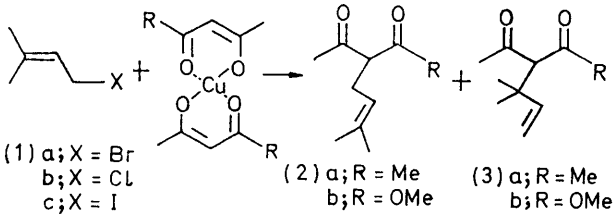
Formation of 1,1-Dimethylallyl Derivatives by Reaction of 3,3-Dimethylallyl Halides with Copper(II) Chelates of Acetylacetone and Methyl Acetoacetate

By **J. Allen Miller,* Charles M. Scrimgeour,** and (in part) (Miss) **Rona Black,** Department of Chemistry, University of Dundee, Dundee DD1 4HN
John Larkin, Derek C. Nonhebel, and **Hamish C. S. Wood,** Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow

Alkylation of the copper(II) chelates of acetylacetone and methyl acetoacetate by 3,3-dimethylallyl halides yields both 3,3-dimethylallyl and 1,1-dimethylallyl products. Formation of 1,1-dimethylallyl derivatives of these β-polyketide analogues appears to be the results of a direct *C*-alkylation, and is a significant characteristic of the copper chelate reactions, which has not been observed previously with other alkylation reactions of β-diketones or β-keto-esters.

A RECENT paper [1] has described the alkylation of alkali metal salts of acetylacetone, and of other poly-β-carbonyl compounds, with 3,3-dimethylallyl derivatives, to produce 3,3-dimethylallyl *C*-alkylated products. In the same paper, attention was drawn to the question of the biosynthesis of those phenolic isoprenoids whose phenolic portion is derived by the acetate–malonate pathway, and which may be formed by the prenylation of a polyketide substrate.[2] One of the attractions of the 'polyketide alkylation' theory is that chelation of the polyketide could control the site of alkylation.[3] It thus seemed appropriate that the previous study of the alkylation of simple salts of β-dicarbonyl compounds should be extended to alkylation of the related metal chelates.

The copper(II) chelates of acetylacetone and of methyl acetoacetate were prepared by standard methods, and initially their reactions with 3,3-dimethylallyl bromide (1a) in chloroform were studied. In the reaction with the chelate of acetylacetone, the major product was readily identified as 3-(3,3-dimethylallyl)pentane-2,4-dione (2a), which has previously been isolated from the alkylation of the sodium salt of acetylacetone. The other product was formed in yields generally below 20%, and was isolated by preparative g.l.c. It had an extremely simple n.m.r. spectrum [τ 3·78 (1H, dd), 4·75—5·10



(1) a; X = Br
b; X = Cl
c; X = I

(2) a; R = Me
b; R = OMe

(3) a; R = Me
b; R = OMe

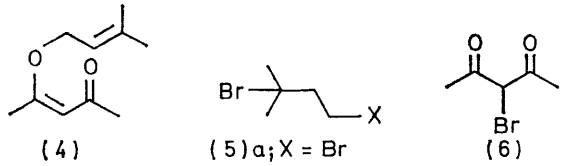
(2H, m), 6·20 (1H, s), 7·75 (6H, s), and 8·80 (6H, s)], indicating that it was 3-(1,1-dimethylallyl)pentane-2,4-dione (3a), and this was confirmed by i.r. bands for a non-conjugated ketone (1690 cm^{-1}) and for a CH_2=CH– group (1000 and 912 cm^{-1}). Unlike the spectrum of (2a), the n.m.r. spectrum of (3a) showed no evidence of enolisation in deuteriochloroform, presumably owing to the bulky nature of the tertiary allylic side-chain.

The formation of compound (3a) is of considerable interest, since structures with tertiary allylic centres are not normally easy to form, except by unimolecular

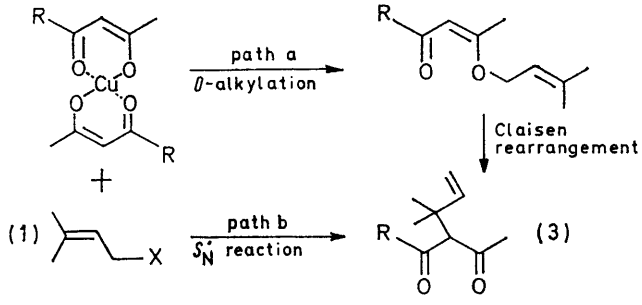
[1] J. Carnduff, J. Larkin, J. A. Miller, D. C. Nonhebel, B. R. Stockdale, and H. C. S. Wood, *J.C.S. Perkin I*, 1972, 692.
[2] W. D. Ollis and I. O. Sutherland in 'Chemistry of Natural Phenolic Compounds,' ed. W. D. Ollis, Oxford, 1961, p. 83.
[3] J. D. Bu'lock, 'The Biosynthesis of Natural Products,' McGraw-Hill, London, 1965, p. 29.

solvolyses,[4] or by sigmatropic processes such as the Claisen rearrangement.[5] In the Scheme, two possible routes to structures of type (3) are outlined; these are akin to two of the more favoured suggestions [2,6] for the biosynthesis of the group of 1,1-dimethylallyl phenols already mentioned. One route (path a) involves *O*-alkylation of acetylacetone followed by Claisen rearrangement, and the other (path b) involves a direct *C*-alkylation, in a mode formally related to an S_N' reaction.

It is known [1] that 4-(3,3-dimethylallyloxy)pent-3-en-2-one, (4), rearranges at 120 °C to give 3-(1,1-dimethylallyl)pentane-2,4-dione (3a). It thus seemed possible



that, under the conditions of the copper(II) chelate alkylation, compound (4) had formed and then rearranged to (3a). However, all attempts to isolate (4) from alkylations at room temperature failed. The preparation [1] of the enol ether (4) is difficult, and leads to such minute quantities of product that it was not possible to perform the more direct test of adding compound (4) to the alkylation reaction mixture. Thus no evidence in favour of path a has been obtained.



SCHEME

With regard to the possibility that (3a) was formed by path b, it is well established that bimolecular reactions of allylic compounds [such as (1a)] which are unsubstituted at the 1-position, but doubly substituted at the 3-position, do not normally result in allylic rearrangement.[7] It therefore appeared that the reaction leading to (3a) might be a unimolecular process, in which the role of the copper ion is to aid ionisation of the allylic bromide. Support for this interpretation comes from a similar rationalisation of the known catalysis by copper(I) chloride of the interconversion of 4-chlorobut-1-ene and 3-chlorobut-1-ene.[8] *

At this stage the matter was further complicated by the discovery that 1,3-dibromo-3-methylbutane (5a) (isoprene dihydrobromide) was also one of the products of the foregoing alkylations, and furthermore, that it reacts slowly with copper acetylacetonate in refluxing chloroform to give compound (3a) as the only alkylated product. Isoprene dihydrobromide (5a) can be prepared [9] by the addition of two mol. equiv. of hydrogen bromide to isoprene, and it is found as a by-product in the preparation of 3,3-dimethylallyl bromide (1a) from isoprene. Its presence in these alkylations was therefore not unexpected. However, it was found that compound (3a) was formed, albeit slowly, even when rigorously pure 3,3-dimethylallyl bromide was used.

In these copper chelate reactions the initial intense blue or green colour is slowly discharged, and a copious white precipitate has formed by the end of the reaction. This precipitate is copper(I) bromide, and its formation appears to be the result of the instability, under the reaction conditions, of copper(II) bromide, a presumed initial product. Copper(II) halides are known to cause halogenation of a variety of organic substrates [10,11] and a separate experiment showed that copper(II) bromide reacted with acetylacetone to form hydrogen bromide, together with small amounts of 3-bromopentane-2,4-dione (6). Therefore, the effective consequence of the instability of copper(II) bromide, under the alkylation reaction conditions, is to generate hydrogen bromide in the presence of 3,3-dimethylallyl bromide (1a), and hence to form isoprene dibromide (5a). Since compound (5a) will only be formed slowly, as a result of the initial alkylation reaction leading to (2a), and since it reacts sluggishly with copper(II) acetylacetonate in refluxing chloroform, the low yield of the 1,1-dimethylallyl compound (3a) from the reactions of 3,3-dimethylallyl bromide (1a) is not surprising.

Although these results implicate isoprene dihydrobromide (5a) in the formation of the 1,1-dimethylallyl product (3a) during the alkylation of copper(II) acetylacetonate by 3,3-dimethylallyl bromide, a qualitative assessment of the relative rates of reaction of pure (5a) and pure (1a) with the chelate indicated that the reaction of (5a) was too slow to explain the formation of up to 20% of (3a) in the reactions of the halides (1) with the chelate. Confirmation of this view came from the reactions of the copper(II) derivative of methyl acetoacetate. This chelate reacts with the bromide (1a) to give the alkylated keto-esters (2b) and (3b), in yields similar to those from the acetylacetonate alkylations. However, the dihydrobromide (5a) was totally

* We thank a referee for drawing this work to our attention.

[4] R. H. DeWolfe and W. G. Young, *Chem. Rev.*, 1956, **56**, 753.
[5] A. Jefferson and F. Scheinmann, *Quart. Rev.*, 1968, **22**, 391.
[6] M. L. Wolform, F. Komitsky, G. Fraenkel, J. H. Looker, E. E. Dickey, P. W. McWain, A. Thompson, P. Mundell, and O. M. Windrath, *J. Org. Chem.*, 1964, **29**, 692; J. R. Chamberlain, J. F. Collins, and M. F. Grundon, *Chem. Comm.*, 1969, 1269.
[7] R. H. DeWolfe and W. G. Young, in ' The Chemistry of Alkenes,' ed. S. Patai, Interscience, London, 1964, p. 688.
[8] J. F. Lane, J. Fentress, and L. T. Sherwood, *J. Amer. Chem. Soc.*, 1944, **66**, 545.
[9] R. V. Levina, V. N. Kostin, and V. A. Tartakovskii, *Zhur. obshchei Khim.*, 1956, **26**, 2998 (*Chem. Abs.*, 1957, **51**, 8658).
[10] For a recent survey, see D. C. Nonhebel in ' Essays in Free Radical Chemistry,' *Chem. Soc. Special Publ.*, No. 24, 1970, p. 409.
[11] T. Koyano, *Bull. Chem. Soc. Japan*, 1971, **44**, 1158; T. Koyano and O. Watanabe, *ibid.*, p. 1378; W. C. Baird, J. H. Surridge, and M. Buza, *J. Org. Chem.*, 1971, **36**, 2088.

inert to the copper(II) chelate of methyl acetoacetate. Thus the formation of compound (3b) cannot be ascribed to the intermediate generation and reaction of isoprene dihydrobromide (5a), and a similar viewpoint is probably valid for the acetylacetonate.

These experiments do not indicate how copper(II) acetylacetonate reacts with isoprene dihydrobromide (5a) to form compound (3a). Further studies have shown that simple alkyl bromides, such as n-propyl bromide and t-butyl bromide, do not react with copper(II) acetylacetonate under comparable conditions. Moreover, 1,3-dibromopropane has also been found to be unreactive towards the copper chelate. Thus a tertiary bromide is apparently necessary for reaction, but this alone is not a sufficient condition. It was considered possible that participation by the primary bromine atom of (5a) was responsible for its apparently special reactivity, despite the fact that 4-Br participation [12] does not seem to have much precedent. In view of the known ability of sulphur to participate in displacement reactions at saturated carbon centres,[12] an analogue of (5a), 3-bromo-3-methylbutyl phenyl sulphide (5b), was synthesised. However compound (5b) did not react with copper(II) acetylacetonate on prolonged refluxing in chloroform; thus this experiment did not support the foregoing argument.

The original question of the mechanism of the formation of 1,1-dimethylallyl compounds in the alkylations with 3,3-dimethylallyl bromide (1a) remains unanswered, despite further experiments. For example, it was found that, in reactions with the methyl acetoacetate complex, the nature of the halogen of the allylic halide was not important in determining the ratio of (2b) to (3b) in the product, although the overall rate decreased substantially in the series (1c) > (1a) > (1b). These data may tentatively be interpreted in terms of processes involving dimethylallyl carbonium ions, although the rate and product composition data already mentioned are not accurate or reproducible enough to allow any firm rationale to be presented.

EXPERIMENTAL

I.r. spectra were run on a Perkin-Elmer 137 spectrometer for liquid films. N.m.r. spectra were determined for solutions in carbon tetrachloride with tetramethylsilane as internal standard, with a Perkin-Elmer R10 spectrometer (60 Hz). G.l.c. was carried out on a Pye series 105 chromatograph. Reagent grade chloroform was used throughout.

3,3-Dimethylallyl Iodide.—3,3-Dimethylallyl chloride (1·04 g) was dissolved in dimethylformamide (20 ml) and sodium iodide (dry; 3·0 g) was added to the stirred solution at room temperature. The mixture was stirred in the dark for 1 h, by which time it had turned dark red, and n.m.r. analysis showed that no chloride remained, and that the only signals present were ascribable to 3,3-dimethylallyl iodide [τ 4·6 (1H, m), 6·15 (2H, d, J 8 Hz), 8·12 (3H, s), and 8·20 (3H, s); $\nu_{max.}$ 1645, 1135vs, and 832 cm^{-1}]. The commercial sample (Kodak) of 3,3-dimethylallyl chloride used for these experiments contained about 10% of the isomeric 1,1-dimethylallyl chloride, but this too was converted into the primary iodide during the exchange reaction. The iodide became discoloured in the light at room temperature, and decomposed on attempted distillation, even at low pressures. The results of microanalysis of a redistilled sample were not satisfactory, giving a low figure for iodine.

1,3-Dibromo-3-methylbutane (Isoprene Dihydrobromide).—Hydrogen bromide in glacial acetic acid (200 ml; 47%) was mixed with isoprene (34 g) and the mixture was set aside at room temperature for 2 h, then washed with cold dilute sodium hydroxide, and dried over magnesium sulphate. Evaporation gave a residue, which was distilled to give 1,3-dibromo-3-methylbutane (92 g, 80%), b.p. (60—61 °C at 8 mmHg) (lit.,[9] 70 °C at 10 mmHg); $\nu_{max.}$ 1385, 1240, 1190, 1175, 1080, 840, and 760 cm^{-1}; τ 6·53 (2H, m), 7·70 (2H, m), and 8·25 (6H, s)

3-Bromo-3-methylbutyl Phenyl Sulphide.—Benzenethiol (11·25 ml) was dissolved in dry dimethylformamide (100 ml) and sodium hydride (50% dispersion in oil; 4·8 g) was added to the stirred solution. After effervescence had ceased, 3,3-dimethylallyl bromide (14·9 g) was added dropwise during 15 min, and the mixture was stirred for a further 2 h. The mixture was then poured into water (1 l) and extracted with ether (3 × 500 ml). The combined extracts were dried and evaporated, and the residual oil treated with hydrogen bromide in glacial acetic acid (20 ml; 45%) at 0 °C for 45 min. The mixture was poured into water (200 ml) and extracted with chloroform (3 × 20 ml); the extracts were combined, washed with dilute aqueous sodium hydroxide, dried, and evaporated. The residual oil was distilled to give 3-bromo-3-methylbutyl phenyl sulphide (18 g, 60%), b.p. 128 °C at 0·2 mmHg (Found: M^+, 260·0065; $C_{11}H_{15}BrS$ requires M, 260·0057); τ 2·35 (5H, m), 6·95 (2H, m), 8·00 (2H, m), and 8·38 (6H, s).

Reaction of Copper(II) Acetylacetonate with 3,3-Dimethylallyl Bromide.—(*a*) A mixture of copper(II) acetylacetonate [13] (19·5 g, 0·072 mol.), 3,3-dimethylallyl bromide (22·5 g, 0·15 mol), and anhydrous potassium carbonate (21·0 g, 0·15 mol) in chloroform (150 ml) was stirred and refluxed for 10 h. The solid was filtered off and washed with chloroform (150 ml). The combined filtrate and washings were evaporated *in vacuo*. The resulting waxy solid was dissolved in methylene chloride and shaken with aqueous acetic acid. The methylene chloride layer was washed with dilute sodium hydrogen carbonate solution (2 × 25 ml) and then with water, dried (Na_2SO_4), and evaporated *in vacuo*. G.l.c. analysis (6 ft column; 20% methyl silicone gum at 100 °C) of the residual oil (10·0 g) showed that it consisted of two components of retention times 4·18 (A) (12—20%) and 7·8 min (B) (80—88%). Pure specimens of the two compounds (both colourless oils) were obtained by preparative g.l.c. The more volatile was 3-(1,1-*dimethylallyl*)*pentane-2,4-dione* (Found: C, 71·55; H, 10·0. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%); $\nu_{max.}$ (film) 3078w, 1720sh, 1690vs, 1640sh, 1000m, and 912s cm^{-1}; τ ($CDCl_3$) 3·78 (1H, dd, J 17 and 12 Hz), 4·75—5·10 (2H, m), 6·20 (1H, s), 7·75 (6H, s), and 8·80 (6H, s). The less volatile compound was identical (i.r. spectrum and g.l.c.) with an authentic sample [1] of 3-(3,3-dimethylallyl)pentane-2,4-dione.

(*b*) After a similar reaction (on one-fifth scale) the crude product (2·2 g) was chromatographed on alumina (50 g) with methylene chloride as eluant. A small quantity of a colourless oil (0·25 g) eluted with the solvent front was identified as 1,3-dibromo-3-methylbutane, by comparison of its i.r. and n.m.r. spectra with those of authentic material.

[12] B. Capon, *Quart. Rev.*, 1964, **18**, 45.
[13] H. D. Murdoch and D. C. Nonhebel, *J. Chem. Soc.*, 1962, 2143.

(*c*) When the reaction was carried out at room temperature for 1 week, the crude product was the same as that when the reaction was carried out in refluxing chloroform.

Reaction of Copper(II) *Acetylacetonate with* 1,3-*Dibromo*-3-*methylbutane*.—Copper(II) acetylacetonate (5·26 g), anhydrous potassium carbonate (5·5 g), and isoprene dihydrobromide (9·2 g) were refluxed together in chloroform (150 ml) for 72 h. The solution was filtered, washed with ammonia solution (*d* 0·88; 3 × 100 ml), dried, and evaporated. The crude product was chromatographed on alumina (40 g) (diethyl ether as eluant; 40 ml fractions). Fractions 1—3 contained only 1,3-dibromo-3-methylbutane, fraction 4 a mixture of 1,3-dibromo-3-methylbutane and 3-(1,1-dimethylallyl)pentane-2,4-dione, and fractions 5—6 pure diketone. No other product was obtained. The yield of 3-(1,1-dimethylallyl)pentane-2,4-dione was in the range 2—5%.

Reaction of Copper(II) *Acetylacetonate with Various Alkyl Bromides*.—These reactions were carried out as in the previous experiment, except that 1,3-dibromo-3-methylbutane was replaced by t-butyl bromide, n-propyl bromide, 1,3-dibromopropane, and 3-bromo-3-methylbutyl phenyl sulphide in turn. Each reaction gave no alkylated product as shown by n.m.r. spectroscopy.

Reaction of Copper(II) *Bromide with Acetylacetone*.—Equimolar amounts of copper(II) bromide and acetylacetone were shaken in chloroform. A white precipitate of copper(I) bromide formed and fumes of hydrogen bromide were evolved. When the reaction was repeated in benzene solution, 3-bromopentane-2,4-dione was formed (liberated iodine from acidic potassium iodide solution) in small amounts.

Reaction of the Copper(II) *Chelate of Methyl Acetoacetate with* 3,3-*Dimethylallyl Halides*.—(a) *With* 3,3-*dimethylallyl bromide*. A mixture of the chelate [14] (14·7 g), 3,3-dimethylallyl bromide (15 g), and anhydrous potassium carbonate (14 g) was stirred in chloroform (150 ml) at room temperature for 18 h, then filtered. The filtrate was washed with ammonia solution (200 ml; *d* 0·88 diluted ×2), and then with water (200 ml), dried, and evaporated to leave an oil (18 g). This oil gave three main peaks on g.l.c. analysis (20% methyl silicone gum at 180 °C), with retention times 6·0, 7·9, and 14·9 min (approximate ratio 1 : 4 : 1). Preparative g.l.c. (20% methyl silicone gum, at 160 °C) gave methyl 3-(1,1-*dimethylallyl*)*acetoacetate* (3b) (retention time 6·0 min) (Found: M^+, 184·1101. $C_{11}H_{16}O_3$ requires M, 184·1100); τ ($CDCl_3$) 3·8 (1H, dd, J 17 and 12 Hz), 4·8—5·1 (2H, m), 6·25 (3H, s), 6·50 (1H, s), 7·76 (3H, s), and 8·77 (6H, s); $\nu_{max.}$ (film) 1730, 1715, 1140, 993, and 917 cm^{-1}; and methyl 3-(3,3-*dimethylallyl*)*acetoacetate* (2b) (retention time 7·9 min) (Found: M^+, 184·1103); τ ($CDCl_3$) 4·6—4·9 (1H, m), 6·12 (3H, s), 6·38 (1H, t, J 8 Hz), 7·35 (2H, t, J 8 Hz), 7·70 (3H, s), and 8·28 (6H, s); $\nu_{max.}$ (film) 1730, 1715, 1203, 1160, and 847 cm^{-1}.

(b) *With* 3,3-*dimethylallyl chloride*. This was performed on a tenth of the scale of the foregoing reaction; 3,3-dimethylallyl chloride (1·04 g) was used in place of the bromide and stirring of the mixture was continued for 12 days. Reaction periods less than 24 h were not sufficient for significant product formation. After 12 days, the characteristic green colour of the chelate had not diminished greatly. Work-up by extraction with ammonia (as before) yielded a pale yellow oil (1·1 g), found to consist mainly of the alkylated esters (2b) and (3b), identified by g.l.c. retention time and by n.m.r., in ratios ranging from 2·1 : 1·0 to 3·8 : 1·0.

(c) *With* 3,3-*dimethylallyl chloride in the presence of sodium iodide*. This was an identical experiment to (b), except that anhydrous sodium iodide (1·5 g) was added to the reaction mixture. The mixture was almost colourless after being stirred overnight (16 h) in chloroform in the dark. Work-up by extraction with ammonia [as in (a)] yielded an oil (1·9 g) consisting of the alkylated esters (2b) and (3b), identified as in experiment (b), in ratios ranging from 2·6 : 1·0 to 3·6 to 1·0.

[2/2283 *Received, 4th October*, 1972]

[14] F. G. Mann and B. C. Saunders, ' Practical Organic Chemistry,' 3rd edn., Longmans, London, 1952, p. 210.