Synthesis and Reactions of 3,3-Dimethylallyl Derivatives of Acetylacetone and Other Poly-β-carbonyl Compounds

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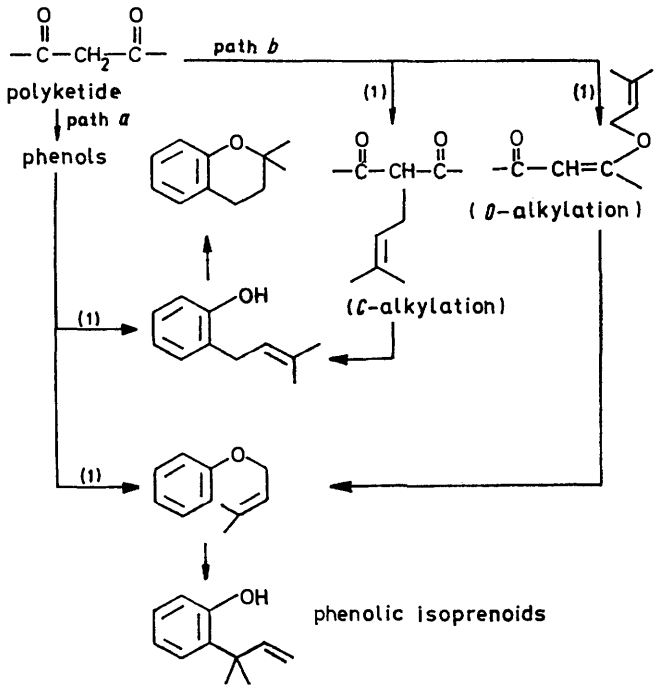
Alkylation of acetylacetone, and of a number of related triketones and lactones, with 3,3-dimethylallyl bromide and 3,3-dimethylallyl diphenyl phosphate gives *C*-alkylated products under a variety of experimental conditions. The *C*- and *O*-(3,3-dimethylallyl) derivatives of acetylacetone undergo ready cyclisation and Claisen rearrangement reactions, respectively, to give products whose isoprenoid part-structures are similar to those found in phenolic isoprenoids. Acetylacetone is converted into 4-bromopent-3-en-2-one under mild conditions by treatment with triphenylphosphine dibromide.

THE recognition of phenolic isoprenoids as a class of natural products [1] rests heavily on the relative ease with which their structures can be subdivided into isoprenoid and phenolic fragments. A widely accepted rationalisation [2] (see Scheme, path *a*) of this feature is that the isoprenoid side chain has been introduced *in vivo* by alkylation of a phenol by 3,3-dimethylallyl pyrophosphate (1), or its higher terpenoid analogues. However, in cases where the phenol is derived from acetate *via* polyketide intermediates, it has been recognised [3] that an alternative process might be alkylation of a polyketide, followed by aromatisation (Scheme, path *b*), and recently some experimental evidence to support this idea has been presented.[4]

Studies of the *in vitro* alkylation of phenols, and of β-dicarbonyl compounds, have attracted attention recently, and the influence of a number of experimental factors, such as the structure of the alkylating agent, solvent, temperature, and the nature of the counter-ion, on the reaction pathway has been established.[5] However, the alkylation of β-dicarbonyl systems with 3,3-dimethylallyl compounds seems to have been neglected, although similar studies on phenols are well documented. This paper reports the results of attempts to synthesise *O*- and *C*-(3,3-dimethylallyl) derivatives of acetylacetone, related triketones, and some β-keto-lactones, and describes some of their chemical transformations which are possibly of relevance to the biosynthesis of phenolic isoprenoids.

Acetylacetone has been treated with both 3,3-dimethylallyl bromide (2) and 3,3-dimethylallyl diphenyl phosphate (3) under a range of solvent and base conditions; the *C*-alkylated product, 3-(3,3-dimethylallyl)pentane-2,4-dione (5a) has been found to predominate in every case. Small amounts of 3,3-bis-(3,3-dimethylallyl)pentane-2,4-dione (6) were sometimes also formed, but on no occasion was the corresponding *O*-alkylated product, 4-(3,3-dimethylallyloxy)pent-3-en-2-one (7) ever isolated from these reactions. It is known [6] that reactive alkylating agents [a classification which would certainly include (2) and (3)] tend to *C*-alkylate β-diketones; thus the failure to observe *O*-alkylation, even in polar aprotic solvents which favour the latter, is perhaps not too unexpected.

The structure of compound (5a) follows largely from its n.m.r. spectrum, which shows absorptions for both



SCHEME Some possible biosynthetic pathways to simplified phenolic isoprenoid structure

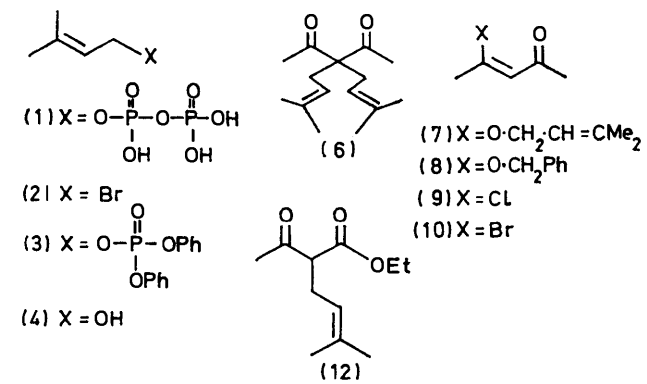
the keto-form (5a) (70%) and the enol form (5b) (30%). In particular, the keto-form showed signals for the proton H_A and the methylene protons H_B as triplets at τ 6·30 (J 7 Hz) and 7·43 (J 7 Hz), respectively. The methylene protons, H_C, of the enolic form resonated as a doublet at τ 7·05 (J 7 Hz). Signals for the acetyl methyl groups of

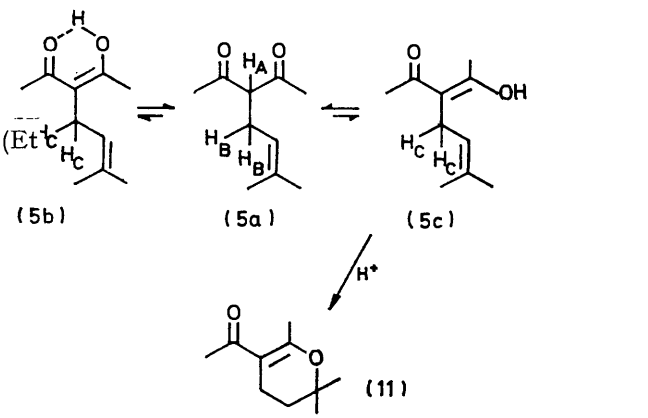
[1] For comprehensive review see W. D. Ollis and I. O. Sutherland in ' Chemistry of Natural Phenolic Compounds,' ed. W. D. Ollis, Pergamon, Oxford, 1961.
[2] T. A. Geissman in ' Biogenesis of Natural Compounds,' ed. P. Bernfield, Pergamon, Oxford, 1963, p. 604.
[3] J. D. Bu'lock, ' The Biosynthesis of Natural Products,' McGraw-Hill, London, 1965, p. 29.
[4] M. Yamazaki, M. Matsuo, and S. Shibata, *Chem. and Pharm. Bull.* (*Japan*), 1965, **13**, 1015; M. Yamazaki and S. Shibata, *ibid.*, 1966, **14**, 96; S. Gatenbeck, P. O. Eriksson, and Y. Hansson, *Acta Chem. Scand.*, 1969, **23**, 699.
[5] R. Gompper, *Angew. Chem. Internat. Edn.*, 1964, **3**, 560; W. J. le Noble, *Synthesis*, 1970, **1**, 1.
[6] W. J. le Noble and J. E. Puerta, *Tetrahedron Letters*, 1966, 1087.

the keto-form appeared at τ 7·80, and the corresponding methyl groups of the enolic form at τ 7·88. Consistent with its enol content, compound (5a) gave a crystalline copper chelate on treatment with methanolic copper(II) acetate.

When 3-(3,3-dimethylallyl)pentane-2,4-dione (5a) was treated with acids, even under mild conditions, it cyclised to give 5-acetyl-3,4-dihydro-2,2,6-trimethyl-2*H*-pyran (11). This behaviour is similar to that of *o*-(3,3-dimethylallyl)phenols, which cyclise readily to 2,2-dimethylchromans under comparable conditions.[7] The cyclisation reactions of (5a) can again be attributed to a ready enolisation to (5c), and subsequent attack of the oxygen on the tertiary carbon atom of the original side-chain olefin.

The alkylation of ethyl acetoacetate also resulted in predominant mono-*C*-alkylation, giving ethyl 2-(3,3-dimethylallyl)-3-oxobutanoate (12), which showed no absorptions for the enol form in its n.m.r. spectrum. Once again, there was a small amount of di-*C*-alkylated product, and no apparent trace of *O*-alkylation.





Similar results were obtained with the triketones, heptane-2,4,6-trione (13) and 1-phenylhexane-1,3,5-trione (14). Alkylation of heptane-2,4,6-trione (13) with dimethylallyl bromide or with dimethylallyl diphenyl phosphate gave 3-(3,3-dimethylallyl)heptane-2,4,6-trione (15a) as the sole product. This compound gave a red colour with neutral iron(III) chloride solution, and the i.r. spectrum showed a sharp absorption at 1723 and a broad band at 1610 cm^{-1}, characteristic of β-dicarbonyl compounds in the enolic form. The absence of a doublet in the n.m.r. spectrum at τ 7·05 [*cf.* (5b)] ruled out the enolic forms (16) and (17), the methylene protons H_B of (15a) and (15b) resonating as a triplet at τ 7·42. The methylene protons H_C gave rise to a very weak signal at τ 6·30, and this signal disappeared slowly on deuteriation. The signal at τ 4·34, which also disappeared on deuteriation, and the triplet at τ 6·58 (J 7 Hz) were assigned to H_D and the methine proton H_A, respectively. Two methyl signals were observed (in addition to those of the prenyl side-chain). That at τ 7·75 was assigned to the acetyl methyl groups of (15a) and (15b), and the higher field signal at τ 7·88 to the enolic methyl group of (15b). Calculations based on the signal intensities of H_A and H_C showed that, in chloroform, the compound is 90% enolised.

1-Phenylhexane-1,3,5-trione (14) was treated similarly with 3,3-dimethylallyl bromide. Two major products were obtained and, athough they could not be obtained sufficiently pure for elemental analysis, spectroscopic data indicated that these were the mono- and di-alkylated derivatives (18) and (19). The n.m.r. spectra showed sharp one-proton signals at τ 3·71 and 3·79, respectively, and, by analogy with the work of Regitz and Geelhaar,[8] these were assigned to the protons H_A in (18) and (19). Confirmation of these enolic structures came from the i.r. spectra (free carbonyl absorption at 1710 hydrogen-bonded carbonyl absorption at 1600 and 1565 cm^{-1}, and from the absence of methylene proton signals in the n.m.r. spectrum of (19) in the region τ 5·40—6·90. The H_B signal of the mono-alkylated product (18) appeared as a triplet at τ 6·49 (J 7 Hz) [*cf.* (15b)].

The heptane-2,4,6-trione (13) was prepared as described by Collie.[9] 3-Acetyl-4-hydroxy-6-methyl-2-pyrone (dehydroacetic acid) (20), obtained by self-condensation[10] of ethyl acetoacetate, was hydrolysed and decarboxylated to give 2,6-dimethyl-4-pyrone (21). On treatment with aqueous sodium hydroxide and barium chloride, the latter compound gave the trione (13) as its barium chelate.

In addition to dehydroacetic acid (20), the self-condensation of ethyl acetoacetate gave a by-product to which was assigned the bispyrone structure (22) on the basis of its u.v. [$\lambda_{max.}$ (EtOH) 270, 276sh, and 330 nm], i.r. (carbonyl absorption at 1735 cm^{-1}), and n.m.r. spectra (two methyl signals at τ 7·40 and 7·60 and two olefinic protons at τ 3·71 and 3·84). 4,7-Dimethyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-dione (22) has been prepared by Fleischmann,[11] by condensation of triacetic acid lactone (24) with ethyl acetoacetate. This preparation was repeated, and the product was shown to be

[7] J. A. Miller and H. C. S. Wood, *J. Chem. Soc.* (*C*), 1968, 1837; C. D. Hurd and W. A. Hoffmann, *J. Org. Chem.*, 1940, **5**, 212.

[8] M. Regitz and H. J. Geelhaar, *Annalen*, 1969, **728**, 108.

[9] J. N. Collie and A. A. B. Reilly, *J. Chem. Soc.*, 1922, 1984.

[10] F. Arndt and P. Nachwey, *Ber.*, 1924, **57**, 1489.

[11] F. N. A. Fleischmann, *J. Chem. Soc.*, 1967, 250; P. F. G. Prail and A. L. Whitear, *Proc. Chem. Soc.*, 1961, 112.

identical to the by-product of the ethyl acetoacetate self-condensation.

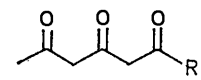
Formation of the by-product could involve deacetylation of dehydroacetic acid (20), followed by condensation of the triacetic acid lactone (24) and ethyl acetoacetate. Such a pathway seems unlikely since deacetylation of dehydroacetic acid requires vigorous conditions [12] (90% sulphuric acid at 135 °C). A more reasonable alternative involves condensation of dehydroacetic acid (20) and ethyl acetoacetate to give the β-keto-lactone (28), which on ' acid ' hydrolysis and dehydration would give the bispyrone (22). The bispyrone (22) is also formed when dehydroacetic acid (20) and diethyl malonate are refluxed together in the presence of solid sodium hydrogen carbonate. This is consistent with the second route. Had deacetylation been the preliminary step, the product would have been the bispyrone (23).

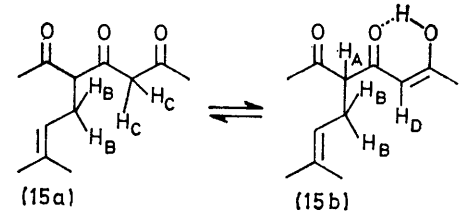
In recent years, considerable progress [13] has been made by other groups concerned with the cyclisation and aromatisation of simple polyketides. For example, both acyclic polyketones [14a] and their cyclised lactone analogues,[14b] such as tetra-acetic acid lactone,[14c] have been converted into aromatic or heterocyclic systems on treatment with basic or acidic reagents. The present investigation was therefore extended to triacetic acid lactone (24), and to 3-acetyl-4-hydroxy-6-phenacyl-2-pyrone (25), both of which were found to undergo *C*-alkylation with 3,3-dimethylallyl bromide in the presence of potassium carbonate.

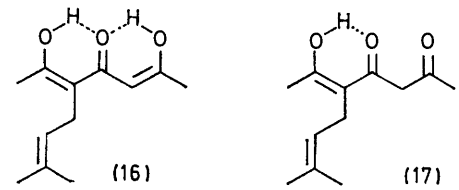
Triacetic acid lactone (24), gave 1,1-bis-(3,3-dimethylallyl)pentane-2,4-dione (29a) as the major product, the n.m.r. spectrum of which, in carbon tetrachloride, showed bands only for the enol form (29b). The enolic hydrogen atom signal appeared at τ −5·30 and a one-proton singlet at τ 4·70 was assigned to H_A. The enolic structure (29b) was confirmed by the i.r. spectrum (broad carbonyl absorption at 1610 and no absorption in the region 1710—1680 cm^{-1}). The compound gave a red colour with methanolic iron(III) chloride.

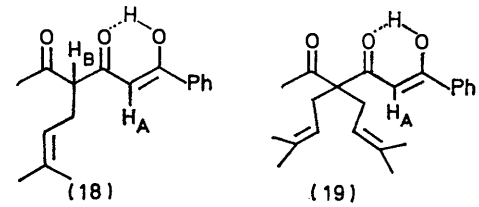
The other product of this reaction gave no colouration with methanolic iron(III) chloride, and was identified as 2,2-bis-(3,3-dimethylallyl)-3,5-dioxohexanoic acid lactone (30), largely on the basis of the n.m.r. spectrum, which showed a four-proton doublet at τ 7·50 for the allylic methylene groups of the side-chains, and a singlet at τ 4·40 for the proton at C-4. The i.r. spectrum showed carbonyl absorption bands at 1770 (γ-lactone) and 1690 cm^{-1}. It seems likely that (29b) was formed from the lactone (30) by hydrolysis, followed by decarboxylation of the resulting acid.

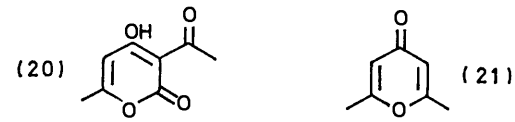
The alkylation of the pyrone (25) with 3,3-dimethylallyl bromide (2) yielded the lactone (26), which showed an enolic proton signal at τ −6·63, a singlet at τ 3·90 for the C-5 proton of the lactone ring, and a triplet (*J* 7 Hz) at τ 5·50 for the methine proton of the substituted phenacyl group in the side chain.

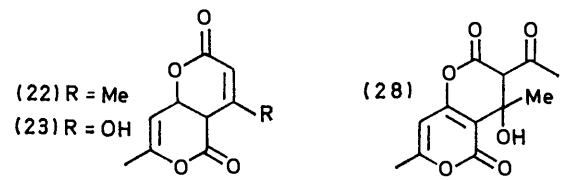


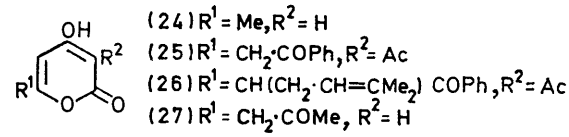












An attempt was made to synthesise tetra-acetic acid lactone (27) by the method described by Scott *et al.*[15] Refluxing triacetic acid lactone (24) and malonyl chloride

[12] M. A. Butt and J. A. Elvidge, *J. Chem. Soc.*, 1963, 4483.
[13] T. Money, *Chem. Rev.*, 1970, 553.
[14] (*a*) T. T. Howarth and T. M. Harris, *J. Amer. Chem. Soc.*, 1971, **93**, 2506; (*b*) T. M. Harris and M. P. Wachter, *Tetrahedron*, 1970, **26**, 5255; (*c*) R. Bentley and P. M. Zwitkowits, *J. Amer. Chem. Soc.*, 1967, **89**, 676.
[15] H. Guilford, A. I. Scott, D. Skingle, and M. Yalpari, *Chem. Comm.*, 1968, 1127; T. Money, F. W. Comer, G. R. B. Webster, I. G. Wright, and A. I. Scott, *Tetrahedron*, 1967, **23**, 3435.

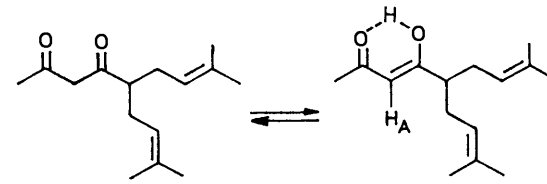
in trifluoroacetic acid gave the bispyrone (23), which, on controlled hydrolysis (M-potassium hydroxide solution at room temperature), gave 6-acetonyl-5-carboxy-4-hydroxy-2-pyrone (31). In contrast to the findings of Scott and his co-workers, refluxing this acid in dioxan (sodium-dried and distilled) in the presence of copper bronze gave acetylphloroglucinol and not tetra-acetic acid lactone (27). This result is surprising since formation of acetylphloroglucinol would require hydrolysis of the α-pyrone followed by Claisen type cyclisation of the linear polyketide intermediate.

Although the direct alkylations described did not produce any isolable enol ethers, it seemed that the preparation of one of these and a study of its properties would be worthwhile. Allylic enol ethers of alkyl acetoacetates have been described in the literature, or can be assumed to have been prepared *in situ* on previous occasions. For example, Lauer and Kilburn [16] prepared ethyl 3-allyloxycrotonate (32) by displacement of chloride from ethyl 3-chlorocrotonate (33) with sodamide and allyl alcohol, and showed that it underwent a smooth thermal rearrangement at 150 °C.

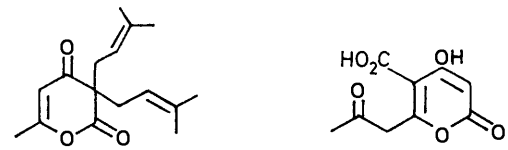
The preparation [17] of ethyl 2-(1,1-dimethylallyl)-3-oxobutanoate (36) by the reaction of ethyl 3-ethoxycrotonate (34) with 3,3-dimethylallyl alcohol (4), in the presence of sodium hydrogen sulphate at 150 °C, presumably involves the formation of the allyl ether (35) by ether exchange and then its thermal rearrangement to (36). However, we could find no record of the preparation of 3,3-dimethylallyl enol ethers of acetylacetone, and methods analogous to those described for acetoacetates were tried.

The ether exchange method was attempted on a mixture of *O*- and *C*-benzyl acetylacetones, formed by direct benzylation of acetylacetone with benzyl diphenyl phosphate (38). Treatment of this mixture with 3,3-dimethylallyl alcohol (4) and mercury(II) acetate resulted in loss of the benzyl enol ether (8) and formation of benzyl 3,3-dimethylallyl ether (39), together with acetylacetone. Thus the enol ether (8) was acting as a benzylating agent, and not as a source of an oxovinyl group.

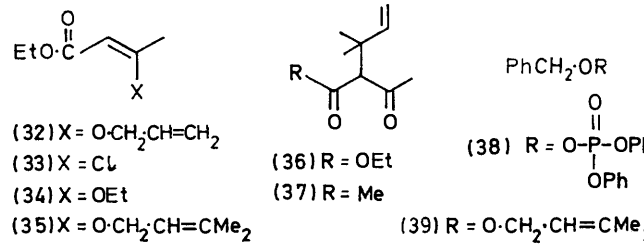
Of the 4-halogenopent-3-en-2-ones (9) and (10) required to examine the halide displacement route to the ether (7), only the 4-chloro-compound has been made (in low yield by a process [18] which has some drawbacks), and an alternative synthesis was sought. It was found that the 4-bromo-compound (10) could be made conveniently from acetylacetone by treatment with triphenylphosphine dibromide, according to a modification of the method published for bromonaphthalene.[19] This consists of a high-temperature reaction between β-naphthol and triphenylphosphine dibromide, and it seemed possible that the method might apply to any ketone with a relatively high enol content. By conducting the reaction in dimethylformamide at room temperature, moderate yields of the bromo-ketone (10) were obtained.



(29a) (29b)



(30) (31)

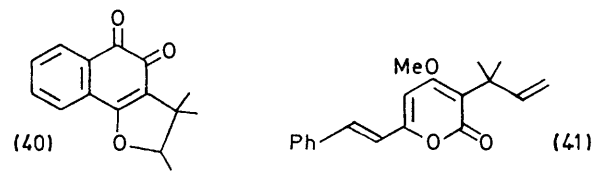


(32) X = O·CH$_2$CH=CH$_2$
(33) X = Cl
(34) X = OEt
(35) X = O·CH$_2$·CH=CMe$_2$

(36) R = OEt
(37) R = Me

(38) R = O-P(=O)(OPh)-OPh

(39) R = O·CH$_2$·CH=CMe$_2$



(40) (41)

Although a variety of conditions was tried, it was not possible to convert the bromide (10) into the ether (7) using 3,3-dimethylallyl alcohol in the presence of base. The enol ether (7) was finally synthesised by displacement of chloride from (9) using 3,3-dimethylallyl alcohol (4) and butyl-lithium in tetrahydrofuran, and isolated, in low yield, by preparative g.l.c.

When heated at 130 °C in a sealed tube, the enol ether (7) rearranged cleanly to 3-(1,1-dimethylallyl)pentane-2,4-dione (37), which gave an extremely simple n.m.r. spectrum owing to the inhibition of enolisation by the bulky side chain. Thus enol ethers of acyclic β-diketones rearrange thermally to give products with the same isoprenoid structural features as the type of *o*-(1,1-dimethylallyl)phenol formed by Claisen rearrangement of 3,3-dimethylallyl phenyl ethers. The implication of Claisen-type processes in biological systems was suggested

[16] W. M. Lauer and E. I. Kilburn, *J. Amer. Chem. Soc.*, 1937, **59**, 2586.
[17] K. Brack and M. Schinz, *Helv. Chim. Acta*, 1951, **34**, 2005.
[18] J. P. Henry, R. M. Manyik, and W. E. Walker, U.S.P. 2,971,983 (*Chem. Abs.*, 1961, **55**, 24,567).
[19] J. P. Schaffer, J. Higgins, and P. K. Shenny, *Org. Synth.*, 1969, **49**, 7.

some time ago,[20] and recent tracer studies by Grundon and his co-workers [21] have confirmed this viewpoint. The relative ease with which allylic enol ethers of β-diketones, or of β-keto-acid derivatives, rearrange thermally, in comparison to allylic ethers of phenols, has been applied to synthetic problems, such as the synthesis of dunnione [22] (40) and of mundulea lactone [23] (41), and moreover, may be a significant factor in biological systems.

In summary, the direct alkylation of acetylacetone and higher analogues with 3,3-dimethylallyl derivatives results in *C*-alkylation in the systems described. The acid-catalysed ring closure of the *C*-alkylated derivative and the thermal rearrangement of the *O*-alkylated derivative both result in the formation of structures analogous to those observed in the *in vitro* reactions of phenolic derivatives. The similarity of these structures to those found in large numbers of phenolic isoprenoids lends chemical support to the argument that *C*- and *O*-alkylation of polyketides is possibly a biosynthetic route to phenolic isoprenoids. An extension of these studies, designed to investigate the effect of different metal chelates on these reactions, is being undertaken.

EXPERIMENTAL

U.v. spectra were determined with a Unicam SP 800A spectrophotometer. I.r. spectra were run on a Perkin-Elmer 257 instrument, either for liquid films or for potassium chloride discs. ^{1}H N.m.r. spectra were determined with Perkin-Elmer R10 spectrometers (60 or 100 MHz) (tetramethylsilane as standard). G.l.c. (analytical and preparative) was carried out on a Pye series 105 Chromatograph. The following stationary phases were employed: (A) methylsilicone gum (E30) on Celite; (B) Carbowax 20M on siliconised Diatomite C.

Alkylation of Acetylacetone (with R. Tosh).—(i) 3,3-*Dimethylallyl bromide in acetone.* 3,3-Dimethylallyl bromide (11·0 g, 0·074 mol), acetylacetone (7·0 g, 0·07 mol), and anhydrous potassium carbonate (9·7 g, 0·07 mol) in acetone (25 ml) were refluxed with stirring for 6 h. The solid was filtered off; evaporation of the filtrate, *in vacuo*, gave a yellow oil (7·2 g). G.l.c. analysis showed that two components were present, in the ratio 92 : 8. Fractional distillation of the oil gave the main product as a liquid, 3-(3,3-dimethylallyl)pentane-2,4-dione (3·4 g, 30%), b.p. 107—108° at 33 mmHg, g.l.c. retention time (R_t) (20% E30 at 100 °C) 8·50 min (Found: C, 71·8; H, 10·0. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%), $\nu_{max.}$ (film) 1720w,sh, 1700vs, 1610sh, and 1585s cm^{-1}, τ ($CDCl_3$) −6·85 (0·2H s, disappeared on deuteriation), 4·92br (1H, t, *J* 7 Hz), 6·30 (0·7H, t, *J* 7 Hz), 7·05 (0·6H, d, *J* 7 Hz), 7·43 (1·4H, t, *J* 7 Hz), 7·8—7·9 (6H, m), and 8·30 (6H, m). The ratio of the signals due to the methylene protons in the keto- and enol forms indicates that the compound is 30% enolic.

The product (1·0 g) was dissolved in methanol (10 ml) and methanolic copper acetate was added. The solid was filtered off; recrystallisation from benzene–light petroleum (b.p. 60—80°) gave the *copper chelate* of 3-(3,3-*dimethylallyl*)*pentane*-2,4-*dione* (0·2 g) as grey needles, m.p. 201—202° (Found: C, 60·4; H, 7·3. $C_{20}H_{30}CuO_4$ requires C, 60·4; H, 7·6%), $\nu_{max.}$ (KCl) 1568vs cm^{-1}.

The residue obtained after distillation consisted mainly of the component having the higher g.l.c. retention time. A pure sample was isolated by preparative g.l.c. and the oil obtained was identified as 3,3-*bis*-(3,3-*dimethylallyl*)*pentane*-2,4-*dione*, R_t (20% E30 at 100 °C) 30·0 min (Found: C, 75·8; H, 10·5. $C_{15}H_{24}O_2$ requires C, 76·2; H, 10·2%), $\nu_{max.}$ (film) 1690s, 1675sh, and 1655sh cm^{-1}, τ ($CDCl_3$) 5·13br (2H, t, *J* 7 Hz), 7·38 (4H, d, *J* 7 Hz), 7·90 (6H, s), 8·30 (6H, s), and 8·39 (6H, s).

(ii) 3,3-*Dimethylallyl bromide in dimethylformamide.* Sodium hydride (50% dispersion in oil; 3·0 g, 0·0625 mol) was washed with dry light petroleum and added to a stirred solution of acetylacetone (6·0 g, 0·06 mol) in dimethylformamide (50 ml). After effervescence had ceased, 3,3-dimethylallyl bromide (10·5 g, 0·07 mol) was added dropwise over 1 h to the stirred solution, and the mixture was stirred for a further 14 h. Water was added and the aqueous solution was extracted with ether (3 × 50 ml). The dried extracts yield a pale yellow oil (9·08 g), which was distilled to give a major fraction of b.p. 70—75° at 15 mmHg, identified as 3-(3,3-dimethylallyl)pentane-2,4-dione (3·5 g, 34%).

(iii) 3,3-*Dimethylallyl bromide in hexamethylphosphoric triamide.* The sodium salt of acetylacetone was prepared and treated exactly as above. The n.m.r. spectrum of the crude oil obtained after extraction showed a very small absorption at τ 5·44 (d, *J* 7 Hz), which may have been due to the enol ether (7). However no trace of this doublet remained after the initial distillation, which again yielded the dione (5a).

(iv) 3,3-*Dimethylallyl diphenyl phosphate.* Acetylacetone (5 g, 0·05 mol), 3,3-dimethylallyl diphenyl phosphate [7] (15·9 g, 0·05 mol), and anhydrous potassium carbonate (13·8 g, 0·1 mol) in anhydrous acetone (125 ml) were stirred and refluxed for 16 h. The white solid was filtered off and washed with acetone (250 ml). The combined washings and filtrate were evaporated *in vacuo*. The oil obtained was dissolved in light petroleum (b.p. 40—60°; 100 ml) and the petroleum layer was washed with dilute sodium hydrogen carbonate solution (2 × 50 ml) and (25 ml), dried (Na_2SO_4), and evaporated *in vacuo*, leaving a pale yellow oil (5·2 g). The i.r. spectrum of the oil was very similar to that of 3-(3,3-dimethylallyl)pentane-2,4-dione. G.l.c. analysis (10% PEG 20M at 130 °C) showed that there was only one product, R_t 3·90 min, identical with that of an authentic sample of 3-(3,3-dimethylallyl)pentane-2,4-dione.

Cyclisation of 3-(3,3-*Dimethylallyl*)*pentane*-2,4-*dione.*—3-(3,3-dimethylallyl)pentane-2,4-dione (0·5 g) was dissolved in nitromethane (10 ml) at 0 °C, and conc. sulphuric acid (0·4 ml) in nitromethane (2 ml) was added with stirring. The mixture was stirred at 0 °C for 90 min and poured into water (50 ml) and light petroleum (50 ml); the organic phase was washed with aqueous sodium hydrogen carbonate (50 ml) and dried. The petroleum was then evaporated and the residual oil distilled to give 5-*acetyl*-3,4-*dihydro*-2,2,6-*trimethyl*-2H-*pyran* (0·42 g, 84%), b.p. 46—48° at 0·05 mmHg (Found: C, 71·7; H, 9·5. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%), $\lambda_{max.}$ (EtOH) 272 nm (ε 20,800), *m/e* 168,

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153, 125, 117, 97, and 56, $\nu_{max.}$ (film) 1680, 1230, and 1120 cm^{-1}; τ 7·70 (2H, t), 7·95br (6H, s, MeC=C and MeC=O), 8·38 (2H, t), and 8·80 (6H, s, Me_2C–O).

Alkylation of Ethyl Acetoacetate with 3,3-*Dimethylallyl Bromide*.—Ethyl acetoacetate (2·08 g, 0·016 mol), 3,3-dimethylallyl bromide (2·6 g, 0·016 mol), and anhydrous potassium carbonate (2·2 g, 0·016 mol) in acetone (15 ml) were refluxed with stirring for 4·5 h. The solid was filtered off and the filtrate was evaporated *in vacuo*. A yellow liquid (2·3 g) remained. G.l.c. analysis (20% E30 at 100 °C) showed a single compound, R_t 12·4 min. Preparative g.l.c. yielded an oil, which gave a pale green colour with neutral iron(III) chloride solution, identified as *ethyl* 2-(3,3-*dimethylallyl*)-3-*oxobutanoate* (Found: C, 66·5; H, 9·65. $C_{11}H_{18}O_3$ requires C, 66·7; H, 9·15%), $\nu_{max.}$ (film) 1740vs, 1720vs, and 1650w cm^{-1}, τ ($CDCl_3$) 4·85br (1H, t, *J* 7 Hz), 5·72 (2H, q, *J* 7 Hz), 6·49 (1H, t, *J* 7 Hz), 7·40 (2H, t, *J* 7 Hz), 7·72 (3H, s), 8·30 (6H, m), and 8·70 (3H, t, *J* 7 Hz).

A trace of a second compound (2%) was observed when higher column temperature were used. At 180 °C, ethyl 2-(3,3-dimethylallyl)-3-oxobutanoate had R_t 0·72 min, whereas, the unidentified product had R_t 2·62 min. Preparative g.l.c. yielded an oil, which gave no colour with neutral iron(III) chloride solution; $\nu_{max.}$ (film) 1740vw, 1720vs, and 1670w,sh cm^{-1}. No other spectral data were available because of shortage of material. This compound was formulated tentatively as ethyl 2,2-bis-(3,3-dimethylallyl)-3-oxobutanoate.

Alkylation of Heptane-2,4,6-trione.[9]—(i) *With* 3,3-*dimethylallyl bromide*. Heptane-2,4,6-trione (1·4 g, 0·01 mol), 3,3-dimethylallyl bromide (1·6 g, 0·011 mol), and anhydrous potassium carbonate (1·4 g, 0·01 mol) in acetone (15 ml) were refluxed with constant stirring for 4 h. The solid was filtered off and filtrate was evaporated *in vacuo* to leave a viscous oil (1·6 g).

G.l.c. analysis (20% E30 at 140 °C) showed a major product (50% of mixture) of R_t 5·4 min. The oil was chromatographed on silica gel with benzene and a pure sample of the major product was obtained by preparative g.l.c. 3-(3,3-*Dimethylallyl*)*heptane-2,4,6-trione* was obtained as an oil and gave a red colour with neutral iron(III) chloride solution (Found: C, 68·4; H, 8·85. $C_{12}H_{18}O_3$ requires C, 68·6; H, 8·6%), $\nu_{max.}$ (film) 1723s, 1660w,sh, and 1610vs cm^{-1}, τ ($CDCl_3$) 4·34 (1H, s), 4·90br (1H, t, *J* 7 Hz), 6·30 (*ca.* 0·2H, s), 6·58 (1H, t, *J* 7 Hz), 7·42 (2H, t, *J* 7 Hz), 7·75 (3H, s), 7·88 (3H, s), and 8·30 (6H, m).

(ii) *With* 3,3-*dimethylallyl diphenyl phosphate*. Heptane-2,4,6-trione (1·4 g, 0·01 mol), 3·3-dimethylallyl diphenyl phosphate (3·2 g, 0·01 mol), and anhydrous potassium carbonate 1·4 g, 0·01 mol) in acetone (50 ml) were refluxed with constant stirring for 14 h. The solid was filtered off and washed with acetone (50 ml.). The combined filtrate and washings were evaporated *in vacuo* to leave a yellow oil (1·4 g).

G.l.c. analysis (20% E30 at 140 °C) showed that the major product had R_t 5·3 min, identical with that of authentic 3-(3,3-dimethylallyl)heptane-2,4,6-trione.

Alkylation of 1-*Phenylhexane-1,3,5-trione with* 3,3-*Dimethylallyl Bromide*.—1-Phenylhexane-1,3,5-trione [24] (5·1 g, 0·025 mol), 3,3-dimethylallyl bromide (3·7 g, 0·025 mol), and anhydrous potassium carbonate (3·45 g, 0·025 mol) in acetone (30 ml) were refluxed, with constant stirring, for 5 h. The solid was filtered off and the filtrate was evaporated *in vacuo* to leave a viscous oil (6·1 g).

T.l.c. on silica (benzene as solvent) showed that the oil consisted of at least seven compounds. Samples of the two major products were obtained by chromatographing the oil on silica gel (150 g) with benzene, but the samples obtained were too impure for elemental analysis. Both products gave red colours on treatment with methanolic iron(III) chloride.

The more mobile compound on silica (benzene as solvent; R_F 0·45) was obtained as a yellow oil (60 mg) and was tentatively identified as 4,4-bis-(3,3-dimethylallyl)-1-phenylhexane-1,3,5-trione, $\nu_{max.}$ (film) 1710m, 1600s, 1565s, and 1270s cm^{-1}, τ ($CDCl_3$) 1·80—2·70 (5H, m), 3·79 (1H, s), 5·10 (2H, t, *J* 7 Hz), 7·34 (4H, d, *J* 7 Hz), 7·86 (3H, s), 8·31 (6H, s), and 8·40 (6H, s).

The other isolated product (t.l.c. on silica; benzene as solvent; R_F 0·20) was obtained as a yellow oil (120 mg) and was identified as 4-(3,3-*dimethylallyl*)-1-*phenylhexane*-1,3,5-*trione*, M^+ 272·1419 ($C_{17}H_{20}O_3$ requires 272·1412), $\nu_{max.}$ (film) 1710m, 1680m, 1600s, and 1565s cm^{-1}, τ ($CDCl_3$) 1·80—2·70 (5H, m), 3·71 (1H, s), 4·90 (1H, t, *J* 7 Hz), 6·49 (1H, t, *J* 7 Hz), 7·35 (2H, m), 7·78 (3H, s), and 8·37 (6H, m).

Dehydroacetic Acid.—Ethyl acetoacetate (100 g) was refluxed with solid sodium hydrogen carbonate (0·05 g); during the reaction the ethanol (28·6 g) which formed distilled over. Heating was continued until the temperature of the mixture reached 206 °C. Distillation gave two fractions: (i) b.p. 34—80° at 14 mmHg, mainly ethyl acetoacetate (20·6 g), and (ii) b.p. 100—120° at 0·2 mmHg, mainly dehydroacetic acid. The latter fraction solidified on cooling. Crystallisation from ethanol gave crystals (16·0 g, 40%), m.p. 108·5—110° (lit.,[10] 109°), $\lambda_{max.}$ (EtOH) 310 nm (log ε 4·079), $\nu_{max.}$ (KCl) 3075w, 1705s, 1638s, 1615m, and 1540s cm^{-1}, τ ($CDCl_3$) —6·97 (1H, s), 3·97 (1H, s), 7·30 (3H, s), and 7·68 (3H, s).

The residue left after distillation was dissolved in ethanol (200 ml) and decolouring charcoal was added. The mixture was heated for 30 min and the solid was filtered off. Evaporation of the filtrate *in vacuo* yielded pink crystals. Crystallisation from ethanol gave the bispyrone as flesh-coloured needles (1·0 g), m.p. 218—220° (lit.,[11] 214°) (Found: C, 62·75; H, 4·5. Calc. for $C_{10}H_8O_4$: C, 62·5; H, 4·2%), $\lambda_{max.}$ (EtOH) 278 (log ε 3·980), 284 (3·964), 332 (4·021) and 338 nm (4·021), $\lambda_{min.}$ 298 nm (3·634), $\nu_{max.}$ (KCl) 3095w, 3060w, 1735vs, 1638m, 1600m, and 1540m cm^{-1}, τ ($CDCl_3$) 3·71 (1H, s), 3·84 (1H, s), 7·40 (3H, s), and 7·60 (3H, s), identical (i.r. and u.v. spectra and m.p.) with an authentic sample [11] of 4,7-dimethyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-dione.

Yields of dehydroacetic acid were improved by working on a larger scale (300 g of ethyl acetoacetate) and heating the mixture until the temperature reached 195 °C.

Condensation of Dehydroacetic Acid with Diethyl Malonate.—Dehydroacetic acid (6·3 g, 0·0375 mol), diethyl malonate (12·0 g, 0·075 mol), and sodium hydrogen carbonate (0·05 g) were refluxed for 4 h. During this period, ethanol (b.p. 68—72°; 1·4 g) distilled over. Excess of diethyl malonate was removed by distillation and a dark viscous oil remained. The oil was chromatographed on neutral alumina with benzene, and the waxy crystals obtained were washed with light petroleum (b.p. 60—80°; 20 ml) and then recrystallised from ethanol. The bispyrone formed flesh-coloured crystals (0·5 g), m.p. 215—217°, identical (i.r. and u.v. spectra and m.p.) with an authentic sample [11] of 4,7-dimethyl-2*H*,5*H*-pyrano[4,3-*b*]pyran-2,5-dione.

[24] M. L. Miles, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, 1965, **30**, 1007.

Alkylation of Triacetic Acid Lactone with 3,3-Dimethylallyl Bromide.—Triacetic acid lactone [12] (2·5 g, 0·02 mol), 3,3-dimethylallyl bromide (3·0 g, 0·02 mol), and anhydrous potassium carbonate (2·8 g, 0·02 mol) in acetone (25 ml) were refluxed with constant stirring for 3 h. The solid was filtered off and the filtrate was evaporated *in vacuo*. T.l.c. (silica) in benzene showed two spots when the plate was developed with 2% sulphuric acid in methanol The faster-moving spot (A; major product, R_F 0·5) gave a yellow colour with the reagent whereas the other product (B; R_F 0·3) gave a greenish-yellow colour. On spraying the plate with methanolic iron(III) chloride solution, the more mobile material gave an immediate red colour whereas the other spot gave a red colour after 30 min at room temperature. Samples of both compounds were obtained by chromatographing the oil on silica gel with benzene.

The first compound eluted from the column was obtained as a viscous oil (100 mg); t.l.c. on silica (benzene as solvent) showed that the material was homogeneous. The compound was identified as 1,1-*bis*-(3,3-*dimethylallyl*)*pentane*-2,4-*dione* (Found: M^+, 236·1779. $C_{15}H_{24}O_2$ requires M, 236·1776), $\nu_{max.}$ (film) 1610vs cm^{-1}, τ (CCl_4) −5·30br (1H), 4·70 (1H, s), 5·02br (2H, t, J 7 Hz), 7·60—8·00 (5H, m), 8·02 (3H, s), 8·34 (6H, s), and 8·42 (6H, s).

The second compound eluted was obtained as a viscous oil (50 mg). T.l.c. analysis on silica gel (benzene as solvent) showed that the material contained a trace of the more mobile compound. However, the new compound was tentatively characterised as 2,2-bis-(3,3-dimethylallyl)-3,5-dioxohexanoic acid lactone, $\nu_{max.}$ (film) 1770s, 1740w, and 1690vs cm^{-1}, (CCl_4) 4·40 (1H, s), 5·05br (2H, t, J 7 Hz), 7·50 (4H, d, J 7 Hz), 7·90 (3H, s), 8·35 (6H, s), and 8·42 (6H, s).

Alkylation of 3-Acetyl-4-hydroxy-6-phenacyl-2-pyrone with 3,3-Dimethylallyl Bromide.—3-Acetyl-4-hydroxy-6-phenacyl-2-pyrone [25] (1·4 g, 0·005 mol), 3,3-dimethylallyl bromide (0·745 g, 0·005 mol), and anhydrous potassium carbonate (0·69 g, 0·005 mol) in acetone (20 ml) were refluxed with constant stirring for 5 h. The solid was filtered off and the filtrate, on evaporation *in vacuo*, gave an oil (1·5 g). Chromatography on silica gel, with chloroform–ethyl acetate (1 : 1) as eluant, gave a pale yellow oil (100 mg). T.l.c. (silica gel) in chloroform–ethyl acetate (1 : 1) showed a single spot and this gave a faint orange colour with methanolic iron(III) chloride. The compound was identified as 3-*acetyl*-6-(1-*benzoyl*-4-*methylpent*-3-*enyl*)-4-*hydroxy*-2-*pyrone* (Found: M^+, 340·1309. $C_{20}H_{20}O_5$ requires M, 340·1311), $\nu_{max.}$ (film) 1730s, 1685s, 1635s, 1600s, and 1550s cm^{-1}, τ ($CDCl_3$) −6·63br (1H), 1·80—2·60 (5H, m), 3·90 (1H, s), 4·92 (1H, t, J 7 Hz), 5·50 (1H, t, J 7 Hz), 7·00—7·50 (5H, m), and 8·35 (6H, m).

Decarboxylation of 6-Acetonyl-5-carboxy-4-hydroxy-2-pyrone.—6-Acetonyl-5-carboxy-4-hydroxy-2-pyrone [15] (1·1 g) and copper bronze (1·0 g) in anhydrous dioxan (15 ml) were refluxed, with exclusion of moisture, for 4·5 h. The reaction was followed by t.l.c. (silica) in ethyl acetate–chloroform (1 : 1). The compounds were located by spraying with methanolic iron(III) chloride. The product (R_F 0·6) gave a dark blue colour whereas the starting material (R_F 0·05) gave an orange colour. The solid was filtered off and the filtrate was evaporated *in vacuo*. The resulting gum was chromatographed on silica gel (30 g) with ethyl acetate–chloroform (1 : 1). The product had the same R_F value (0·6) as authentic acetylphloroglucinol. Recrystallisation from ethyl acetate–petroleum (b.p. 60—80°) gave straw-yellow crystals (250 mg), m.p. 214—215° (lit., 219°) (Found: M^+, 168·0430. Calc. for $C_8H_8O_4$: M, 168·0423). The u.v. and n.m.r. spectra were identical with those of authentic acetylphloroglucinol: $\lambda_{max.}$ (EtOH) 287 nm (log ε 4·183), τ [$(CD_3)_2SO$] 4·12 (1·5H, sharp s), 6·54br (1·5H), and 7·42 (3H, s).

Attempted Preparation of 4-(3,3-Dimethylallyloxy)pent-3-en-2-one by Ether Exchange.—Sodium hydride (50% dispersion in oil; 3·0 g, 0·625 mol) was washed with dry light petroleum and added to a stirred solution of acetylacetone (6·0 g, 0·06 mol) in dimethylformamide (50 ml). After the evolution of hydrogen had ceased, benzyl diphenyl phosphate [26] (38) (20·4 g, 0·06 mol) in dimethylformamide (50 ml) was added over 30 min, and the mixture was stirred for a further 12 h. Extraction in the usual fashion yielded an oil (9·5 g) which was then distilled to give a fraction of b.p. 92—99° at 0·4 mmHg, the n.m.r. spectrum of which showed a singlet at τ 5·22 due to 4-benzyloxypent-3-en-2-one (15% of benzylated product), and absorptions for 3-benzylpentane-2,4-dione. A sample (0·76 g ≡ 0·001 mol of ether) of this mixture was then warmed at 100 °C with a mixture of 3,3-dimethylallyl alcohol (0·086 g, 0·001 mol) and mercury(II) acetate (0·032 g; freshly crystallised). During 20 h at 100 °C, the gradual loss of the peak at τ 5·22 in the n.m.r. spectrum was observed, together with the simultaneous appearance of peaks at τ 4·5 (acetylacetone), and 5·32 (s). The latter absorption corresponded to that of benzyl 3,3-dimethylallyl ether, and this was confirmed by g.l.c. comparison of the reaction mixture with that of pure compound (39).

Benzyl 3,3-Dimethylallyl Ether.—A stirred solution of benzyl alcohol (2·16 g, 0·02 mol) in dimethylformamide (20 ml) was treated with oil-free sodium hydride (0·28 g, 0·02 mol), and then, after effervescence had ceased, with 3,3-dimethylallyl bromide (3·0 g, 0·025 mol). The mixture was stirred for a further 10 h before pouring into water (100 ml) and washing with ether (2 × 50 ml). The combined ethereal extracts were washed with water (3 × 100 ml), dried, and evaporated to give a residual oil (3·35 g), from which benzyl 3,3-dimethylallyl ether (1·16 g, 45%) was obtained as an oil by chromatography on alumina with petroleum as solvent; $\nu_{max.}$ 1670, 1085, 1070, 735, and 698 cm^{-1}, τ 2·72 (5H, Ar), 4·6 (1H, t), 5·33 (2H, s), 5·98 (2H, d), and 8·32br (6H, s).

4-Bromopent-3-en-2-one.—Triphenylphosphine (29 g, 0·11 mol) was dissolved in dimethylformamide (350 ml) at −5 °C, and bromine (17·6 g, 0·11 mol) was added during 30 min so that the temperature of the mixture did not rise above 0 °C. Acetylacetone (10 g, 0·1 mol) and then triethylamine (10 g, 0·1 mol) were added dropwise during 30 min, and the mixture was stirred at room temperature for 12 h, after which time the colour had darkened. The mixture was poured into water (500 ml) and extracted with ether (4 × 50 ml), and the combined extracts were washed with water (4 × 500 ml) and dried. Evaporation left an oil, from which a mixture of *cis*- and *trans*-4-bromopent-3-en-2-one (6·4 g, 38%) was distilled, b.p. 54—55° at 15 mmHg (lit.,[27] 47—48° at 8 mmHg). The n.m.r. spectrum showed absorptions at τ 3·3 and 3·45 (ratio 9 : 1) for the olefinic protons of the two bromo-ketone isomers, at τ 7·26 (partially resolved singlets, MeC=), and at τ 7·84br (s, MeC=O).

[25] T. M. Harris and C. M. Harris, *Chem. Comm.*, 1966, 699.
[26] G. W. Kenner and J. Mather, *J. Chem. Soc.*, 1956, 3524.
[27] L. F. Chelparova and L. M. Mashlyakovskii, *Zhur. org. Khim.*, 1966, **2**, 602.

Of the absorptions due to the olefinic protons, the low-field signal was a broadened singlet, and is assigned to the isomer with a *cis* geometry (of the olefinic proton and methyl); that at higher field was a resolved quartet (J 1·5 Hz), assigned to the *trans*-isomer.

Attempted Preparation of 4-(3,3-*Dimethylallyloxy*)*pent*-3-*en*-2-*one*.—(i) *From* 4-*bromopent*-3-*en*-2-*one*. Petroleum-washed sodium hydride (0·12 g, 0·0025 mol) was added to a solution of 3,3-dimethylallyl alcohol (0·215 g, 0·0025 mol) in dimethylformamide (5 ml). When kept at 40 °C the resultant solution remained homogeneous, and was then treated with 4-bromopent-3-en-2-one (0·326 g, 0·002 mol). A red colouration developed overnight, and the mixture was then poured into water (50 ml) and washed with ether (2 × 20 ml). The combined ether extracts were washed with water (5 × 20 ml), dried, and evaporated to leave an oil which was found (g.l.c.; n.m.r.) to consist of a mixture of starting materials only. The same result was obtained from a similar experiment using potassium carbonate (0·002 mol) in acetone (10 ml), instead of sodium hydride and dimethylformamide.

(ii) *From* 4-*chloropent*-3-*en*-2-*one*. n-Butyl-lithium (2·35M-solution in hexane; 8 ml, 0·02 mol) was added carefully to a stirred solution of 3,3-dimethylallyl alcohol (2·15 g, 0·025 mol) in anhydrous tetrahydrofuran (20 ml) at 0° under nitrogen. The mixture was stirred for 45 min, during which time it became yellow. 4-Chloropent-3-en-2-one (4·4 g, 0·038 mol) in anhydrous tetrahydrofuran (20 ml) was added with stirring, and the solution then turned a deep red colour. Stirring was continued overnight at room temperature. Methanol (5 ml) was then added and the solvent was distilled off. The residual oil was dissolved in benzene and the solution was filtered. T.l.c. (alumina) in benzene showed that the oil was a complex mixture but the major component had R_F 0·4. 4-(3,3-*Dimethylallyloxy*)*pent*-3-*en*-2-*one* was obtained as an oil (100 mg) by chromatographing the benzene solution on neutral alumina (140 g) and eluting with benzene, followed by preparative g.l.c. (20% E30 at 100°) (Found: C, 71·15; H, 9·6. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%), $\lambda_{max.}$ (n-hexane) 250 nm (ε 14,000), $\nu_{max.}$ (film) 1678s and 1582vs cm^{-1}, τ (CCl_4) 4·60 (2H, m), 5·72 (2H, d, J 6 Hz), 7·78 (3H, s), 7·93 (3H, s), 8·20 (3H, s), and 8·28 (3H, s).

Thermal Rearrangement of 4-(3,3-*Dimethylallyloxy*)*pent*-3-*en*-2-*one*.—4-(3,3-Dimethylallyloxy)pent-3-en-2-one was heated in a sealed tube at 130° for 2·5 h. G.l.c. analysis of the products (20% E30 at 130°) showed the presence of one compound, R_t 6 6 min, identical (R_t and i.r. spectrum) with authentic 3-(1,1-dimethylallyl)pentane-2,4-dione (R_t of starting material, 9·5 min).

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