

## Synthesis of $\delta$ -Damascone [*trans*-1-(2,6,6-Trimethylcyclohex-3-enyl)but-2-en-1-one] and $\beta$ -Damascenone [*trans*-1-(2,6,6-Trimethylcyclohexa-1,3-dienyl)but-2-en-1-one]<sup>1</sup>

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Diels–Alder addition of penta-1,3-diene to 3-bromo-4-methylpent-3-en-2-one catalysed by aluminium chloride gave stereoisomeric 4-acetyl-4-bromo-3,5,5-trimethylcyclohexenes (11) and (12), dehydrobromination of which led to 1-acetyl-2,6,6-trimethylcyclohexa-1,3-diene (8). Condensation of this dienone (8) with acetaldehyde and dehydration of the resulting aldol (19) produced  $\beta$ -damascenone (1). The same sequence of reactions on the adduct (5) of penta-1,3-diene and 4-methylpent-3-en-2-one led to  $\delta$ -damascone (20).

Use of copper(I) bromide in dimethylformamide is suggested for *cis*-dehydrobromination of  $\alpha$ -bromo-ketones.

IN 1970, the group at Firmenich & Co. reported<sup>2</sup> the isolation of  $\beta$ -damascenone (1) from Bulgarian rose oil (*Rosa damascena* Mill.), to the odour of which it contributes an important note, though it is only a minor constituent. This ketone has since been found as a trace component in other natural materials<sup>3,4</sup> and much effort has been devoted to its synthesis,<sup>2,5,6</sup> and that of  $\beta$ -damascone (2), which also occurs widely in nature.<sup>3,7</sup>

The cyclohexene ring with its essential substituents can in principle be constructed by a Diels–Alder reaction in four different ways (if acetylenic dienophiles are omitted), shown in Scheme 1. We selected reaction (iii) because both reactants are easily available and a simple modification was expected to allow introduction of the second double bond found in the cyclohexane ring of  $\beta$ -damascenone (1). [Reaction (iv) is of little value

<sup>1</sup> Preliminary account, K. S. Ayyar, R. C. Cookson, and D. A. Kagi, *J.C.S. Chem. Comm.*, 1973, 161.

<sup>2</sup> E. Demole, P. Enggist, U. Sauberli, M. Stoll, and E. Sz. Kovats, *Helv. Chim. Acta*, 1970, **53**, 541; G.P. 1,807,568.

<sup>3</sup> E. Demole and D. Berthet, *Helv. Chim. Acta*, 1971, **54**, 681; 1972, **55**, 1866.

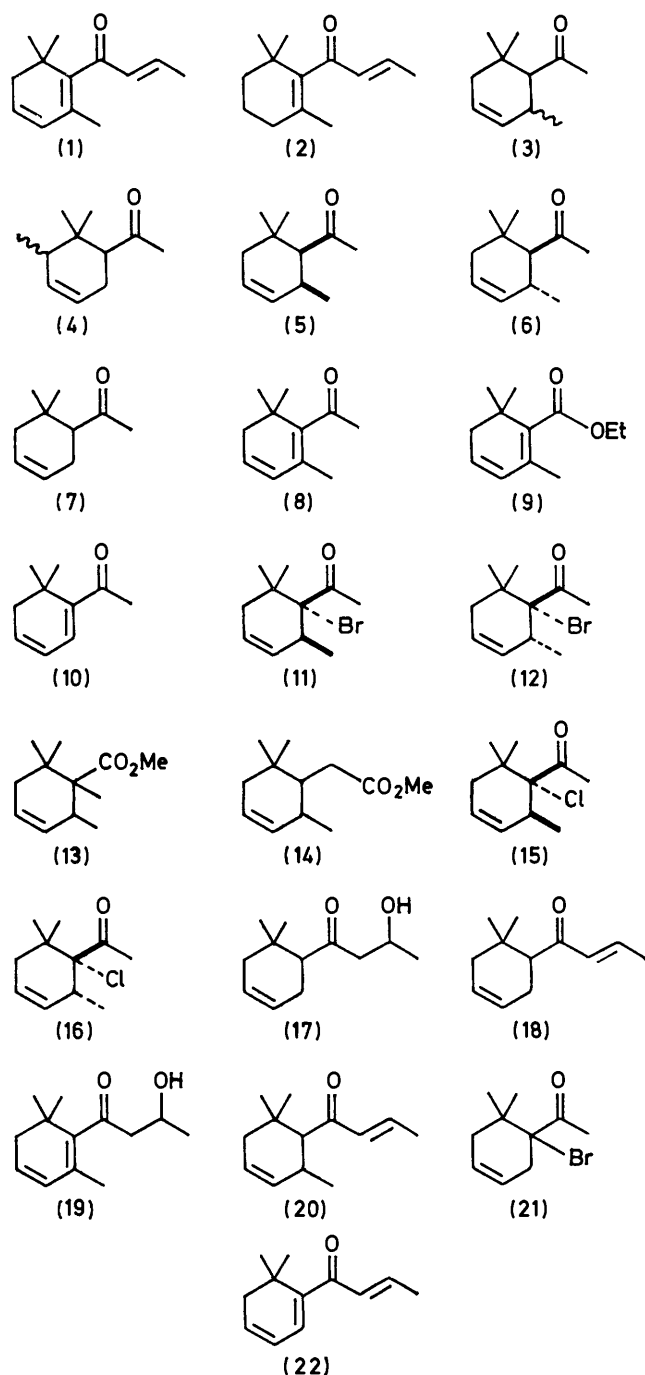
<sup>4</sup> M. Winter and P. Enggist, *Helv. Chim. Acta*, 1971, **54**, 1891; K. Karlsson, I. Wahlberg, and C. R. Enzell, *Acta Chem. Scand.*, 1972, **26**, 2837; J. Strating and P. Van Eerde, *J. Inst. Brewing*, 1973, **79**, 414.

<sup>5</sup> G. Ohloff and G. Uhde, *Helv. Chim. Acta*, 1970, **53**, 531; K. H. Schulte-Elte, V. Rautenstrauch, and G. Ohloff, *Helv. Chim. Acta*, 1971, **54**, 1805; K. H. Schulte-Elte, B. L. Muller, and G. Ohloff, *ibid.*, p. 1899; G.P. 2,022,216; K. H. Schulte-Elte, B. L. Muller, and G. Ohloff, *Helv. Chim. Acta*, 1973, **56**, 310; V. Rautenstrauch, *ibid.*, p. 2492; G. Büchi and J. C. Vederas, *J. Amer. Chem. Soc.*, 1972, **94**, 9128.

<sup>6</sup> G. Büchi and H. Wüest, *Helv. Chim. Acta*, 1971, **54**, 1767.

<sup>7</sup> B. Kimland, A. J. Aasen, and C. R. Enzell, *Acta Chem. Scand.*, 1972, **26**, 2177.

because of the fast rearrangement of 4-methylpenta-1,3-diene to 2-methylpenta-1,3-diene.<sup>8]</sup>



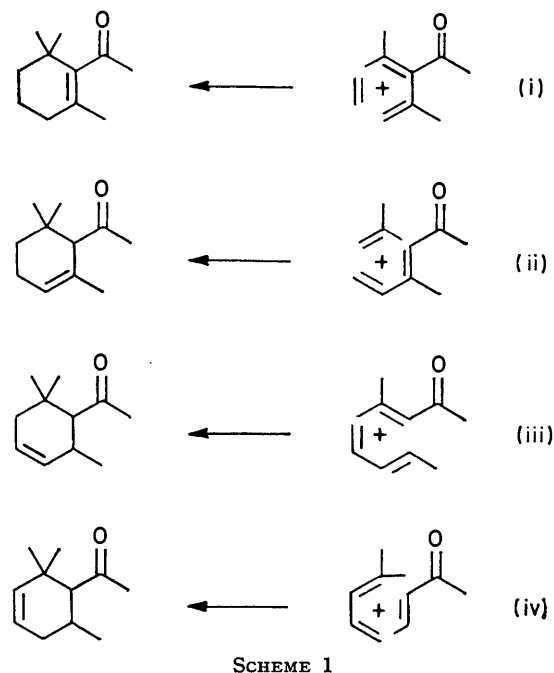
Penta-1,3-diene has been stated<sup>9</sup> to react with mesityl oxide at 200 °C to give a 10% yield of a mixture of the adducts (3) and (4) in the ratio 65 : 35, each as an

\* The stereochemistry will be discussed in a later paper including reaction with other  $\beta\beta$ -dimethyl dienophiles.

<sup>8</sup> K. Alder and M. Schumacher, *Fortschr. Chem. org. Naturstoffe*, 1953, **10**, 1.

epimeric mixture. (This seems to be the meaning intended by the contradictory paper reporting the reaction.) Although Lewis-acid catalysis of Diels–Alder reactions has been known since 1960,<sup>10</sup> no case has been reported involving a  $\beta\beta$ -disubstituted dienophile. The known acceleration by Lewis acids of the reaction of dienophiles of the type  $C=C-X=Y$  having conjugated substituents carrying atoms Y with unshared electrons available for co-ordination to the catalyst, and the increased structural and stereochemical specificity of the catalysed reaction,<sup>11</sup> made the Lewis-acid catalysed addition of penta-1,3-diene to mesityl oxide an attractive first step in the synthesis, in spite of the reported impracticability of the thermal reaction.

The penta-1,3-diene used was a commercial mixture of *cis*- and *trans*-isomers containing, according to the n.m.r. spectrum, about 70% of the required *trans*-isomer. The diene, diluted with dichloromethane, was slowly added to a solution of the complex of mesityl oxide and



SCHEME 1

aluminium chloride in boiling dichloromethane. Up to a four- or five-fold excess of diene had to be added to obtain almost complete conversion of mesityl oxide into the adduct, which was isolated in 45% yield as a mixture of *cis*- and *trans*-isomers \* (5) and (6) in the ratio *ca.* 87 : 13 (the *cis*-isomer predominating in accordance with Alder's rule). Presumably only part of the *trans*-diene underwent the Diels–Alder reaction while the remainder

<sup>9</sup> M. R. Musaev, E. T. Suleimanova, L. Kasumov, M. I. Mirgasanova, and S. D. Mekhtiev, *Doklady Akad. Nauk S.S.S.R.*, 1969, **25**, 27.

<sup>10</sup> G. I. Fray and R. Robinson, *J. Amer. Chem. Soc.*, 1961, **83**, 249; B.P. 835,840; P. Yates and P. Eaton, *J. Amer. Chem. Soc.*, 1960, **82**, 4436.

<sup>11</sup> J. Sauer, *Angew. Chem. Internat. Edn.*, 1967, **6**, 16.

and the *cis*-diene were consumed by the competing cationic polymerisation. Other Lewis acids, including boron trifluoride and trichloride, tin(IV) chloride, and titanium(IV) chloride, gave inferior results. The exact nature of the initiation step in such polymerisations is not clear, but it may involve the acid  $H^+AlCl_4^-$  formed from traces of water or other co-catalyst,<sup>12</sup> which adds a proton to the diene to give the initial allylic carbocation. However, neither scrupulous exclusion of moisture nor addition of proton bases such as 2,6-di-*t*-butylpyridine<sup>13</sup> or 1,8-bisdimethylaminonaphthalene,<sup>14</sup> which are capable of co-ordinating with  $H^+$  but not with the more bulky  $AlCl_3$ , suppressed the polymerisation. Possibly the complexed mesityl oxide delivers a proton directly to the diene to produce the initial allylic carbocation, or it may be produced by addition of the diene to the carbonyl carbon atom or the  $\beta$ -carbon atom of the complex. In any event, the best way of avoiding polymerisation remains dilution of the reaction medium by addition of the diene diluted in a large volume of solvent over a long period of time, taking advantage of the fact that the rate of the Diels–Alder reaction is proportional to the concentration of the diene whereas the rate of the polymerisation is probably proportional to the square of the concentration. By such methods a yield of 85% (by g.l.c.) of the adduct could be obtained by the use of only 2 mol of penta-1,3-diene (*i.e.* 1.4 mol of *trans*-diene) to 1 mol of mesityl oxide.<sup>15</sup> There was no sign of the structural isomer (4).

The less reactive butadiene required a higher temperature, but at 65 °C in carbon tetrachloride it added to the mesityl oxide–aluminium chloride complex to give the adduct (7) in 50% yield.

Bromination with *N*-bromosuccinimide followed by dehydrobromination has been used to convert  $\beta$ -ionone into dehydro- $\beta$ -ionone<sup>16</sup> and  $\beta$ -damascone (2) into  $\beta$ -damascenone<sup>2</sup> (1). Applied to the mixture of adducts (5) and (6) this sequence yielded a mixture containing about 40% of the required dienone (8), estimated by g.l.c. and n.m.r., contaminated mainly by other double-bond isomers. Equilibration of the isomers by treatment with acid or base did not cause efficient conversion into the apparently conjugated isomer (8), presumably because the carbonyl group is twisted out of the plane of the  $\alpha\beta$ -double bond by repulsion between the methyl groups.\* Subsequently, Büchi and Wüest<sup>6</sup> described a synthesis of ethyl safranate (9) and its acid-catalysed equilibration with the other two conjugated diene isomers in the ratio 60 : 20 : 20.

The dehydrogenation sequence was more successful

\* This is confirmed by the u.v. spectrum of the dienone (8), the  $\epsilon_{max}$  value of which is only half that of (10) lacking the 2-methyl group.

<sup>12</sup> G. A. Olah in 'Friedel–Crafts and Related Reactions,' ed. G. A. Olah, Interscience, London, 1963, vol. 1, p. 210; T. M. Powell and E. B. Reid, *J. Amer. Chem. Soc.*, 1945, **67**, 1020; J. D. Heldman, *ibid.*, 1944, **66**, 1789.

<sup>13</sup> H. C. Brown and B. Kanner, *J. Amer. Chem. Soc.*, 1953, **75**, 3865.

<sup>14</sup> R. W. Alder, P. S. Bowman, W. R. S. Steele, and D. R. Winterman, *Chem. Comm.*, 1968, 723.

when applied to the butadiene adduct (7) which lacks the complication of the extra methyl group. Consecutive treatment with *N*-bromosuccinimide and *NN*-dimethylaniline gave a mixture of isomers, which with acid isomerised nearly completely to the conjugated dienone (10). (This synthesis was, however, less efficient than the one described later.)

Although various other methods of dehydrogenation of the mixture of (5) and (6) were investigated, a more promising approach to the dienone (8) appeared to involve incorporating a halogen atom into the initial diene or dienophile and then eliminating hydrogen halide from the adduct. Reaction of penta-1,3-diene with 3-bromomesityl oxide under the conditions developed for mesityl oxide, followed by steam distillation and redistillation, gave the adduct as a mixture of *cis*- and *trans*-isomers\* (11) and (12) in the ratio *ca.* 80 : 20 and a yield of 50% [raised to 87% (g.l.c.) from 2 mol. equiv. of penta-1,3-diene (*i.e.* 1.4 mol. equiv. of *trans*-diene) by using higher dilution<sup>15</sup>]. The pure isomers could be separated by chromatography.

Treatment of the mixture of adducts (11) and (12) with lithium fluoride (the chloride and bromide behaved similarly) in dimethylformamide containing lithium carbonate<sup>17</sup> at 120 °C for 70 h gave the dienone (8) in 78% yield together with small amounts of double-bond isomers. When the reaction was followed by n.m.r. spectroscopy the *trans*-isomer (12) was found to disappear within 3 h, confirmed by dehydrobromination of the pure *trans*-isomer (12) under the same conditions. The long time necessary for the dehydrobromination of the mixture of isomers was therefore due to the reluctance of the stereoisomer (11) to undergo *cis*-elimination of  $HBr$ .<sup>18</sup>

To accelerate conversion of the *cis*- $\alpha$ -bromo-ketone (11) into the dienone (8) a method was developed for its epimerisation to the *trans*-stereoisomer (12). The  $Cu^I$ – $Cu^{II}$  system seemed to offer a suitable basis because copper(I) bromide, oxide, and cyanide reduce  $\alpha$ -halogeno-ketones to the parent ketone with formation of the copper(II) salt,<sup>19</sup> and copper(II) halides are well known halogenating agents of positions  $\alpha$  to carbonyl groups.<sup>20</sup> The reaction of the mixture of  $\alpha$ -bromo-ketones (11) and (12) with an excess of copper(I) bromide and lithium carbonate in dimethylformamide at 120 °C was followed by n.m.r. spectroscopy. After 1 h the ratio of *cis*- (11) to *trans*-isomer (12) had changed from *ca.* 80 : 20 to *ca.* 50 : 50 with some dehydrobromination to the dienone (8). This composition was confirmed by separation of the products; the amount of *trans*-isomer (12) was greater

<sup>15</sup> P. Lombardi and R. C. Cookson, unpublished work.

<sup>16</sup> H. B. Henbest, *J. Chem. Soc.*, 1951, 1074.

<sup>17</sup> R. P. Holysz, *J. Amer. Chem. Soc.*, 1953, **75**, 4432; R. S. Kittila, 'Dimethylformamide Chemical Uses,' E. I. Du Pont De Nemours, Delaware, U.S.A., 1967, p. 138; A. J. Parker, *Quart. Rev.*, 1962, **16**, 163; J. P. Bégué and M. Charpentier-Morize, *Angew. Chem. Internat. Edn.*, 1971, **10**, 327.

<sup>18</sup> Cf. R. N. Iacona, A. T. Rowland, and H. R. Nace, *J. Org. Chem.*, 1964, **29**, 3495; H. R. Nace and R. N. Iacona, *ibid.*, p. 3498.

<sup>19</sup> R. G. R. Bacon and O. J. Stewart, *J. Chem. Soc. (C)*, 1969, 301.

<sup>20</sup> L. C. King and G. K. Ostrum, *J. Org. Chem.*, 1964, **29**, 3459.

than that present in the original mixture. When the reaction was allowed to continue at 120 °C for 4 h dehydrobromination was nearly complete: in comparison, with lithium bromide in place of copper(I) bromide after 5 h at 120 °C dehydrobromination had proceeded to the extent of only *ca.* 20%. Unfortunately, the dienone (8) isolated from the reaction with copper(I) bromide was only *ca.* 80% pure because of contamination with double-bond isomers. Addition of proton buffers such as 1,8-bisdimethylaminonaphthalene<sup>14</sup> or epichlorhydrin<sup>21</sup> failed to arrest the isomerisation. If the Lewis acidity of copper(II) bromide is responsible, the problem is inherent in the method, which is not therefore suitable for this particular case. However, in most unsaturated ketones the equilibrium is strongly in favour of the conjugated isomer, and then this method of dehydrobromination of  $\alpha$ -bromo-ketones should be useful when the adjacent hydrogen and bromine atoms are *cis* and hard to eliminate by other methods.

An alternative conversion of the  $\alpha$ -bromo-ketones (11) and (12) into the dienone (8) in 67% yield involved allylic bromination with *N*-bromosuccinimide in carbon tetrachloride followed by reduction with zinc and acetic acid in ether.

Reduction with zinc and acetic acid in ether of the mixture of bromo-ketones (11) and (12) or of either pure isomer separately gave a mixture of the same *cis*- (5) and *trans*-ketones (6) in the ratio *ca.* 90 : 10. Treatment of the mixture of bromo-ketones (11) and (12) with sodium methoxide in methanol produced the rearranged esters (13) and (14) in the ratio *ca.* 80 : 20. The ester (13) appeared to be a mixture of the two stereoisomers as expected from non-stereospecific Favorskii rearrangement under these conditions.<sup>22</sup> The configuration of the minor product (14) is uncertain. Although small proportions of analogous esters have been reported recently from Favorskii rearrangement of other  $\alpha$ -halogeno-ketones,<sup>23</sup> its formation in such substantial amounts here is unexpected. With sodium methoxide in methanol the *cis*-bromo-ketone (11) gave only the epimeric esters (13). The implication that the other Favorskii ester (14) arose exclusively from the *trans*-bromo-ketone (12) is consistent with the identity of the reactant and product ratios in the case of the mixed bromo-ketones [(11) : (12)  $\equiv$  (13) : (14)  $\equiv$  80 : 20].

Addition of penta-1,3-diene to 3-chloromesityl oxide as for the bromo-compound gave the *cis*- and *trans*-chloro-ketones (15) and (16) in the ratio *ca.* 80 : 20 and 50% yield. Again, reduction of the mixture or of either pure stereoisomer with zinc and acetic acid in ether produced the ketones (5) and (6) in the ratio *ca.* 90 : 10. A method was found for conversion of the bromo-ketones (11) and (12) into the *cis*-chloro-ketone (15). Although no halogen exchange occurred when the bromo-ketones were heated with lithium chloride and lithium carbonate

<sup>21</sup> M. P. Hartshorn and E. R. H. Jones, *J. Chem. Soc.*, 1962, 1312.

<sup>22</sup> H. O. House and F. A. Richey, *J. Org. Chem.*, 1967, **32**, 2151; H. O. House and W. F. Gilmore, *J. Amer. Chem. Soc.*, 1961, **83**, 3980.

at 120 °C in dimethylformamide, with copper(I) chloride in place of lithium chloride after 2 h the *cis*-chloro-ketone (15) was formed in 65% yield. Presumably the exchange occurs by reduction of the bromo-ketones (11) and (12) by copper(I) ion to give a copper(II) enolate that is then chlorinated. It is not clear why the *cis*-halogeno-ketone predominates more from the reaction of the bromo-ketones (11) and (12) with copper(I) chloride than in the equilibration of the bromo-ketones with copper(I) bromide. Unless the equilibrium between the epimers differs this much because of the difference in effective size of chlorine and bromine, one must assume that the product (15) from the reaction with copper(I) chloride is not equilibrated. The *cis*-halogeno-ketone might well be formed faster than the *trans*- from reaction of the enolate with copper(II) halide and the chloro-ketone may be equilibrated by reduction-rehalogenation more slowly than the bromo- because of the stronger Cl-C bond.

To complete the synthesis of  $\beta$ -damascenone (1) from the key intermediate (8) a two-carbon unit had to be added at the methyl ketone group, most obviously and cheaply through aldol addition to acetaldehyde. Methods that did not selectively pre-form the enolate anion of the methyl ketone merely induced self-condensation of acetaldehyde. A further difficulty is that the most rapidly formed or most stable enolate of the dienone may not involve the side chain but the ring. A way of ensuring that only the side-chain enolate favours aldol addition is to use a divalent metal,<sup>24</sup> such as magnesium, which can induce reaction through a cyclic transition state to form the chelated product (Scheme 2).



SCHEME 2

Preliminary experiments were carried out on the more accessible methyl ketone (7), which was treated with *N*-methylanilinomagnesium bromide followed by acetaldehyde. The resulting aldol (17) lost water when treated with toluene-*p*-sulphonic acid in benzene to give the crotonoyl derivative (18) in 58% yield [from (7)]. Application of this method to the dienone (8) produced the aldol (19), elimination of water from which by use of toluene-*p*-sulphonic acid in methylene chloride or sodium acetate in acetic anhydride gave  $\beta$ -damascenone in 70% yield from the dienone (8). The  $\beta$ -damascenone made in this way had spectral properties identical with those of the natural material.

<sup>23</sup> F. G. Bordwell and J. Almy, *J. Org. Chem.*, 1973, **38**, 575; Ch. R. Engel, S. K. Roy, J. Capitaine, J. Bilodeau, C. McPherson-Foucar, and P. Lachance, *Canad. J. Chem.*, 1970, **48**, 361.

<sup>24</sup> A. T. Nielsen, C. Gibbons, and C. A. Zimmerman, *J. Amer. Chem. Soc.*, 1951, **73**, 4696; H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *ibid.*, 1973, **95**, 3310.

The adducts (5) and (6) similarly yielded  $\delta$ -damascone (20) as a mixture of the two epimers with a pleasant rosy smell similar to that of  $\beta$ -damascenone (1).

The synthetic sequence used for  $\beta$ -damascenone (1) was repeated with butadiene instead of penta-1,3-diene in the Diels-Alder reaction with bromomesityl oxide. The reaction in dichloromethane was very slow but in boiling chloroform the adduct (21) was formed in 45% yield. (Carbon tetrachloride was unsuitable because the dienophile-aluminium chloride complex precipitated.) Reduction of the bromo-adduct with zinc gave the mesityl oxide adduct (7). Dehydrobromination with lithium chloride and lithium carbonate in dimethylformamide was complete within 12 h with formation of the dienone (10) in 90% yield (no isomerisation occurred in this case). Aldol condensation followed by dehydration of the intermediate hydroxy-ketone with sodium acetate in acetic anhydride gave the trienone (22) in 35% yield. It had an odour resembling mango, similar to that of the dienone (18) but stronger.

#### EXPERIMENTAL

I.r. spectra were recorded on a Unicam SP 200G grating spectrophotometer. N.m.r. spectra were recorded on a Perkin-Elmer R-12 60 MHz spectrometer with carbon tetrachloride as solvent and tetramethylsilane as internal reference. Mass spectra were recorded at 70 eV on an A.E.I. MS12 spectrometer. G.l.c. analyses were performed on a Perkin-Elmer F-11 gas chromatograph using stainless steel columns, or a Pye Series 104 chromatograph using glass columns. Each instrument was fitted with a flame ionisation detector. Preparative g.l.c. was carried out on a Pye Series 104 chromatograph. The following columns were used: (A) 3 m  $\times$  2 mm 10% Carbowax 20 M on 80–100 mesh Diatomite C; (B) 3 m  $\times$  6 mm 10% Carbowax 20 M on 60–72 mesh Diatomite C; (C) 2 m  $\times$  4 mm 5% Carbowax 20 M on 80–100 mesh Diatomite C; (D) 3 m  $\times$  2 mm 10% XE 60 on 80–100 mesh Diatomite C; (E) 2 m  $\times$  2 mm 15% PPG on 80–100 mesh Diatomite C. The peak areas in g.l.c. analyses were used as a direct measure of the ratios of isomers, and are probably correct to within a few per cent.<sup>25</sup> U.v. spectra were recorded on a Perkin-Elmer 350 spectrophotometer. M.p.s were determined with a Kofler hot-stage apparatus. Silica gel was 100–200 mesh as supplied by W. R. Grace, Limited. Unless otherwise stated petroleum refers to the fraction of b.p. 40–60°. 'Worked up as usual' means washed with saturated sodium hydrogen carbonate solution and then with saturated brine, dried (MgSO<sub>4</sub>), and evaporated under reduced pressure.

*trans-4-Acetyl-3,5,5-trimethylcyclohexene (6) and its cis-Isomer (5).*—To powdered, anhydrous aluminium chloride (13.7 g, 0.10 mol) under nitrogen was added dry dichloromethane (30 ml). Mesityl oxide (20.0 g, 0.20 mol) in dichloromethane (75 ml) was then added with stirring over 30 min, and the mixture was heated under reflux for 1 h. Penta-1,3-diene (mixture of isomers) (70.0 g, 1.03 mol) in dichloromethane (300 ml) was added dropwise over 6 h. The mixture was then stirred overnight at room temperature. Liquid paraffin (100 ml) and 10% hydrochloric acid (200 ml) were added and the mixture was steam distilled for 3 h. The steam distillate was extracted with ether (5  $\times$  75 ml)

and the product worked up as usual. The residue was distilled to give a liquid, b.p. 52–54° at 1 mmHg (15.0 g, 0.09 mol, 45%), shown by g.l.c. [column (A), 120 °C] to consist of two components in the proportions *ca.* 13 : 87 in order of increasing retention time. These were separated by preparative g.l.c. [column (B), 130 °C]: *trans-4-acetyl-3,5,5-trimethylcyclohexene (6)* (Found: C, 79.6; H, 10.75. C<sub>11</sub>H<sub>18</sub>O requires C, 79.5; H, 10.85%); *m/e* 166 (*M*<sup>+</sup>, 33%), 123 (100), 109 (39), 107 (33), 81 (39), 69 (33), 67 (27), 55 (27), 43 (82), and 41 (50);  $\tau$  9.17–8.86 (9H, 4 overlapping lines, 3- and 5-Me), 8.60–8.04 (2H, m, 6-H<sub>2</sub>), 7.87 (3H, s, Ac), 7.90–7.30 (2H, m with br s overlapping, 3- and 4-H), and 4.54br (2H, s, 1- and 2-H);  $\nu_{\max}$  (film) 1 710 (Ac) and 695 cm<sup>-1</sup> (*cis*-CH=CH); *cis-4-acetyl-3,5,5-trimethylcyclohexene (5)* (Found: C, 79.55; H, 10.8%); *m/e* 166 (*M*<sup>+</sup>, 4%), 138 (39), 123 (95), 109 (11), 107 (23), 81 (12), 69 (8), 67 (9), 55 (12), 53 (11), 43 (100), and 41 (23);  $\tau$  9.18–8.89 (9H, 3 overlapping lines, 3- and 5-Me), 8.68–8.18 (2H, m, 6-H<sub>2</sub>), 7.97 (3H, s, Ac), 7.70–7.30 (2H, m, 4- and 3-H), and 4.86–4.16 (2H, m, 1- and 2-H);  $\nu_{\max}$  (film) 1 710 (Ac), and 1 692 and 710 cm<sup>-1</sup> (*cis*-CH=CH).

*5-Acetyl-4,4-dimethylcyclohexene (7).*—To powdered, anhydrous aluminium chloride (29.4 g, 0.22 mol) under nitrogen was added dry carbon tetrachloride (10 ml). Mesityl oxide (21.7 g, 0.22 mol) in carbon tetrachloride (100 ml) was added over 20 min with stirring. The mixture was heated to 65 °C during 1 h, and then buta-1,3-diene gas was passed through the stirred solution. The reaction was terminated when nearly all the mesityl oxide had disappeared (n.m.r.) (*ca.* 12 h). The mixture was cooled and poured into ice (50 g) and 10% hydrochloric acid (200 ml). The carbon tetrachloride layer was washed with saturated brine (2  $\times$  50 ml), dried (MgSO<sub>4</sub>), and evaporated under reduced pressure and the residue combined with the aqueous solutions. This mixture was extracted with petroleum (5  $\times$  75 ml) and the combined extracts were washed with 10% hydrochloric acid (1  $\times$  50 ml) and worked up as usual. The residue was distilled to give *5-acetyl-4,4-dimethylcyclohexene (7)*, b.p. 48–50° at 1.5 mmHg (17.1 g, 0.11 mol, 50%). A sample prepared by further distillation (Found: C, 79.15; H, 10.35. C<sub>10</sub>H<sub>16</sub>O requires C, 78.9; H, 10.6%) showed *m/e* 152 (*M*<sup>+</sup>, 34%), 137 (10), 109 (41), 93 (19), 82 (26), 67 (43), 55 (17), 43 (100), 41 (27), and 39 (20);  $\tau$  9.09 (3H, s, 4-Me), 9.01 (3H, s, 4-Me), 7.91 (3H, s, Ac), 8.30–7.20 (5H, m, 6-H<sub>2</sub>, 5-H, and 3-H<sub>2</sub>), and 4.43 (2H, m, 1-H and 2-H);  $\nu_{\max}$  (film) 1 710 (Ac), and 1 655 and 655 cm<sup>-1</sup> (*cis*-CH=CH).

*1-Acetyl-6,6-dimethylcyclohexa-1,3-diene (10) from the Monoene (7).*—*N*-Bromosuccinimide (6.5 g, 36 mmol) was added to *5-acetyl-4,4-dimethylcyclohexene (7)* (5.0 g, 33 mmol) in carbon tetrachloride (50 ml). The mixture was heated under reflux for 1 h and then cooled to room temperature. *NN*-Dimethylaniline (15 ml) and petroleum (30 ml) were added. Solid was filtered off and the solvent removed under reduced pressure. The mixture was then heated at 100 °C under nitrogen for 1.5 h, cooled, poured into ice (20 g) and 10% hydrochloric acid (50 ml), and extracted with petroleum (5  $\times$  50 ml). The combined extracts were worked up as usual to give a residue (3.8 g), g.l.c. [column (C), 130 °C] of which indicated the presence of three main components, including the dienone (10). The residue was distilled to give two fractions: (i) b.p. 46–55° at 0.5 mmHg

<sup>25</sup> J. A. Berson, Z. Hamlet, and W. A. Mueller, *J. Amer. Chem. Soc.*, 1962, **84**, 297.

(0.9 g), a mixture of 1-acetyl-6,6-dimethylcyclohexa-1,3-diene (10) (described below) and 5-acetyl-4,4-dimethylcyclohexene (7) in the ratio *ca.* 75 : 25 [g.l.c., column (C), 130 °C; n.m.r.]; and (ii) b.p. 55–75° at 0.5 mmHg (2.6 g), shown by g.l.c. [column (C), 130 °C] to be a mixture of several components. A portion (2.0 g) was dissolved in benzene (200 ml) and toluene-*p*-sulphonic acid (2.0 g) was added. The mixture was heated under reflux for 12 h and then cooled. Ether (100 ml) was added and the product was worked up as usual. The residue (1.8 g) was chromatographed on a column of silica gel (100 g) to obtain 1-acetyl-6,6-dimethylcyclohexa-1,3-diene (10) (1.4 g, 9 mmol) with 9 : 1 benzene-ether as eluant, showing a single peak on g.l.c. columns (C), (D), and (E) at 120 °C. The n.m.r. spectrum showed some minor contamination with other compounds (presumably double-bond isomers). Spectral and analytical properties are described below for material of high purity obtained by a better method.

*1-Acetyl-2,6,6-trimethylcyclohexa-1,3-diene* (8) from the *Epimeric Monoenes* [(5) and (6)].—The mixture [(5) and (6)] (1.00 g, 6.0 mmol) was treated with *N*-bromosuccinimide (1.08 g, 6.1 mmol) followed by *NN*-dimethylaniline (4 ml) as described for the preparation of the dienone (10). The residue (600 mg) which was obtained gave n.m.r. and g.l.c. [column (A), 130 °C] data which indicated it to be a mixture containing *ca.* 40% of 1-acetyl-2,6,6-trimethylcyclohexa-1,3-diene (8) (described below) with what appeared to be isomeric compounds. Attempts to isomerise this mixture to the dienone (8) by treatment with acid or base did not give significant change in composition. The spectral and analytical properties of the dienone (8) are described below for material of high purity obtained by a better method.

*3-Bromo-4-methylpent-3-en-2-one*.<sup>26</sup>—A mixture of mesityl oxide (200.0 g, 2.00 mol) and sodium hydrogen carbonate (168.0 g, 2.00 mol) in carbon tetrachloride (700 ml) was stirred under anhydrous conditions and cooled (ice-bath). Bromine (333.0 g, 2.08 mol) in carbon tetrachloride (300 ml) was then added dropwise during 2.5 h. The mixture was stirred at room temperature for *ca.* 12 h. Solid was filtered off and the excess of bromine and carbon tetrachloride was distilled off under reduced pressure. The residue (577.0 g) was dissolved in ethanol-water (1 : 1, 500 ml) and sodium hydrogen carbonate (252.0 g, 3.00 mol) was added. The mixture was stirred and heated at reflux for 3 h. After an additional 12 h at room temperature the solid was filtered off and the filtrate diluted to 3 l with water. It was then extracted with petroleum (4 × 500 ml). The combined extracts were washed with water (3 × 50 ml), dried (CaCl<sub>2</sub>), and distilled, and the residue (403.0 g) was fractionated at reduced pressure to give 3-bromo-4-methylpent-3-en-2-one, b.p. 68–71° at 15 mmHg (lit.,<sup>26</sup> 60–61° at 20 mmHg) (223.0 g, 1.25 mol, 62%);  $\tau$  7.99 (3H, s, MeC; *trans* to Ac), 7.96 (3H, s, other MeC), and 7.61 (3H, s, Ac);  $\nu_{\max}$  (film) 1 695 (Ac) and 1 600 cm<sup>-1</sup>.

*The Epimeric 4-Acetyl-4-bromo-3,5,5-trimethylcyclohexenes* [(11) and (12)].—A suspension of aluminium chloride (10.0 g, 0.07 mol) in dichloromethane (20 ml) was stirred under anhydrous conditions in a nitrogen atmosphere. 3-Bromo-4-methylpent-3-en-2-one (50.0 g, 0.28 mol) in dichloromethane (50 ml) was then added dropwise at room temperature. The mixture was stirred and heated at reflux for 2 h, and then while penta-1,3-diene (81.6 g, 1.20 mol) in dichloromethane (200 ml) was added dropwise during 5 h. After a further 12 h stirring at room temperature the mixture was decomposed by slow addition of 10%

hydrochloric acid (200 ml). Paraffin oil (100 ml) was added and the mixture was steam distilled to give a yellow liquid (44.0 g, 0.18 mol, crude yield 63%). Although the n.m.r. spectrum of this product indicated it to be a mixture of stereoisomers, g.l.c. analysis [column (A), 130 °C] showed only one peak. The crude product was distilled to give a partially crystalline oil, b.p. 62–65° at 0.3 mmHg (35.0 g, 0.15 mol, 50%). Careful chromatography of a portion (1.4 g, 5.8 mmol) of this material on silica gel (150 g) afforded *trans-4-acetyl-4-bromo-3,5,5-trimethylcyclohexene* (12), m.p. 89–92° (sublimed 30–35° at 0.5 mmHg) (240 mg, 1.0 mmol) with 1 : 1 petroleum-benzene as eluant, shown to be a single component on g.l.c. [column (A), 140 °C]; *m/e* 246–244 (*M*<sup>+</sup>, 0.01%), 170 (30), 165 (58), 79 (38), 78 (42), 77 (46), 51 (25), 43 (100), and 41 (27);  $\tau$  9.08 (3H, d overlapping s at 8.96, 3-Me), 8.96 and 8.84 (6H, 2s, 5-Me<sub>2</sub>), 8.61–7.23 (2H, m, 6-H<sub>2</sub>), 7.51 (3H, s, Ac), 7.23–6.70 (1H, m, 3-H), and 4.98–4.20 (2H, m, H-1 and H-2);  $\nu_{\max}$  (Nujol) 1 695 (Ac) and 1 655 cm<sup>-1</sup> (cis-CH=CH); and *cis-4-acetyl-4-bromo-3,5,5-trimethylcyclohexene* (11), m.p. 87–90° (sublimed 35–40° at 0.5 mmHg) (965 mg, 4.0 mmol) with 1 : 1 petroleum-benzene as eluant, shown to be a single component on g.l.c. [column (A), 140 °C] with the same retention time as its *trans*-stereoisomer (12); *m/e* 246–244 (*M*<sup>+</sup>, 3%), 165 (20), 121 (40), 107 (30), 150 (20), 91 (30), 82 (60), 43 (100), and 41 (35);  $\tau$  8.91 and 8.76 (6 H, 2s, 5-Me<sub>2</sub>), 8.99 (3 H, d, *J ca.* 7 Hz, 3-Me), 8.07–7.70 (2 H, m, 6-H<sub>2</sub>), 7.54 (3 H, s, Ac), 7.38–6.80 (1 H, m, 3-H), and 4.90–4.20 (2 H, m, 1-H and 2-H);  $\nu_{\max}$  (Nujol) 1 705 (Ac) and 1 655 cm<sup>-1</sup> (cis-CH=CH). The ratio of *trans*- to *cis*-stereoisomers in the mixture obtained from the Diels-Alder reaction was shown to be *ca.* 20 : 80 by the composition of the fractions obtained from column chromatography.

*1-Acetyl-2,6,6-trimethylcyclohexa-1,3-diene* (8) from the *Epimeric Cyclohexenes* [(11) and (12)].—A suspension of dry lithium fluoride (5.18 g, 0.20 mol) and lithium carbonate (14.80 g, 0.20 mol) in dry dimethylformamide (100 ml) was stirred at 120 °C under nitrogen. The bromo-ketone [a mixture of *trans*- (12) and *cis*- (11) stereoisomers] (31.40 g, 0.13 mol) in dimethylformamide (100 ml) was added and stirring and heating were continued for 78 h. Lithium fluoride (5.18 g) and lithium carbonate (14.80 g) were added every 12 h. The reaction was monitored by n.m.r. spectroscopy, which indicated that the *trans*-stereoisomer (12) was dehydrobrominated within 3 h. After the reaction was complete (55 h) the mixture was cooled, solid matter was filtered off, and the solid was washed with petroleum (4 × 100 ml). The washings were added to the main filtrate, which was then poured into dilute acetic acid (1 : 1; 400 ml) and extracted with petroleum (4 × 100 ml). The combined extracts were worked up as usual to give 1-acetyl-2,6,6-trimethylcyclohexa-1,3-diene (8) (19.80 g, 0.12 mol, crude yield 92%) which was *ca.* 85% one component [g.l.c., column (A), 130 °C]. Chromatography on silica gel (800 g) afforded the dienone (8) with 9 : 1 benzene-ether as eluant. A sample prepared by distillation, b.p. 42–45° at 0.1 mmHg (Found: C, 80.55; H, 9.85. C<sub>11</sub>H<sub>16</sub>O requires C, 80.5; H, 9.75%), showed *m/e* 164 (*M*<sup>+</sup>, 36%), 121 (55), 105 (57), 93 (14), 91 (31), 79 (22), 77 (24), 44 (88), and 43 (100);  $\tau$  8.93 (6 H, s, 6-Me<sub>2</sub>), 8.29 (3 H, s, 2-Me), 7.90 (2 H, m 5-H<sub>2</sub>), 7.79 (3 H, s, Ac), and 4.24 (2 H, m, 3-H and 4-H);  $\nu_{\max}$  (film) 1 688, 1 678, and 1 642 cm<sup>-1</sup> (C=C-CO);  $\lambda_{\max}$  (cyclohexane) 275 nm ( $\epsilon$  5 150).

<sup>26</sup> H. Pauly and H. Lieck, *Ber.*, 1900, **33**, 500.

*Treatment of trans-4-Acetyl-4-bromo-3,5,5-trimethylcyclohexene (12) with Lithium Chloride and Lithium Carbonate in Dimethylformamide.*—To a stirred suspension of dry lithium chloride (40 mg, 0.9 mmol) and lithium carbonate (70 mg, 0.9 mmol) in dry dimethylformamide (5 ml) under nitrogen was added the *trans*-bromo-ketone (12) (70 mg, 0.3 mmol) in dimethylformamide (2 ml). The mixture was stirred and heated at 120 °C for 3 h, then cooled, poured into water (30 ml), and extracted with ether (4 × 30 ml). The combined extracts were washed with saturated brine (2 × 40 ml), dried (MgSO<sub>4</sub>), and evaporated to give 1-acetyl-2,6,6-trimethylcyclohexa-1,3-diene (8) (40 mg, 0.2 mmol) (n.m.r., g.l.c., and i.r.).

*Treatment of the Epimeric 4-Acetyl-4-bromo-3,5,5-trimethylcyclohexenes [(11) and (12)] with Copper(I) Bromide in Dimethylformamide.*—To the  $\alpha$ -bromo-ketones (11) and (12) (1.59 g, 6.5 mmol) in dimethylformamide (20 ml) was added copper(I) bromide (2.35 g, 16.0 mmol). The mixture was stirred under nitrogen, heated to 130 °C over 0.5 h and then stirred at 130 °C for 1 h. The mixture was cooled and then poured into ice (30 g) and water (70 ml) and extracted with petroleum (4 × 50 ml). The combined extracts were washed with 10% hydrochloric acid (50 ml) and worked up as usual to give a mixture (1.38 g) shown by g.l.c. [column (A), 130 °C] to be a mixture of the diene (8) (together with minor amounts of compounds of similar retention time, presumably double bond isomers) and the  $\alpha$ -bromo-ketones (11) and (12) enriched in the *trans*-isomer (12) (n.m.r.). When chromatographed on silica gel (150 g) the product mixture (1.38 g) gave *trans*-4-acetyl-4-bromo-3,5,5-trimethylcyclohexene (12) (370 mg, 1.6 mmol) with 1:1 petroleum–benzene as eluant; *cis*-4-acetyl-4-bromo-3,5,5-trimethylcyclohexene (11) (300 mg, 1.3 mmol) with 1:1 petroleum–benzene as eluant; and 1-acetyl-2,6,6-trimethylcyclohexa-1,3-diene (8) (490 mg, 3.0 mmol) with 9:1 benzene–ether as eluant. The ratio of the *trans*- to the *cis*- $\alpha$ -bromo-ketone [*i.e.* (12) : (11)] in the mixture obtained from the reaction was therefore *ca.* 55 : 45.

*Treatment of the Bromo-ketones (11) and (12) with Copper(I) Bromide and Lithium Carbonate in Dimethylformamide.*—The mixture of  $\alpha$ -bromo-ketones (500 mg, 2.1 mmol) in dimethylformamide (5 ml) was added to a stirred suspension of copper(I) bromide (590 mg, 4.1 mmol) and lithium carbonate (300 mg, 4.1 mmol) in dimethylformamide (10 ml). The mixture was heated to 120 °C over 0.5 h and then stirred at this temperature for 3 h, cooled, poured into ice (30 g) and 10% hydrochloric acid (30 ml), and extracted with petroleum (5 × 40 ml). The combined extracts were worked up as usual. The residue (430 mg) was shown by g.l.c. [column (A), 130 °C] to contain the dienone (8) together with minor amounts of compounds of similar retention time and the bromo-ketones (11) and (12) (confirmed by n.m.r.). The ratio of dehydrobrominated material to  $\alpha$ -bromo-ketones (11) and (12) was *ca.* 75 : 25 (g.l.c.). However, this method was not investigated further owing to the apparent ready isomerisation of the dienone (8) to its double-bond isomers.

*Treatment of the Bromo-ketones (11) and (12) with Lithium Bromide in Dimethylformamide.*—Reaction of the  $\alpha$ -bromo-ketones (11) and (12) with lithium bromide in dimethylformamide was carried out under the same conditions as with copper(I) bromide in dimethylformamide but with the same molar proportion of lithium bromide in place of copper(I) bromide. After 5 h at 130 °C dehydrobromination to the dienone (8) had proceeded to the extent of only *ca.*

20% [g.l.c., column (A), 130 °C, and n.m.r.]. After 24 h under these conditions the mixture contained *ca.* 40% of the dienone (8). The remainder of the mixture was the *cis*- $\alpha$ -bromo-ketone (11).

*1-Acetyl-2,6,6-trimethylcyclohexa-1,3-diene (8) by Bromination followed by Reduction of the Bromo-ketones (11) and (12).*—The  $\alpha$ -bromo-ketones (mixture of *cis*- and *trans*-stereoisomers as obtained from Diels–Alder reaction) (2.0 g, 8.0 mmol) and *N*-bromosuccinimide (2.9 g, 16.0 mmol) in carbon tetrachloride (50 ml) were heated at reflux for 45 min. The mixture was cooled to room temperature and the solid was filtered off and washed with petroleum (30 ml). The filtrate was evaporated under reduced pressure. The residue was dissolved in ether (15 ml) and added to a stirred mixture of zinc powder (4.0 g, 61.0 mmol) in ether (15 ml) and acetic acid (5 ml). Stirring was continued for 1 h, zinc was filtered off, and the filtrate was diluted to 100 ml with ether. The ethereal solution was worked up as usual and the residue (1.5 g) was chromatographed on silica gel (90 g) to give 1-acetyl-2,6,6-trimethylcyclohexa-1,3-diene (8) (0.9 g, 5.5 mmol, 67%) with 9 : 1 benzene–ether as eluant. This was shown to be *ca.* 90% one component by g.l.c. analysis [column (A), 140 °C].

*Treatment of trans-4-Acetyl-4-bromo-3,5,5-trimethylcyclohexene (12) with Zinc and Acetic Acid in Ether.*—To zinc powder (500 mg, 7.7 mmol) in ether (10 ml) and acetic acid (3 ml) was added the *trans*- $\alpha$ -bromo-ketone (12) (50 mg, 0.2 mmol). The mixture was stirred and heated at reflux for 4 h, and then stirred at room temperature for 12 h. The mixture was filtered into ether (75 ml) and water (30 ml). The ether layer was worked up as usual to give a mixture of *trans*-4-acetyl-3,5,5-trimethylcyclohexene (6) and its *cis*-stereoisomer (5) (30 mg, 0.18 mmol) in the ratio *ca.* 10 : 90 [g.l.c., column (A), 120 °C, and n.m.r.].

*Treatment of cis-4-Acetyl-4-bromo-3,5,5-trimethylcyclohexene (11) with Zinc and Acetic Acid in Ether.*—Reduction of the *cis*-bromo-ketone (11) with zinc powder as described for its *trans*-stereoisomer (12) gave a mixture of *trans*-4-acetyl-3,5,5-trimethylcyclohexene (6) and its *cis*-stereoisomer (5) in the ratio *ca.* 10 : 90 [g.l.c., column (A), 120 °C, and n.m.r.].

The mixture of  $\alpha$ -bromo-ketones (11) and (12) from the Diels–Alder reaction also gave the dehalogenated derivatives (5) and (6) in the ratio *ca.* 10 : 90 on reduction with zinc by the same method.

*Treatment of trans-4-Acetyl-4-bromo-3,5,5-trimethylcyclohexene (12) and its cis-Stereoisomer (11) with Sodium Methoxide in Methanol.*—To a solution of sodium methoxide in methanol [from sodium (3.5 g, 0.15 mol) in dry methanol (100 ml)] was added the Diels–Alder mixture of  $\alpha$ -bromo-ketones (11) and (12) (5.0 g, 0.02 mol) in methanol (25 ml). The mixture was then heated at reflux for 3 h, cooled, and poured into petroleum (40 ml), ice (20 g), and 10% acetic acid (40 ml). The aqueous mixture was extracted with 1 : 1 petroleum–ether (4 × 75 ml). The combined extracts were worked up as usual to give a mixture (4.1 g) of three main components in the ratio *ca.* 10 : 70 : 20 [g.l.c., column (A), 150 °C]. N.m.r. spectroscopy indicated the presence of a small amount of 1-acetyl-2,6,6-trimethylcyclohexa-1,3-diene (8), confirmed by enhancement of the g.l.c. peak by a pure sample of the dienone (8). Separation of the two major components by preparative g.l.c. [column (B), 155 °C] gave successively *methyl* 1,2,6,6-tetramethylcyclohex-3-enecarboxylate (13) as a mixture of stereoisomers (Found: C, 73.35; H, 10.1. C<sub>12</sub>H<sub>20</sub>O<sub>2</sub> requires C, 73.45;

H, 10.2%); *m/e* 196 ( $M^+$ , 55%), 137 (70), 121 (60), 109 (40), 107 (25), 105 (20), 95 (40), 91 (35), 82 (45), 81 (45), 69 (40), 67 (50), 55 (55), and 41 (100);  $\tau$  9.15 (3 H, d, *J* ca. 7 Hz, 2-Me), 9.13 (3 H, s, 1-Me), 9.04 (6 H, s, 6-Me), 8.41—7.78 (2 H, m, 5-H<sub>2</sub>), 7.33—6.73 (1 H, m, 2-H), 6.38 (3 H, s, CO<sub>2</sub>Me), and 4.90—4.31 (2 H, m, 3- and 4-H);  $\nu_{\max}$  (film) 1 730 (CO<sub>2</sub>Me) and 1 650 cm<sup>-1</sup> (*cis*-CH=CH); and methyl 2,6,6-trimethylcyclohex-3-enylacetate (14); *m/e* 196 ( $M^+$ , 18%), 181 (24), 121 (78), 107 (100), 95 (33), 91 (33), 81 (45), 69 (53), 67 (51), 55 (42), and 41 (91);  $\tau$  9.14, 9.08, and 9.02 (9 H, 3 lines overlapping, 3 × Me), 8.43—7.72 (5 H, m, 5-H<sub>2</sub>, CH<sub>2</sub>·CO<sub>2</sub>Me, 1-H), 7.72—7.20 (1 H, m, 2-H), 6.42 (3 H, s, CO<sub>2</sub>Me), and 4.91—4.23 (2 H, m, 3- and 4-H);  $\nu_{\max}$  (film) 1 740 (CO<sub>2</sub>Me) and 675 cm<sup>-1</sup> (*cis*-CH=CH).

3-Chloro-4-methylpent-3-en-2-one.<sup>26</sup>—This had b.p. 54—56° at 15 mmHg (lit.<sup>26</sup> 47° at 12 mmHg);  $\tau$  8.01 (3 H, s, MeC=trans to Ac), 7.90 (3 H, s, other MeC=), and 7.67 (3 H, s, Ac);  $\nu_{\max}$  (film) 1 695 (Ac) and 1 605 cm<sup>-1</sup>.

The Epimeric 4-Acetyl-4-chloro-3,5,5-trimethylcyclohexenes (15) and (16).—3-Chloro-4-methylpent-3-en-2-one (1.50 g, 11.0 mmol) in dichloromethane (15 ml) was added dropwise, at room temperature, to a stirred suspension of aluminium chloride (1.13 g, 8.0 mmol) in dichloromethane (4 ml) under anhydrous conditions in a nitrogen atmosphere. The mixture was heated at reflux for 1.5 h and then heating was continued as penta-1,3-diene (4.60 g, 68.0 mmol) in dichloromethane (45 ml) was added dropwise during 5 h. The mixture was stirred at room temperature for 12 h. Paraffin oil (40 ml) and 10% hydrochloric acid (50 ml) were added and the mixture was steam distilled for 3 h. The distillate was extracted with ether (5 × 50 ml) and the combined extracts were worked up as usual to give a mixture of *trans*-4-acetyl-4-chloro-3,5,5-trimethylcyclohexene (16) and its *cis*-stereoisomer (15) (1.60 g, 8.0 mmol, crude yield 70%). Careful chromatography of this mixture on silica gel (100 g) gave (i) the *trans*-isomer (16), m.p. 58—61° (sublimed 20—25° at 0.5 mmHg) (0.12 g, 0.6 mmol, 6%) with 1:1 petroleum-benzene as eluant [single peak on g.l.c., column (A), 140 °C]; *m/e* 202—200 ( $M^+$ , very small), 165 (23), 164 (20), 121 (73), 107 (18), 105 (14), 91 (20), 82 (27), 77 (18), 67 (14), 55 (18), 43 (100), and 41 (31);  $\tau$  9.11 (3 H, l line of d with other line obscured by s at 8.90, 3-Me), 8.98 and 8.90 (6 H, 2s, 5-Me<sub>2</sub>), 8.68—8.11 (1 H, m, 6-H), 7.64 (3 H, s, Ac), 7.84—7.24 (1 H, m, 6-H), 7.14—6.54 (1 H, m, 3-H), and 4.98—4.23 (2 H, m, 1-H and 2-H);  $\nu_{\max}$  (Nujol) 1 705 (Ac) and 1 660 cm<sup>-1</sup> (*cis*-CH=CH); (ii) an intermediate fraction containing a mixture of the *trans*- (16) and *cis*- (15) stereoisomers (0.21 g, 1.1 mmol) (Found: C, 65.45; H, 8.3; Cl, 18.1. C<sub>11</sub>H<sub>17</sub>ClO requires C, 65.8; H, 8.5; Cl, 17.7%); and (iii) the *cis*-isomer (15), m.p. 64—67° (sublimed 20—25° at 0.7 mmHg) (0.77 g, 3.9 mmol, 35%) with 1:1 petroleum-benzene as eluant [single peak on g.l.c., column (A), 140 °C with the same retention time as its *trans*-stereoisomer (16)]; *m/e* 202—200 ( $M^+$ , 26%), 165 (18), 121 (79), 107 (26), 105 (24), 91 (31), 82 (89), 79 (18), 77 (19), 68 (27), 67 (18), 55 (13), 53 (13), 43 (100), and 41 (26);  $\tau$  8.98 and 8.83 (6 H, 2s, 5-Me<sub>2</sub>), 8.95 (3 H, d, *J* 7 Hz, 3-Me), 7.67 (3 H, s, Ac), 8.41—7.05 (3 H, m, 6-H<sub>2</sub> and 3-H), and 4.90—4.21 (2 H, m, 1-H and 2-H);  $\nu_{\max}$  (Nujol) 1 710 (Ac) and 1 665 cm<sup>-1</sup> (*cis*-CH=CH).

The yield of purified (column chromatography)  $\alpha$ -chloro-ketones (16) and (15) was 50% (ratio 20:80).

Treatment of *trans*-4-Acetyl-4-chloro-3,5,5-trimethylcyclohexene (16) with Zinc and Acetic Acid in Ether.—The *trans*-chloro-ketone (16) was treated with zinc as described for

the *trans*-bromo-compound (12). This gave a mixture of *trans*-4-acetyl-3,5,5-trimethylcyclohexene (6) and its *cis*-stereoisomer (5) in the ratio ca. 10:90 [g.l.c., column (A), 120 °C, and n.m.r.].

Treatment of the *cis*-Chloro-ketone (15) with Zinc and Acetic Acid in Ether.—The *cis*-isomer (15) was reduced with zinc as described above to give a mixture of *trans*-4-acetyl-3,5,5-trimethylcyclohexene (6) and its *cis*-stereoisomer (5) in the ratio ca. 10:90 [g.l.c., column (A), 120 °C, and n.m.r.].

Reduction of the mixture of  $\alpha$ -chloro-ketones obtained by Diels-Alder reaction of penta-1,3-diene with 3-chloro-4-methylpent-3-en-2-one also gave a mixture of *trans*- (6) and *cis*-stereoisomers (5) in the ratio ca. 10:90.

Treatment of the Bromo-ketones (12) and (11) with Copper(I) Chloride and Lithium Carbonate in Dimethylformamide.—Copper(I) chloride (2.05 g, 20.0 mmol) and lithium carbonate (1.20 g, 16.0 mmol) were stirred in dimethylformamide (20 ml) and the mixture of  $\alpha$ -bromo-ketones (11) and (12) (2.00 g, 8.2 mmol) in dimethylformamide (10 ml) was added. The mixture was heated to 120 °C over 0.5 h and then stirred at 120 °C for 2 h, cooled, poured into 10% hydrochloric acid (50 ml), and extracted with petroleum (4 × 50 ml). The combined extracts were worked up as usual. The residue (1.80 g), shown by g.l.c. [column (A), 130 °C] to contain two components, was chromatographed on silica gel (110 g) to give *cis*-4-acetyl-4-chloro-3,5,5-trimethylcyclohexene (15) (1.05 g, 5.3 mmol, 65%) with 1:1 petroleum-benzene as eluant; and 1-acetyl-2,6,6-trimethylcyclohexa-1,3-diene (8) (0.20 g, 1.2 mmol, 15%) with 9:1 benzene-ether as eluant.

*trans*-1-(6,6-Dimethylcyclohex-3-enyl)but-2-en-1-one (18).—To a solution of ethylmagnesium bromide [from magnesium turnings (0.92 g, 38 mmol) and ethyl bromide (4.20 g, 38 mmol) in dry ether (10 ml)], *N*-methylaniline (4.1 g, 38 mmol) in dry benzene (5 ml) was added with stirring and cooling (ice-bath). 5-Acetyl-4,4-dimethylcyclohexene (7) (5.00 g, 33 mmol) in benzene (5 ml) was added to the cooled mixture, which was stirred at room temperature for 30 min and then cooled (ice-bath) while acetaldehyde (1.90 g, 43 mmol) in benzene (10 ml) was added during 20 min. The mixture was stirred for a further 30 min at 0 °C and then poured into ice (20 g) and 10% hydrochloric acid (50 ml). The mixture was extracted with petroleum (5 × 50 ml) and the combined extracts were washed with 10% hydrochloric acid (5 × 50 ml) and worked up as usual. The residue (6.00 g) was diluted with dry benzene (100 ml) and toluene-*p*-sulphonic acid (0.20 g) was added. The mixture was heated under reflux and the water formed was removed azeotropically in a Dean-Stark apparatus. The resultant benzene solution was worked up as usual. G.l.c. analysis of the residue (5.60 g) [column (A), 140 °C] showed the presence of unchanged methyl ketone (7) together with a new component. This material was distilled under reduced pressure to give *trans*-1-(6,6-dimethylcyclohex-3-enyl)but-2-en-1-one (18), b.p. 60—62° at 0.5 mmHg (3.40 g, 19 mmol, 58%); g.l.c. [column (A), 140 °C] showed the presence of only one component (Found: C, 80.5; H, 9.9. C<sub>12</sub>H<sub>18</sub>O requires C, 80.85; H, 10.15%); *m/e* 178 ( $M^+$ , 44%), 163 (18), 135 (15), 109 (33), 93 (11), 94 (15), 95 (18), 82 (18), 81 (15), 79 (22), 69 (100), 55 (22), and 41 (40);  $\tau$  9.06 (6 H, s, 6-Me<sub>2</sub>), 8.12 (3 H, dd, *J* 6.5 and 1 Hz, =CH·CH<sub>3</sub>), 8.30—7.10 (5 H, m, ring 2-H<sub>2</sub>, 1-H, and 5-H<sub>2</sub>), 4.43 (2 H, m, ring 3- and 4-H), 3.91 (1 H, dq, *J* 16 and 1 Hz, CO-CH=), and 3.22 (1 H, dq, *J* 6.5 and 16 Hz, =CH·CH<sub>3</sub>);  $\nu_{\max}$  (film) 1 685, 1 660, 1 625 (—CH=CH—CO—), and 970 cm<sup>-1</sup> (*trans*-CH=CH);  $\lambda_{\max}$  (cyclohexane) 224 nm ( $\epsilon$  11 300).



3-Hydroxy-1-(2,6,6-trimethylcyclohexa-1,3-dienyl)butan-1-one (19).—Acetaldehyde (4.4 g, 100 mmol) was condensed with 1-acetyl-2,6,6-trimethylcyclohexa-1,3-diene (8) (2.8 g, 16 mmol) as described above for 5-acetyl-4,4-dimethylcyclohexene (7). The crude product (2.7 g) contained ca. 30% of unchanged dienone (8) (n.m.r.). Usually it was found convenient to use this mixture without further purification to obtain crude  $\beta$ -damascenone (1). However, purification by column chromatography on silica gel (120 g) afforded unchanged dienone (8) (750 mg, 4 mmol) with benzene as eluant and 3-hydroxy-1-(2,6,6-trimethylcyclohexa-1,3-dienyl)butan-1-one (19) (1.9 g, 9 mmol, 55%) with 9 : 1 benzene-ether as eluant;  $m/e$  208 ( $M^+$ , 13%), 149 (34), 133 (24), 121 (100), 105 (38), 91 (24), 87 (17), 45 (34), and 43 (47);  $\tau$  8.93 (6 H, s, 6-Me<sub>2</sub>), 8.83 (3 H, d,  $J$  ca. 6 Hz, CH<sub>3</sub>·CHOH), 8.28 (3 H, s, 2-Me), 7.91 (2 H, m, ring 5-H<sub>2</sub>), 7.39 (2 H, d,  $J$  6 Hz, CH<sub>2</sub>·CO), 6.83br (1 H, s, exchanges with D<sub>2</sub>O, OH), 5.80 (1 H, q,  $J$  6 and 6 Hz, CHOH), and 4.22 (2 H, m, ring 3- and 4-H);  $\nu_{\max}$  (film) 3 445 (OH), 1 685, and 1 645 cm<sup>-1</sup> (-CH=C-CO-).

$\beta$ -Damascenone (1) [trans-1-(2,6,6-Trimethylcyclohexa-1,3-dienyl)but-2-en-1-one].—1-Acetyl-2,6,6-trimethylcyclohexa-1,3-diene (8) (5.5 g, 33 mol) was condensed with acetaldehyde as described above for 5-acetyl-4,4-dimethylcyclohexene (7). The crude mixture (5.7 g) containing the hydroxy-ketone (19) was dissolved in dichloromethane (100 ml) and toluene-*p*-sulphonic acid (800 mg) was added. The mixture was heated under reflux for 15 min and the water which was formed was removed azeotropically. The solution was cooled to room temperature and ether (100 ml) was added. The mixture was worked up as usual to give a residue (5.4 g) which was shown to be ca. 60% one component by g.l.c. [column (A), 140 °C]. The residue was distilled under reduced pressure to give  $\beta$ -damascenone (1), b.p. 116–118° at 13 mmHg (lit.,<sup>2</sup> 57° at 0.001 mmHg) (2.6 g, 14 mmol, 41%), showing i.r., n.m.r., and mass spectral data which agreed with those reported for natural  $\beta$ -damascenone (1).

In one case on a small scale the conversion of the dienone (8) into the aldol (19) was nearly quantitative and dehydration of this product gave  $\beta$ -damascenone (1) in 70% yield after column chromatography.

$\delta$ -Damascone (20) [trans-1-(2,6,6-Trimethylcyclohex-3-enyl)but-2-en-1-one].—The 4-acetyl-3,5,5-trimethylcyclohexenes [(6) and (5)] (5.0 g, 30 mmol) (mixture of *trans*- and *cis*-stereoisomers as obtained from Diels-Alder reaction) were treated with acetaldehyde, and the resultant mixture was dehydrated as described for 5-acetyl-4,4-dimethylcyclohexene (7). Distillation of the dehydrated product under reduced pressure gave  $\delta$ -damascone (20) (mixture of stereoisomers), b.p. 65–67° at 0.6 mmHg (2.8 g, 15 mmol, 50%) (Found: C, 81.2; H, 10.3. C<sub>13</sub>H<sub>20</sub>O requires C, 81.25; H, 10.4%);  $m/e$  192 ( $M^+$ , 48%), 177 (17), 137 (13), 123 (56), 109 (21), 107 (19), 91 (15), 93 (15), 81 (36), 69 (100), 55 (17), and 41 (52);  $\tau$  9.12 and 9.03 (9 H, 2s, 6-Me<sub>2</sub> overlapping the d due to 2-Me), 8.16 (3 H, dd,  $J$  6.5 and 1 Hz, -C=C-CH<sub>3</sub>), 8.40–7.22 (4 H, m, ring 5-H<sub>2</sub>, 1-H, and 2-H), 4.72–4.22 (2 H, m, ring 3- and 4-H), 3.93 (1 H, dq,  $J$  16 and 1 Hz, -CO-CH=C-), and 3.29 (1 H, dq,  $J$  6.5 and 16 Hz, -C=CH-CH<sub>3</sub>);  $\nu_{\max}$  (film) 1 695, 1 665, 1 630 (-CH=C-CO-), and 970 cm<sup>-1</sup> (*trans*-CH=CH);  $\lambda_{\max}$  (cyclohexane) 223 nm ( $\epsilon$  10 100).

$\beta$ -Damascenone (1) from  $\delta$ -Damascone (20).— $\delta$ -Damascone (20) (500 mg, 2.6 mmol) was treated with *N*-bromosuccinimide (510 mg, 2.9 mmol) followed by *NN*-dimethylaniline (5 ml) as described above for the preparation of 1-acetyl-6,6-

dimethylcyclohexa-1,3-diene (10). The residue (340 mg) contained ca. 30% of  $\beta$ -damascenone (1) [g.l.c., column (A), 140 °C, and n.m.r.]. Treatment under acidic or basic conditions failed to isomerise this mixture cleanly to  $\beta$ -damascenone (1) and therefore this procedure was not investigated further.

4-Acetyl-4-bromo-5,5-dimethylcyclohexene (21).—Powdered, anhydrous aluminium chloride (18.0 g, 0.14 mol) was added to dry chloroform (50 ml). To this mixture was added dropwise with stirring 3-bromo-4-methylpent-3-en-2-one (30.0 g, 0.17 mol) in chloroform (150 ml). The mixture was stirred and heated at reflux for 1 h, and then while buta-1,3-diene gas was passed through the mixture. When nearly all the dienophile had disappeared (n.m.r.) (ca. 14 h) the mixture was treated as described above for the preparation of 5-acetyl-4,4-dimethylcyclohexene (7) except that after extraction the crude mixture was steam distilled to give almost pure 4-acetyl-4-bromo-5,5-dimethylcyclohexene (21) (17.0 g, 0.07 mol, 45%). A sample obtained by distillation had b.p. 65–67° at 1 mmHg;  $m/e$  230–232 ( $M^+$ , 5%), 151 (23), 123 (10), 109 (14), 107 (32), 91 (23), 93 (17), 95 (13), 79 (19), 77 (15), 67 (19), 55 (16), 43 (100), and 41 (27);  $\tau$  8.91 and 8.80 (6 H, 2s, 5-Me<sub>2</sub>), 8.20–7.70 (2 H, m, 6-H<sub>2</sub>), 7.59 (3 H, s, Ac), 7.35–6.90 (2 H, m, 3-H<sub>2</sub>), and 4.41 (2 H, m, 2-H and 1-H);  $\nu_{\max}$  (film) 1 710 (Ac), and 1 660 and 665 cm<sup>-1</sup> (*cis*-CH=CH-).

Treatment of the Bromo-ketone (21) with Zinc and Acetic Acid in Ether.—The bromo-ketone (21) (500 mg, 2.2 mmol) was added to zinc powder (280 mg, 4.3 mmol) and acetic acid (1 ml) in ether (40 ml). The mixture was stirred at room temperature for 6 h and then was filtered into petroleum (30 ml) and water (30 ml). The aqueous mixture was extracted with petroleum (3 × 30 ml) and the combined extracts were worked up as usual to give 5-acetyl-4,4-dimethylcyclohexene (7) (300 mg, 1.9 mmol) which was identified by its n.m.r., i.r., and g.l.c. data.

1-Acetyl-6,6-dimethylcyclohexa-1,3-diene (10).—Anhydrous lithium chloride (2.8 g, 66 mmol) and lithium carbonate (8.0 g, 110 mmol) were added to dimethylformamide (70 ml). This mixture was heated under dry nitrogen to 120 °C and then the bromo-ketone (21) (9.9 g, 43 mmol) in dimethylformamide (10 ml) was added. The mixture was heated and stirred at 120–130 °C for 5 h, cooled, poured into 10% hydrochloric acid (30 ml), petroleum (30 ml), and ice (30 g), and extracted with petroleum (5 × 50 ml). The combined extracts were washed with 10% hydrochloric acid (1 × 50 ml) and worked up as usual to give 1-acetyl-6,6-dimethylcyclohexa-1,3-diene (10) (5.9 g, 39 mmol, 90%). This material was more than 95% one component by g.l.c. analysis [column (A), 120 °C]. A sample prepared by micro-distillation had b.p. 30–35° (bath) at 0.2 mmHg (Found: C, 79.8; H, 9.15. C<sub>10</sub>H<sub>14</sub>O requires C, 80.0; H, 9.35%);  $m/e$  150 ( $M^+$ , 22%), 135 (8), 107 (56), 91 (37), 79 (17), 77 (11), 65 (11), 51 (6), 43 (100), and 41 (11);  $\tau$  8.83 (6 H, s, 6-Me<sub>2</sub>), 7.85 (2 H, m, 5-H<sub>2</sub>), 7.79 (3 H, s, Ac), 3.94 (2 H, 4- and 3-H), and 3.32 (1 H, m, 2-H);  $\nu_{\max}$  (film) 1 665 cm<sup>-1</sup> (-CH=CH-CO-);  $\lambda_{\max}$  (cyclohexane) 295 nm ( $\epsilon$  11 100).

1-(6,6-Dimethylcyclohexa-1,3-dienyl)-3-hydroxybutan-1-one.—1-Acetyl-6,6-dimethylcyclohexa-1,3-diene (10) (2.0 g, 13 mmol) was treated with acetaldehyde as described above for 5-acetyl-4,4-dimethylcyclohexene (7) to give an oil (2.5 g). This was purified by chromatography on silica gel (100 g) to give unchanged dienone (10) (850 mg, 5 mmol) with benzene as eluant and the hydroxy-ketone (1.0 g, 5 mmol, 40%) with 9 : 1 benzene-ether as eluant;  $m/e$  194 ( $M^+$ , 17%),

135 (42), 119 (30), 107 (100), 106 (34), 91 (59), 79 (15), 77 (15), 65 (14), 44 (42), 43 (96), and 41 (17);  $\tau$  8.85 (3 H, d,  $J$  6 Hz,  $\text{CH}_3\text{CHOH}$ ), 8.84 (6 H, s,  $\text{CMe}_2$ ), 7.85 (2 H, m, ring 5- $\text{H}_2$ ), 7.33 (2 H, d,  $J$  6 Hz,  $\text{CO}\cdot\text{CH}_2$ ), 6.47br (1 H, s, exchanges with  $\text{D}_2\text{O}$ , OH), 5.85 (1 H, q,  $J$  6 and 6 Hz,  $\text{CHOH}$ ), 3.93 (2 H, m, ring 4- and 3-H), and 3.31 (1 H, m, ring 2-H);  $\nu_{\text{max}}$  (film) 3 450 (OH) and 1 660  $\text{cm}^{-1}$  ( $-\text{CH}=\text{C}-\text{CO}-$ ).

*trans*-1-(6,6-Dimethylcyclohexa-1,3-dienyl)but-2-en-1-one.—The foregoing hydroxy-ketone (750 mg, 3.9 mmol) was added to a mixture of acetic anhydride (2.5 g) and anhydrous sodium acetate (250 mg, 3.1 mmol) and heated at 100 °C for 1.5 h. Water (10 ml) was then added and the mixture was heated at 80 °C for 5 min and extracted with petroleum

(4  $\times$  50 ml). The combined extracts were worked up as usual to give the *butenone* (22) (620 mg, 3.5 mmol, 91%), shown by g.l.c. analysis [column (A), 140 °C] to be more than 95% one component. A sample purified further by preparative g.l.c. [column (B), 140 °C] showed  $m/e$  176 ( $M^+$ , 83%), 161 (36), 107 (100), 106 (51), 91 (70), 79 (16), 77 (16), 69 (85), 41 (83), and 39 (38);  $\tau$  8.84 (6 H, 2s superimposed,  $\text{CMe}_2$ ), 8.12 (3 H, d,  $J$  6.5 Hz,  $=\text{CH}\cdot\text{CH}_3$ ), 7.88 (2 H, m, ring 5- $\text{H}_2$ ), 4.00 (2 H, m, ring 4-H and 3-H), 3.67 (1 H, d,  $J$  16 Hz,  $\text{CO}\cdot\text{CH}=\text{C}$ ), 3.52 (1 H, m, ring 2-H), and 3.26 (1 H, dq,  $J$  6.5 and 16 Hz,  $=\text{CH}\cdot\text{CH}_3$ );  $\nu_{\text{max}}$  (film) 1 665, 1 645, 1 615 ( $-\text{CH}=\text{C}-\text{CO}-$ ), and 970  $\text{cm}^{-1}$  (*trans*  $-\text{CH}=\text{CH}$ );  $\lambda_{\text{max}}$  (n-hexane) 238 and 305 nm ( $\epsilon$  7 200 and 5 100).

[5/174 Received, 27th January, 1975]