the isovaleryl group, there were two methyl signals at τ 8.60 and 8.81 ($OCMe_2$). A double doublet (*J* 16, 6 Hz) centred at τ 7.25 and other multiplets at τ 7.80 could, by analogy with earlier work,[7] be assigned to the methylene protons of the dihydropyran ring and the dimethylallyl group; the latter also showed characteristic vinylic hydrogen and methyl signals. The orientation of structure (**35**) was confirmed by the small alkaline shift of the u.v. maximum (11.5 nm).

Hydrogenolysis of the ketone (**22**) gave the phenol (**33**) which was prenylated as described above. Amongst the products isolated was the ketone (**23**) [whose structure followed from its spectroscopic properties and by analogy with the corresponding compound (**22**)] and the required dihydrodeoxyhumulone (**16**) [M^+ 348.2299 ($C_{21}H_{32}O_4$)]. The latter would not crystallise, but its spectra fully supported the proposed structure. In particular, in its ^{1}H n.m.r. spectrum there were three distinct OH signals at τ 4.2, 0.23, and 0.0. The two lower field signals were due to the rapidly equilibrating but non-equivalent chelated OH groups [see (**42**)]. In general we have found[13] that



(42)

when the substituents R and R^1 in structures of type (**42**) are significantly different, *e.g.* for the chromans (**39**), (**40**), and (**35**), or the phenol (**11**), the separation between the two signals to lower field is larger than that for compound (**16**), and the signal to lowest field, corresponding to a marked preferential chelation, appears at considerably lower field, typically τ −3 to −4. This is contrary to an earlier suggestion.[14]

During the column chromatography of the products of the prenylation of the ketone (**33**), the deoxyhumulone (**16**) was followed by fractions showing the u.v. spectrum of humulone, and t.l.c. showed a component with a very similar R_F value to natural humulone (**1**). ^{1}H N.m.r. spectroscopy revealed the presence of a mixture of the two required 'half-hydrogenated' humulones (**30**) and (**31**) containing *ca.* 27% of the isomer (**30**). This mixture had evidently been formed by spontaneous air-

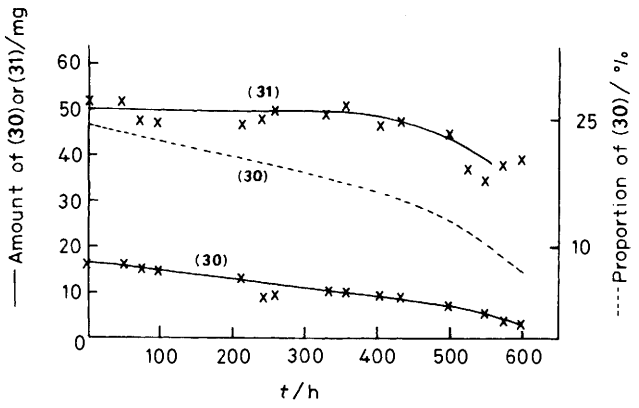
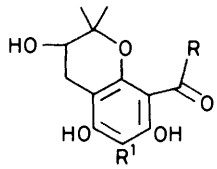


Figure. Relative rates of air-oxidation of the humulones (**30**) and (**31**)

oxidation of the phenol (**16**). The ^{1}H n.m.r. signals due to the major isomer were identical with those reported by Verzele[4] for the dihydrohumulone (**31**), prepared by the regioselective partial hydrogenation of humulone (**1**).

The dihydrohumulone (**30**) gave (a) a different low-field chelated OH signal from (**31**); (b) a doublet at τ 6.94 (*J* 7 Hz) due to its C-5 dimethylallyl CH_2 group; and (c) vinyl methyl signals seen as shoulders on the corresponding signals from its isomer (**31**). After 5 days, the spectrum of the mixture showed that the proportion of the minor component (**30**) had reduced to 20% of the total, and therefore the effect was examined more rigorously. Air-oxidation of the phenol (**16**) in the presence of lead(II) acetate was carried out as before for the analogues (**12**), (**13**), and (**15**), giving a reasonable yield (40%) of the lead(II) salts of the dihydrohumulones. Acid treatment of the salts afforded a mixture of the humulones (**30**) and (**31**) as an oil which showed a single spot on t.l.c. Analysis of the ^{1}H n.m.r. spectrum showed that the isomer (**30**) comprised 23.5% of the total. The solution, open to the air, was monitored for 600 h and the individual quantities of (**30**) and (**31**) measured by their low-field enol signals relative to the low-field signal of salicylaldehyde (see Figure). It can be seen that little or no change took place in the amount of isomer (**31**) in 400 h, but that the amount of isomer (**30**) decreased continuously from the outset, reaching 16% of the total at this time. Thereafter both isomers began to oxidise, but (**30**) continued to disappear at a faster rate, comprising 10.5% of the total after 550 h. Several new signals appeared during the oxidation and there was a corresponding appearance of new products, shown by t.l.c. It is of interest that the mother-liquors from the oxidation of the phenol (**16**) in methanol–lead(II) acetate afforded, after p.l.c. and fractional crystallisation, small quantities of the crystalline chromanol (**43**), whose structure followed from its spectroscopic properties and elemental analysis. The formation of this chromanol (**43**) in small amounts was not unexpected since we have also shown that air-oxidation of the deoxyhumulones (**17**),[11] (**18**),[11] and (**14**)[15] gives the corresponding chromanols (**44**), (**45**), and (**46**).

These results, together with those for the isomeric pairs (**26**) and (**27**),[11] and (**28**) and (**29**), appear to establish a generality of the observed faster rate of air-oxidation for the humulone isomers with the unsaturated side chain at C-5 than those with the side chain C-3. Epoxidation[16–18] of isolated olefinic bonds is well known, but it would seem that the doubly allylic CH_2 group in the C-5 side chains of compounds (**1**), (**26**), (**28**), and (**30**) enhances the reactivity towards oxidation at this site. It therefore appears that this is an initial or very early step in the air-oxidation of natural humulone (**1**). The effect is, however,



(**43**) R = Me_2CHCH_2, R^1 = $Me_2CHCH_2CH_2$
(**44**) R = Me, R^1 = $Me_2CHCH_2CH_2$
(**45**) R = Me, R^1 = $Me_2C{=}CHCH_2$
(**46**) R = Me_2CHCH_2, R^1 = $Me_2C{=}CHCH_2$

not dramatic and this is presumably because other, competitive oxidations are taking place simultaneously.

Experimental

Mass spectra were obtained with a Varian CH-5D instrument by electron impact (e.i.), unless otherwise stated, with a direct insertion probe at 70 eV and 50 μA, or field desorption (f.d.) at a wire current of 15—20 μA. U.v. spectra were determined on a Unicam SP 800 instrument. N.m.r. spectra were determined at 90 MHz on a Perkin-Elmer R32 spectrometer for solutions in $CDCl_3$ unless stated otherwise. T.l.c. was performed on Whatman silica gel 50 F.T.L.C. 'Light petroleum' indicates the fraction boiling at 40—60 °C and ether refers to diethyl ether. Silicic acid used for column chromatography was Malinckrodt 100 mesh AnalaR. Elemental analyses were not obtained for compounds isolated as small quantities of oil, or for those which were unstable to air; where accurate mass measurements were used to infer the molecular formulae, the t.l.c. characteristics and ^{1}H n.m.r. spectra both indicated a pure compound.

Prenylation of 2,4,6-*Trihydroxybenzophenone*.—2,4,6-Trihydroxybenzophenone (6.0 g) in dry dioxane (125 ml) was added to a solution of 2-methylbut-3-en-2-ol (4.5 g) in dry dioxane (121 ml). Boron trifluoride–ether (6.0 ml) was added and the mixture stirred at 20 °C for 5.5 h. Ether (400 ml) was added and the solution washed with water (3 × 200 ml) and 1% sodium carbonate solution (2 × 200 ml), dried ($MgSO_4$), and the solvent evaporated under reduced pressure to give an oil (8.0 g). Chromatography on silicic acid (125 g) and elution with ether–light petroleum (1:24) gave the deoxybenzoylhumulone (**12**) as a yellow solid (1.23 g, 13%). Recrystallisation from light petroleum gave pure 2,4,6-*trihydroxy*-3,5-*bis*(3-*methylbut*-2-*enyl*)*benzophenone* (**12**), m.p. 93—94 °C, $\lambda_{max.}$(ethanol) 316 and 254 nm, $\lambda_{max.}$(alkaline ethanol) 355 and 242 nm; τ 8.28 (6 H, s, $CH_2CH{=}CMe_2$), 8.23 (6 H, s, $CH_2CH{=}CMe_2$), 6.66 (4 H, d, *J* 7 Hz, 2 × $ArCH_2$), 4.77 (2 H, t, *J* 7 Hz, 2 × $CH_2CH{=}Me_2$), 3.68 (1 H, s, OH, *para* to C=O), 2.43 (5 H, m, 5 × Ar*H*), and 1.10 (2 H, s, 2 × OH); *m*/*z* (e.i.) (%) 366 (M^+, 18), 351 (26), 298 (22), 261 (9), 105 (58), and 77 (40) (Found: C, 75.4; H, 7.2. $C_{23}H_{26}O_4$ requires C, 75.4; H, 7.1%).

Elution with ether–light petroleum (2:23) gave an oil which crystallised slowly from chloroform–light petroleum. Recrystallisation afforded 6-*benzoyl*-5,7-*dihydroxy*-2,2-*dimethyl*-3-(3-*methylbut*-2-*enyl*)*chroman* (**34**) (333 mg, 3.5%), m.p. 141—145 °C, $\lambda_{max.}$(ethanol) 314 (ε 13 600) and 255 nm (5 700); $\lambda_{max.}$(alkaline ethanol) 405 (2 700) and 319 nm (12 000); τ 8.78 and 8.57 (6 H, 2 s, $OCMe_2$), 8.39 and 8.28 (6 H, 2 s, $C{=}CMe_2$), 8.4—7.5 (4 H, partially overlapping m, $ArCH_AH_BCHCH_2CH{=}C$), 7.23 (1 H, dd, *J* 4.7, 16 Hz, $ArCH_ACH_B$), 4.82 (1 H, m, CH=C), 4.14 (1 H, s, ArH), 3.01 (1 H, s, ArOH), 2.39 (5 H, m, 5 × ArH), and −0.77 (1 H, s, ArOH) (Found: C, 75.1; H, 7.2. $C_{23}H_{26}O_4$ requires C, 75.4; H, 7.1%).

Elution with ether–light petroleum (3:22) gave an oil which crystallised slowly from chloroform–light petroleum. Re-

crystallisation afforded the 8-*benzoyl*-5,7-*dihydroxy*-2,2-*diethyl*-3-(3-*methylbut*-2-*enyl*)*chroman* (**36**) (184 mg, 2%), m.p. 139—144 °C; $\lambda_{max.}$(ethanol) 312 (ε 12 100) and 254 nm (4 100); $\lambda_{max.}$(alkaline ethanol) 347 (20 800) and 247sh nm; τ 9.2 and 9.11 (6 H, 2 s, $OCMe_2$), 8.44 and 8.30 (6 H, 2 s, $C{=}CMe_2$), 8.5—7.5 (4 H, overlapping m, $ArCH_AH_BCHCH_2CH{=}C$), 7.35 (1 H, dd, *J* 16, 5 Hz, $ArCH_AH_B$), 4.89 (1 H, br, t, *J* 6.5 Hz, $C{=}CH$), 4.05 (1 H, s, ArH), 3.9 (1 H, br s, ArOH), 2.55 (5 H, m, 5 × ArH), and −2.21 (1 H, s, ArOH); *m/z* (e.i.) (%) 367 (21), 366 (M^+, 50), 352 (27), 351 (100), 298 (8), 297 (11), 295 (17), 243 (65), 241 (24), 165 (70), 109 (14), 105 (51), 77 (14), and 69 (13) (Found: C, 75.3; H, 7.0. $C_{23}H_{26}O_4$ requires C, 75.4; H, 7.1%). Elution with ether–light petroleum (9:11) and recrystallisation of the crude solid from chloroform–light petroleum gave 2,4,6-*trihydroxy*-3-(3-*methylbut*-2-*enyl*)*benzophenone* (**9**) (148 mg, 2%), m.p. 102—103 °C, $\lambda_{max.}$(methanol) 311 (ε 10 180) and 252sh nm (4 790); $\lambda_{max.}$(alkaline methanol) 344 (14 070) and 253sh nm (10 780); τ 8.26, 8.22 (6 H, 2 s, $CH_2CH{=}CMe_2$), 6.66 (2 H, d, *J* 7 Hz, $ArCH_2$), 4.75 (1 H, t, *J* 7 Hz, $CH_2CH{=}CMe_2$), 4.1 (1 H, s, ArH), 2.45 (5 H, m, 5 × ArH), and −0.36 (1 H, s, OH); *m/z* (%) 298 (M^+, 80), 243 (100), 165 (62), 105 (57), 77 (48), and 69 (23) (Found: C, 72.5; H, 6.3. $C_{18}H_{18}O_4$ requires C, 72.5; H, 6.1%).

Chromatography of the Sodium Carbonate Extract.—The sodium carbonate extract [from a similar preparation from 2,4,6-trihydroxybenzophenone (2.0 g)] after acidification (2M-hydrochloric acid and extraction into ether (2 × 100 ml) was dried ($MgSO_4$) and chromatographed on silicic acid (column 40 × 3 cm). Elution with ether–light petroleum (6:94) gave the 2-*benzyl*-3,5-*dihydroxy*-6-(3-*methylbut*-2-*enyl*)*cyclohexa*-2,4-*dien*-1-*one* (**19**) as colourless crystals (448 mg, 14%), m.p. 140—144 °C, $\lambda_{max.}$(methanol) 349 (ε 12 990), 287 (6 250), 238sh nm (10 940); $\lambda_{max.}$(alkaline methanol) 347 (16 960) and 243 nm (27 450); τ 8.4 and 8.34 (12 H, 2 s, 2 × $CH_2CH{=}CMe_2$), 7.3 (4 H, d, 2 × $CH_2CH{=}CMe_2$), 5.06 (2 H, m, 2 × $CH_2CH{=}CMe_2$), 6.54, 4.54 [1 H, 2 s, $COCH_2CO$ + $C{=}C(OH)CH{=}C$], and 2.5 (5 H, m, 5 × ArH); *m/z* (%) 366 (M^+, 3), 297 (100), 105 (60), 77 (28), 69 (47), and 59 (48) (Found: C, 75.7; H, 7.2. $C_{23}H_{26}O_4$ requires C, 75.4; H, 7.2%).

Combination of the sodium carbonate extracts of several preparations and chromatography as above enabled the separation of the following minor products. Elution with redistilled ethyl acetate–light petroleum (6:94) gave first an unidentified oil [(650 mg), $\lambda_{max.}$ (methanol) 350 nm] and secondly, colourless crystals of 4-benzyl-3,5-dihydroxy-2,6,6-tris(3-methylbut-2-enyl)cyclohexa-2,4-dien-1-one (**37**) (236 mg, 1%) recrystallised from methanol–water, m.p. 127—129 °C (lit.,[8] 154 °C); $\lambda_{max.}$ (methanol) 358 (ε 14 030), 284 (6 350), and 245sh nm (9 710); $\lambda_{max.}$(alkaline methanol) 365 nm (19 200); τ 8.42, 8.36 (12 H, 2 s, $CH_2CH{=}CMe_2$), 8.22 (6 H, s, $CH_2CH{=}CMe_2$), 7.2—7.55 (4 H, m, 2 × $CH_2CH{=}CMe_2$), 6.77 (2 H, d, *J* 7 Hz, $CH_2CH{=}CMe_2$), 5.07 (2 H, t, *J* 8 Hz, 2 × $CH_2CH{=}CMe_2$), 4.8 (1 H, br t, $CH_2CH{=}CMe_2$), 2.56 (5 H, m, 5 × Ar*H*), and −6.5, −8.45 (OH); *m/z* (f.d.) (%) 434 (M^+, 100); e.i. *m/z* (%) 434 (16), 365 (42), 309 (60), 297 (100), 105 (60), 77 (23), and 69 (44) (Found: C, 77.5; H, 8.0. Calc. for $C_{28}H_{34}O_4$: C, 77.4; H, 7.9%).

Hydrogenation of the Ketones (**9**) *and* (**19**).—The ketone (**19**) (3.0 g) was hydrogenated over Pd–C (200 mg) in methanol (150 ml) at 1 atm pressure and 20 °C for 4 h, after which time 2 mol of hydrogen per mol had been consumed. The catalyst was removed by filtration and the filtrate diluted with an excess of water and then extracted into ether and dried ($MgSO_4$). Evaporation of the solvent left an oil which was crystallised from light petroleum (b.p. 30—40 °C) to give the product, 2,4,6-trihydroxy-3-isopentylbenzophenone (**32**) as yellow crystals (1.46 g, 59%). The above procedure was repeated with the ketone (**9**) (1.18 g) to give similarly 2,4,6-*trihydroxy*-3-*isopentylbenzophenone* (**32**) (0.55 g, 59%), m.p. 94—97 °C, $\lambda_{max.}$ (methanol) 311 (ε 14 330) and 251 nm (7 500); $\lambda_{max.}$(alkaline methanol) 342 nm (16 440); τ 9.07 (6 H, d, *J* 7 Hz, $CH_2CH_2CHMe_2$), 8.4—8.9 (m, $CH_2CH_2CHMe_2$), 7.47 (2 H, t, *J* 7 Hz, $CH_2CH_2CHMe_2$), 4.1 (1 H, s, ArH), 2.42 (5 H, m, COPh), and 0.0 (1 H, s, OH); *m/z* (%) 300 (M^+, 43), 243 (100), 165 (87), 105 (12), and 77 (15) (Found: C, 72.3; H, 7.0%; M^+, 300.1362. $C_{18}H_{20}O_4$ requires C, 72.0; H, 6.7; *M*, 300.1361).

Oxidation of the Deoxybenzoylhumulone (**12**) *to give the Humulone* (**24**).—The deoxybenzoylhumulone (**12**) (3.02 g) and lead(II) acetate trihydrate (2. 6 g) in methanol (30 ml) was treated with a slow stream of oxygen. After 3 weeks the lead(II) salt was separated by centrifugation, washed with cold methanol, re-centrifuged, and dried with a stream of nitrogen to give a pale yellow solid (665 mg). Treatment with 2M-sulphuric acid and isolation *via* ether gave 2-*benzoyl*-3,5,6-*trihydroxy*-4,6-*bis*(3-*methylbut*-2-*enyl*)*cyclohexa*-2,4-*dien*-1-*one* (**24**) (282 mg, 9%) as an oil; $\lambda_{max.}$(acidic methanol) 350sh (ε 2 755), 307 (4 450), and 251 nm (7 401); $\lambda_{max.}$(alkaline methanol) 345 (4 130) and 270 nm (7 380); τ 8.40, 8.37, 8.33, 8.30 (12 H, 4 s, 2 × $CH_2CH{=}CMe_2$), 7.35 (2 H, d, *J* 7.5 Hz, $CH_2CH{=}CMe_2$), 6.90 (2 H, d, *J* 7.5 Hz, $CH_2CH{=}CMe_2$), 4.85 (2 H, br t, 2 × $CH_2CH{=}CMe_2$), 2.55 (5 H, m, COPh), and −8.46 (−25 °C) (1 H, s, OH); *m/z* (%) 382 (M^+, 0.4), 262 (15), 244 (22), 122 (10), 105 (100), 77 (44), and 69 (23) (Found: M^+, 382.1772. $C_{23}H_{26}O_5$ requires *M*, 382.1780).

Preparation of 2-*Cycloheptylidene-ethanol* (**38**).—Cycloheptylideneacetic acid [m.p. 52—54 °C (lit.,[9] 54 °C)], prepared by the method of Kon and May[9] (1.75 g) in anhydrous ether (4 ml) was added to lithium aluminium hydride (0.516 g) in anhydrous ether (10 ml) during 10 min with stirring. After the mixture had been stirred for a further 20 min, water (0.5 ml) was added dropwise, the product was extracted with ether (3 × 10 ml), and the ether layers were combined, dried ($MgSO_4$), and the solvent evaporated under reduced pressure to leave 2-*cycloheptylidene-ethanol* (**38**) (1.33 g, 83%) as an oil, b.p. 208—212 °C, τ 8.78 (1 H, br s, OH), 8.50 (8 H, m, $CH_2CH_2CH_2$), 7.77 (4 H, m, $CH_2CH_2C{=}C$), 5.89 (2 H, d, *J* 7 Hz, CH_2OH), and 4.62 (1 H, t, *J* 7 Hz, C=CH) (Found: C, 77.2; H, 11.6. $C_9H_{16}O$ requires C, 77.1; H, 11.5%).

Alkenylation of 2′,4′,6′-*Trihydroxyisovalerophenone with* 2-*Cycloheptylidene-ethanol.*—Dry 2′,4′,6′-trihydroxyisovalerophenone (1.0 g) in dry dioxane (20 ml) was added to a solution of 2-cycloheptylidene-ethanol (**38**) (1.33 g) in dry dioxane (20 ml). Boron trifluoride–ether (1.0 ml) was added and the mixture stirred at 20 °C for 8 h. Ether (75 ml) was then added and the solution washed with water (2 × 75 ml) and 1% aqueous sodium carbonate (2 × 75 ml) and dried ($MgSO_4$); the ether was then evaporated under reduced pressure to give a brown oil (1.74 g). The sodium carbonate extract was acidified with dilute hydrochloric acid, extracted with ether (75 ml), dried ($MgSO_4$), and evaporated to give a dark brown oil (367 mg).

The carbonate-insoluble oil (1.74 g) was chromatographed on silicic acid (75 g). Elution with ether–light petroleum (1:39) afforded as the first major component 3′,5′-bis(cycloheptylidenemethyl)-2′,4′,6′-trihydroxyisovalerophenone (**13**). This compound was never obtained completely pure; t.l.c. showed the presence of at least one of many compounds of similar R_F in each of the column fractions. A low R_F spot, blue-black with $FeCl_3$, due to spontaneous oxidation to the humulone (**25**) was present in most of the fractions but the evidence indicated that the major component of these fractions was the deoxyhumulone (**13**), R_F 0.95 (in formic acid–ethyl formate–hexane 1:8:12); $\lambda_{max.}$(ethanol) 294 nm; $\lambda_{max.}$(alkaline ethanol) 341 nm; τ 9.05 (d,

J 6.5 Hz, $CHMe_2$), 8.5 (m, $CH_2CH_2CH_2$), 7.85 (m, CH_2CH_2C=), 7.11 (d, *J* 7 Hz, CH_2CHMe_2), 6.67 (d, *J* 7 Hz, CH_2CH=), 4.76 (t, *J* 7 Hz, CH_2CH=), 3.5 (br s, OH), and −0.29 (s, 2 × OH).

Elution with ether–light petroleum (1:9) yielded a mixture of two compounds which were separated by preparative t.l.c. using ethyl acetate–light petroleum (2:23). Extraction of the lower R_F band afforded the *5,7-dihydroxy-6-isovalerylchroman-2-spirocycloheptane* (**39**) (19 mg, 1%) as an oil, R_F 0.8, $\lambda_{max.}$(ethanol) 294, 225sh nm; $\lambda_{max.}$(alkaline ethanol) 305, 241sh nm; τ 9.18 (6 H, d, *J* 6.5 Hz, CH_2CHMe_2), 8.7—8.1 [12 H, m, $(CH_2)_6$], *ca.* 7.9 (1 H, overlapping m, CH_2CHMe_2), 7.80 (2 H, overlapping t, *J* 6.5 Hz, $ArCH_2CH_2$), 7.52 (2 H, t, *J* 6.5 Hz, $ArCH_2CH_2$), 7.12 (2 H, d, *J* 7 Hz, CH_2CHMe_2), 4.29 (1 H, s, ArH), 3.13 (1 H, s, ArOH), and −3.41 (1 H, s, chelated ArOH); *m/z* (%) 332 (M^+, 24), 275 (13), 223 (100), 205 (11), 165 (44), 122 (27), 95 (31), 81 (55), 67 (32), 58 (100), and 55 (33); *m/z* (f.d.) (%) 332 (100), 333 (25) (Found: M^+, 332.1984. $C_{20}H_{28}O_4$ requires *M*, 332.1987).

The higher band (R_F 0.85) gave the *3-(2-cycloheptylidene-ethyl)-5,7-dihydroxy-6-isovalerylchroman-2-spirocycloheptane* (**40**) (15 mg, 1%) as an oil, $\lambda_{max.}$(ethanol) 294 and 226sh nm; $\lambda_{max.}$(alkaline ethanol) 305 and 245sh nm; τ 9.08 (6 H, d, *J* 6.5 Hz, CH_2CHMe_2), 8.7—8.1 [21 H, m, $CH_2(CH_2)_4CH_2C$= and $(CH_2)_6$ and $ArCH_2CH_2CH$], *ca.* 7.9 [6 H, m, $CH_2(CH_2)C$=$CHCH_2$], 7.7—7.2 (2 H, m, $ArCH_2$), 7.12 (2 H, d, *J* 7 Hz, CH_2CHMe_2), 4.87 (1 H, t, *J* 6 Hz, C=$CHCH_2$), 4.27 (1 H, s, ArH), 3.11 (1 H, br s, ArOH), and −3.09 (1 H, s, chelated OH); *m/z* (%) 454 (M^+, 22), 369 (23), 331 (24), 223 (100), 205 (16), 165 (25), 135 (27), 95 (26), 93 (23), 91 (22), 81 (72), 79 (32), 69 (35), 67 (52), 57 (28), 55 (71), 43 (41), and 41 (48); *m/z* (f.d.) (%) 454 (100), 455 (32) (Found: M^+, 454.3086. $C_{29}H_{42}O_4$ requires *M*, 454.3083).

Elution with ether–light petroleum (1:3) gave the mono-substituted phenol (**10**) as an oil (180 mg, 11%); crystallisation from chloroform–light petroleum gave *2',4',6'-trihydroxy-3'-(2-cycloheptylidene-ethyl)isovalerophenone* (**10**), m.p. 120—125 °C, $\lambda_{max.}$(ethanol) 293 and 225sh nm; $\lambda_{max.}$(alkaline ethanol) 332 and 246sh nm; τ 9.08 (6 H, d, *J* 7 Hz, CH_2CHMe_2), 8.6—8.3 (8 H, m, 4 × $CH_2CH_2CH_2$), 7.9—7.5 (4 H, m, 2 × CH_2CH_2C=), 7.12 (2 H, d, *J* 7 Hz, CH_2CHMe_2), 6.71 (2 H, d, *J* 7 Hz, $ArCH_2CH$=), 4.78 (1 H, t, *J* 7 Hz, CH_2CH=C), 4.21 (1 H, s, ArH), 3.79 (1 H, br s, ArOH), 1.30 (1 H, br s, ArOH), and −1.56 (1 H, br s, ArOH); *m/z* (%) 332 (M^+, 19), 275 (5), 224 (22), 223 (100), 205 (32), 165 (23), 163 (12), and 153 (9) (Found: C, 72.4; H, 8.2. $C_{20}H_{28}O_4$ requires C, 72.3; H, 8.5%).

During the chromatography a fraction eluted with ether–light petroleum (1:24) contained a component giving a blue-black spot on t.l.c. with ferric chloride. The resulting oil (264 mg) in methanol (5 ml) was treated with lead(II) acetate trihydrate (213 mg) in methanol (5 ml) and the subsequent precipitate collected, washed with cold methanol, and dried (38 mg). The lead(II) salt was treated with 3M-sulphuric acid, extracted into ether, washed with saturated aqueous sodium chloride and water, dried ($MgSO_4$), and evaporated under reduced pressure to give 4,6-bis(2-cycloheptylidene-ethyl)-3,5,6-trihydroxy-2-isovalerylcyclohexa-1,4-dien-1-one (**25**) (21 mg) as an oil, R_F 0.82 [formic acid–ethyl formate–hexane (1:8:12)], $\lambda_{max.}$(acidic ethanol) 325sh, 282, and 234 nm; $\lambda_{max.}$(alkaline ethanol) 370sh, 321, and 227 nm; τ 9.07, 9.02 (6 H, 2 d, each *J* 7 Hz, CH_2CHMe_2), 8.55 (16 H, br m, 8 × $CH_2CH_2CH_2$), 7.4—8.1 (*ca.* 12 H, br m, 5 × C=CCH_2 and OH and $COCH_2CHMe_2$), 7.24 (d, *J* 7 Hz, $COCH_2CHMe_2$), 6.95 (d, *J* 7 Hz, C=$CHCH_2C$=), 4.97, 4.88 (2 H, 2 overlapping t, br, each *J* 7 Hz, 2 × C=CH), and −8.82 (s, OH); *m/z* (f.d.) (%) 470 (M^+, 100), 471 (100); *m/z* (e.i.) (%) 470 (M^+, 5), 364 (8), 348 (50), 347 (18), 346 (20), 289 (22), 239 (100), 238 (31), 223 (20), 210 (20), 197 (24), 182 (26), 123 (50), 81 (89), 67 (49), 57 (28), and 55 (46).

Prenylation of 2',4',6'-Trihydroxy-3-isopentylbenzophenone (**32**).—The ketone (**32**) (2.0 g) was prenylated as previously in dry dioxane (50 ml) for 8 h. Work-up as described above afforded a sodium carbonate insoluble fraction (A) and a carbonate soluble fraction (**B**). The residue from fraction (A) [oil (2 g)] was chromatographed on silicic acid (column, 35 × 3 cm). Elution with redistilled ethyl acetate–light petroleum (3:97) gave *2,4,6-trihydroxy-3-isopentyl-5-(3-methylbut-2-enyl)-benzophenone* (**15**) as bright yellow crystals (840 mg, 34%), m.p. 86—89 °C; $\lambda_{max.}$(methanol) 314 (ε 12 260) and 253 nm (7 385); $\lambda_{max.}$(alkaline methanol) 362 (17 400) and 255sh nm (9 330); τ 9.08 (6 H, d, *J* 7 Hz, CH_2CHMe_2), 8.4—8.8 (m, CH_2CHCMe_2), 8.28, 8.24 (6 H, 2 s, C=CMe_2), 7.48 (2 H, m, $CH_2CH_2CHMe_2$), 6.66 (2 H, d, *J* 7 Hz, $ArCH_2C$=C), 4.76 (1 H, br t, *J* 7 Hz, Me_2C=CH), 3.77 (s, br, OH), 2.45 (5 H, m, 5 × ArH), 1.40 (1 H, s, OH), and 0.80 (1 H, s, OH); *m/z* (%) 368 (M^+, 100), 313 (55), 311 (73), 255 (82), 177 (88), 105 (83), 77 (52), and 69 (11) (Found: C, 74.8; H, 7.5. $C_{23}H_{28}O_4$ requires C, 75.0; H, 7.6%). Chromatography of fraction (**B**) on seven 20 × 20 cm chromatoplates and elution with ethyl formate–hexane (4:5) gave, after extraction with ether, drying, and removal of the solvent, two components.

(a) *2-Benzoyl-3,5-dihydroxy-6-isopentyl-6-(3-methylbut-2-enyl)cyclohexa-2,4-dien-1-one* (**21**) (114 mg, 4.7%) was obtained as an oil; $\lambda_{max.}$(acidic methanol) 351 (ε 9 560), 286 (6 374), and 238 nm (9 890); $\lambda_{max.}$(alkaline methanol) 349 (10 990) and 240 nm (15 710); τ 9.16 (br s, CH_2CHMe_2), 8.6—8.8 (overlapped m, br, $CH_2CH_2CHMe_2$), 8.4, 8.3 (2 s, C=CMe_2), 8.15 (br m, $CH_2CH_2CHMe_2$), 7.37 (m, CH_2CH=CMe_2), 6.48 (s, $COCH_2$-CO), 5.04 (m, CH_2CH=CMe_2), 4.55 (br s, HOC=C), 2.58 (m, COPh), and −7.3 (br s, OH); *m/z* (f.d.) (%) 369 (100), 301 (63) (Found: M^+, 368.1976. $C_{23}H_{28}O_4$ requires *M*, 368.1987).

(b) The second component was *6-benzoyl-3,5-dihydroxy-2-isopentyl-6-(3-methylbut-2-enyl)cyclohexa-2,4-dien-1-one* (**41**) (116 mg, 4.7%) isolated as an oil, $\lambda_{max.}$(acidic methanol) 356 (ε 11 760) and 254 nm (5 600); $\lambda_{max.}$(alkaline methanol) 350 (10 320) and 235sh nm (6 270); τ 9.22 (6 H, d, *J* 6 Hz, CH_2CHMe_2), 8.6—8.8 (m, CH_2CHMe_2), 8.45 and 8.38 (6 H, 2 s, C=CMe_2), 8.15 (2 H, m, $Me_2CHCH_2CH_2$), 7.42 (2 H, br d, *J* 7 Hz, CH_2CH=CMe_2), 6.49 and 6.35 (2 s, $COCH_2CO$), 5.07 (1 H, br t, *J* 7 Hz, CH_2CH=CMe_2), 4.17 (0.6 H, s, COCH=COH), and 2.45 (5 H, m, COPh) (irradiation at τ 5.07 collapsed the doublet at τ 7.42 to a broad singlet), *m/z* (%) 368 (M^+, 45), 300 (30), 298 (25), 297 (100), 269 (20), 244 (30), 243 (40), 165 (25), 105 (85), 77 (33), and 69 (70); *m/z* (f.d.) (%) 368 (100), 300 (20) (Found: M^+, 368.1987. $C_{23}H_{28}O_4$ requires *M*, 368.1987).

Hydrogenolysis of the Ketone (**21**).—The above ketone (97 mg) was hydrogenated over 5% Pd–C (20 mg) in methanol (8 ml). After the uptake of 2 mol of hydrogen per mol, and work-up in the usual way, the product (42 mg) (m.p. 95—98 °C) was shown by t.l.c. and mixed m.p. (93—98 °C) to be identical with the authentic ketone (**32**), m.p. 94—97 °C.

Oxidation of the Dihydrodeoxybenzoylhumulone (**15**).—The dihydrodeoxybenzoylhumulone (**15**) (840 mg) in methanol (10 ml) containing lead(II) acetate trihydrate (725 mg) was treated with a slow stream of oxygen. After 2 weeks the precipitated lead salt was centrifuged and washed with ice-cold methanol to leave a pale yellow solid (321 mg). Ether (20 ml) was added and the mixture shaken vigorously with 2M-sulphuric acid (2 × 20 ml), dried, and the solvent removed to leave a mixture of the 6-isopentyl-4-(3-methylbut-2-enyl)- and 4-isopentyl-6-(3-methylbut-2-enyl)-2-benzoyl-3,5,6-trihydroxycyclohexa-2,4-dien-1-one (**28**) and (**29**) (141 mg, 16%); τ (35 °C) 9.1 [m, $CH_2CH_2CHMe_2$ of (**28**) and (**29**)], 8.5—8.9 [m, CH_2CH_2CH-Me_2 of (**28**) and (**29**)], 8.44, 8.32, 8.28 [3 s, CH_2CH=CMe_2 of (**28**) and (**29**)], 7.58 [m, $CH_2CH_2CHMe_2$ of (**29**)], 7.37 [d, *J* 7.5 Hz,

$CH_2CH{=}CMe_2$ of (**29**)], 6.88 [d, *J* 7.5 Hz, $CH_2CH{=}CMe_2$ of (**28**)], 4.85 [br t, $CH_2CH{=}CMe_2$ of (**28**) and (**29**)], 2.9 (br, OH), 2.57 [m, Ar*H* of (**28**) and (**29**)], and −8.6 [br, OH of (**28**) and (**29**)]; τ (−25 °C) −8.62 [s, chelated OH of (**28**)], −8.69 (s, chelated *OH* of (**29**)]. Ratio (**28**):(**29**), 1:1.6.

Oxidation of the Dihydrohumulones (**28**) *and* (**29**).—The solution of the two humulones (**28**) and (**29**) (ratio from low-field OH signals measured at −25 °C, 1:1.6 respectively) was kept in $CDCl_3$ (0.4 ml) and examined by ^1H n.m.r. spectroscopy (at −25 °C) at regular time intervals, the ratio of (**28**) and (**29**) being determined by integration of the low-field enol signals. The results are shown in the Table.

Preparation of 2′,4′,6′-Trihydroxy-3′-isopentylisovalerophenone (**33**).—(a) *From 3,5-dihydroxy-2-isovaleryl-6,6-bis(3-methylbut-2-enyl)cyclohexa-2,4-dien-1-one* (**22**). The ketone (**22**)[7] (3.48 g) in methanol (60 ml) was hydrogenated over 5% Pd–C (1.0 g) until the hydrogen uptake ceased (1 h). The solution was filtered and the methanol evaporated under reduced pressure to yield an oil. Crystallisation and recrystallisation from chloroform–light petroleum gave pure 2′,4′,6′-trihydroxy-3′-isopentylisovalerophenone (**33**) (1.185 g, 42%), m.p. 172—174 °C (lit.,[19] 173—175 °C).

(b) *From 2′,4′,6′-trihydroxy-3′-(3-methylbut-2-enyl)isovalerophenone* (**11**). The ketone (**11**)[7] (660 mg) in methanol (30 ml) was similarly hydrogenated over 5% Pd–C (200 mg). After work-up and recrystallisation as above the product (**33**) (602 mg, 91%) was obtained, m.p. 172—174 °C.

Prenylation of 2′,4′,6′-Trihydroxy-3-isopentylisovalerophenone (**33**).—The above ketone (**33**) (1.85 g) in dry dioxane (15 ml) was added to a solution of 2-methylbut-3-en-2-ol (0.574 g) in dioxane (15 ml). Freshly distilled boron trifluoride–ether (0.59 ml) was added and the mixture stirred at 20 °C for 7 h, then ether (100 ml) was added and the solution washed with water (3 × 75 ml), dried ($MgSO_4$), and the ether evaporated under reduced pressure. The resultant oil was chromatographed on silicic acid (100 g). Elution with ether–light petroleum (1:19) yielded 2′,4′,6′-*trihydroxy-3′-isopentyl-5′-(3-methylbut-2-enyl)isovalerophenone* (**16**) (505 mg, 22%) as an oil, $\lambda_{max.}$(ethanol) 296 and 341sh nm, $\lambda_{max.}$(alkaline ethanol) 341 nm; τ 9.03 (12 H, d, *J* 6.5 Hz, 2 × $CH_2CH_2CHMe_2$), 8.8—8.2 (5 H, m, $CH_2CH_2CHMe_2$), 8.2, 8.16 (6 H, 2 s, $CH{=}CMe_2$), 7.74 (1 H, m, *J* 6.5 Hz, $COCH_2CHMe_2$), 7.48 (2 H, m, $ArCH_2CH_2$), 7.04 (2 H, d, *J* 6.5 Hz, $COCH_2$), 6.64 (2 H, d, *J* 7.5 Hz, $ArCH_2CH{=}$), 4.77 (1 H, t, *J* 7.5 Hz, $CH{=}CMe_2$), 4.20 (1 H, s, OH), 0.29 (1 H, s, ArOH), and −0.07 (1 H, s, ArOH); *m/z* (%) 349 (20), 348 (M^+, 76), 347 (20), 346 (10), 333 (9), 305 (14), 293 (57), 292 (23), 291 (100), 277 (20), 275 (20), 236 (25), 235 (59), 177 (16), 69 (13), 57 (11), 55 (11), 43 (23), and 41 (24) (Found: M^+, 348.2299. $C_{21}H_{32}O_4$ requires *M*, 348.2300).

Elution with ether–light petroleum (1:4) gave a mixture of 6-isopentyl-4-(3-methylbut-2-enyl)- and 4-isopentyl-6-(3-methylbut-2-enyl)-3,5,6-trihydroxy-2-isovalerylcyclohexa-2,4-dien-1-ones (**30**) and (**31**). The ratio of (**30**):(**31**) in the fractions eluted from the column was *ca.* 1:3.5 (see below in the preparation from Pb^{II} salts).

Elution with ether–light petroleum (3:7) yielded the *ketone* (**21**) as an oil (672 mg, 29%), R_F 0.55 [pink with $FeCl_3$ in ethyl acetate–light petroleum (1:4)]; $\lambda_{max.}$(acid ethanol) 326, 272, and 233 nm; $\lambda_{max.}$(alkaline ethanol) 348 and 315sh nm; τ 9.17 (6 H, d, *J* 6 Hz, $CH_2CH_2CHMe_2$), 9.03, 9.05 (6 H, 2 d, each *J* 7 Hz, $COCH_2CHMe_2$), 8.68 (2 H, m, $CH_2CH_2CHMe_2$), 8.45 (6 H, br s, $CH{=}CMe_2$), 7.6—8.3 (4 H, m, $CH_2CH_2CHMe_2$ and $COCH_2CHMe_2$), 7.42 (2 H, br d, *J* 7 Hz, $CH_2CH{=}CMe_2$), 7.05 (2 H, m, $COCH_2CHMe_2$), 6.59 (br s, $COCH_2CO$), 5.13 (1 H, br t, *J* 7 Hz, $CH{=}CMe_2$), 4.23 (s, *HC*=COH), −8.29, −8.60, and −8.82 (chelated OH signals); *m/z* (%) 348 (M^+, 11) 330 (10), 280 (15), 278 (10, 277 (**44**), 249 (15), 224 (12), 223 (20), 69 (100), 57 (22), 43 (25), and 41 (71) (Found: M^+, 348.2313. $C_{21}H_{32}O_4$ requires *M*, 348.2300).

Oxidation of the Dihydrodeoxyhumulone (**16**) *to give the Dihydrohumulones* (**30**) *and* (**31**) *in the Presence of Lead*(II) *Acetate*.—The dihydrodeoxyhumulone (**16**) (500 mg) in methanol (4 ml) was added to a solution of lead(II) acetate trihydrate (570 mg) in methanol (4 ml) and oxygen was bubbled slowly through the solution for 22 h. The precipitated lead(II) salt (308 mg) was collected and washed as described above. After a further 4 days, a further crop (21 mg) was collected and combined with the main crop.

The mother-liquors, after evaporation of the methanol under reduced pressure, was treated with 3M-sulphuric acid, extracted into ether, washed, dried, and the ether evaporated to leave an oil (315 mg). P.l.c. eluting with formic acid–ethyl formate–hexane (1:8:12) gave a brown coloured band (R_F 0.46) which, after extraction and crystallisation from hexane, gave the crude chromanol (**43**) and a pale yellow solid (9.2 mg), m.p. 123—128 °C, τ 9.05 (12 H, d, *J* 7 Hz, 2 × $CHMe_2$), 8.62, 8.64 (6 H, 2 s, $C{=}CMe_2$), 8.2—8.8 (4 H, m, $CH_2CH_2CHMe_2$ and OH), 7.80 (1 H, m, $COCH_2CHMe_2$), 7.49 (2 H, m, $CH_2CH_2CHMe_2$), 7.25—6.90 (overlapping d, *J* 7 Hz, $COCH_2$ and m, $ArCH_2CHOH$), 6.20 (m, *CH*OH), 4.74 (s, OH), and −3.62 (s, OH). Recrystallisation from hexane gave 3,5,7-*trihydroxy-6-isopentyl-8-isovaleryl-2,2-dimethylchroman* (**43**), m.p. 134—138 °C, $\lambda_{max.}$ (ethanol) 294 and 232sh nm, $\lambda_{max.}$(alkaline ethanol) 388 nm; *m/z* (%) 264 (M^+, 47), 349 (5), 308 (24), 307 (100), 293 (22), 289 (17), 275 (9), and 235 (29) (Found: C, 69.1; H, 8.7. $C_{21}H_{32}O_5$ requires C, 69.2; H, 8.8%). The mother-liquors contained small amounts of other oxidation products which were not investigated rigorously.[15]

Oxidation of the Mixture of the Dihydrohumulones (**30**) *and* (**31**).—The mixture of lead salts of the humulones (**30**) and (**31**) (164 mg), as prepared above, was treated with 3M-sulphuric acid, extracted into ether, washed with water, dried ($MgSO_4$), and the solvent evaporated under reduced pressure to yield an oil (67.6 mg) containing the two dihydrohumulones (**31**) and (**30**) in the ratio 3.42:1 as measured by their ^1H n.m.r. low-field OH signals. $\lambda_{max.}$(acidic ethanol) 355sh, 320sh, 284, and 237 nm; $\lambda_{max.}$(alkaline ethanol) 355sh, 325, and 228 nm; τ 8.95—9.20 (m, all $CHMe_2$), 8.6—8.85 (m, $CH_2CH_2CHMe_2$), 8.5, 8.35, 8.30 (3 s, $C{=}CMe_2$), 7.9 (m, $COCH_2CHMe_2$), 7.75—7.45 [m, $C(OH)CH_2C{=}CMe_2$ and $C{=}C{\cdot}CH_2CH_2CHMe_2$], 7.23 (d, *J* 7 Hz, $COCH_2CHMe_2$), 6.92 (d, *J* 7 Hz, $C{=}CHCH_2CH{=}CMe_2$), 5.2 (br, OH), 4.95 (t, br, $CH{=}CMe_2$), 2.5 (br, OH), −8.82 [s, OH of (**30**)], and −8.89 [s, OH of (**31**)]. Salicylaldehyde (10.85 mg) was added to the mixture and its OH signal (τ −0.98) was used as an internal reference by which to measure the quantities of the humulones (**30**) and (**31**) in the solution during air-oxidation. The solution was kept at 20 °C in the ^1H n.m.r. tube and its spectrum recorded periodically over the next 600 h. Between spectra air was allowed into the tube which was then shaken. The relative masses of the humulones (**30**) and (**31**) as a function of time are shown in the Figure.

5,7-Dihydroxy-6-isovaleryl-2,2-dimethyl-3-(3-methylbut-2-enyl)chroman (**35**).—This compound was isolated during the chromatography of the products of the prenylation of 2′,4′,6′-trihydroxy-3′-isopentenylisobutyrophenone.[7] Elution with ether–light petroleum (1:3) gave the *chroman* (**35**) (157 mg from 8.1 g of 2′,4′,6′-trihydroxyisovalerophenone) as an oil, $\lambda_{max.}$ (ethanol) 293 nm; $\lambda_{max.}$(alkaline ethanol) 304 nm; τ 9.04 (6 H, d, *J* 6.5 Hz, CH_2CHMe_2), 8.81 and 8.60 (6 H, 2 s, $OCMe_2$), 8.41 and 8.29 (6 H, 2 s, $C{=}CMe_2$), 8.12 (dd, overlapping, *J* 8, 4.5 Hz,

$ArCH_2CHCH_2$), *ca.* 7.80 (4 H, m, $ArCH_AH_BCHCH{=}CMe_2$ and $COCH_2CHMe_2$), 7.25 (1 H, dd, *J* 16, 4.5 Hz, $ArCH_AH_BCH$), 7.07 (2 H, d, *J* 7 Hz, $COCH_2CHMe_2$), 4.8 (1 H, m, $CH{=}CMe_2$), 4.27 (1 H, s, ArH), 3.24 (1 H, s, ArOH), and −3.36 (1 H, s, ArOH); *m/z* (%) 346 (M^+, 47), 331 (100), 289 (26), 278 (20), 276 (19), 261 (13), 223 (33), 165 (28), 109 (11), 85 (13), 69 (48), 57 (26), 55 (17), 43 (28), and 41 (53); *m/z* (f.d.) (%) 346 (100), 347 (26) (Found: M^+, 346.2125. $C_{21}H_{30}O_4$ requires *M*, 346.2144).

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