

## Synthesis of Dihydrotagetone (2,6-Dimethyloct-7-en-4-one)

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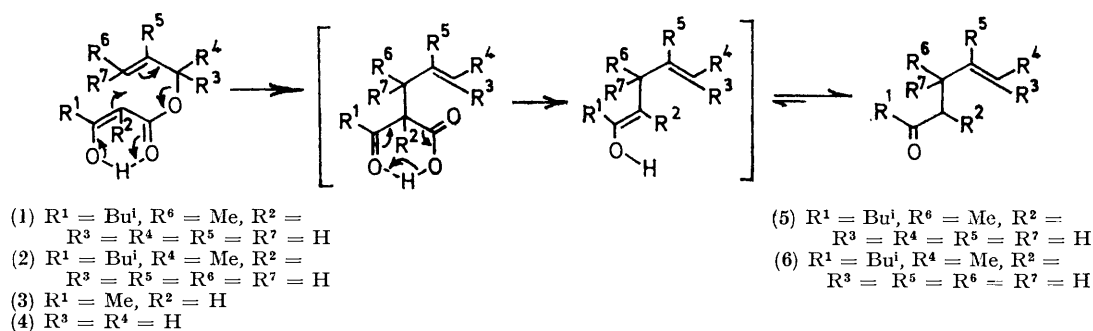
The acyclic monoterpene dihydrotagetone (2,6-dimethyloct-7-en-4-one) has been prepared from isobutyl methyl ketone in two stages. The key step involves a simple extension of the Carroll reaction.

VARIOUS syntheses of dihydrotagetone (2,6-dimethyloct-7-en-4-one) (5),<sup>1</sup> an important constituent of *Tagetes glandulifera*, have been reported.<sup>2-4</sup> Since all these preparations require a considerable number of steps, we have investigated a route (Scheme) involving the use of the Carroll reaction,<sup>5</sup> which would offer the advantages of simplicity and directness. Reported examples of the Carroll reaction are limited, with few exceptions,<sup>6,7</sup> to those in which R<sup>1</sup> = Me and R<sup>2</sup> = H. We considered, however, that this did not indicate a fundamental

comparison with authentic material<sup>9</sup> prepared from isopropyl bromide and sodium acetoacetate.

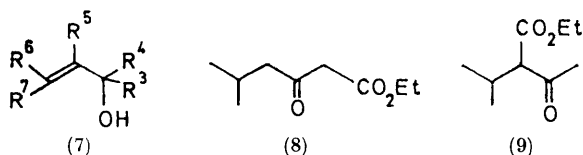
The transesterification and pyrolysis steps were carried out in one combined operation (see Experimental section) giving a product whose spectral characteristics were identical with those of the natural material isolated from tagetes oil.†

Two minor components, (A) and (B), were also found in the distillation fractions containing dihydrotagetone. A g.l.c.-mass spectral study showed these materials to



SCHEME

limitation of the scope of this reaction, but rather resulted from the ready accessibility of β-keto-esters (3) prepared from diketene and the appropriate allylic alcohol (7). This conclusion was borne out by subsequent experiments in which a yield of ca. 35% of the required product was obtained.



The but-2-enyl 5-methyl-3-oxohexanoate (1) required for the synthesis of dihydrotagetone (5) was prepared by transesterification of ethyl 5-methyl-3-oxohexanoate (8) with but-2-en-1-ol. The β-keto-ester (8) was obtained by ethoxycarbonylation of isobutyl methyl ketone as described by Levine and Hauser<sup>8</sup> but with sodium hydride as catalyst. The absence of the isomeric ethyl α-isopropylacetoacetate (9) was shown by g.l.c.

† We thank Dr. J. W. K. Burrell for this material.

<sup>1</sup> T. G. H. Jones and F. B. Smith, *J. Chem. Soc.*, 1925, 127, 2530.

<sup>2</sup> O. P. Vig, K. L. Matta, and I. Raj, *J. Indian Chem. Soc.*, 1964, 41, 752.

<sup>3</sup> P. Teisseire and B. Corbier, *Recherches*, 1969, 17, 5.

<sup>4</sup> O. P. Vig, K. L. Matta, M. S. Bhatia, and R. C. Anand, *Indian J. Chem.*, 1970, 8, 107.

<sup>5</sup> (a) M. P. Carroll, *J. Chem. Soc.*, 1941, 507; (b) W. Kimel and A. C. Cope, *J. Amer. Chem. Soc.*, 1943, 65, 1992.

have molecular weights of 156 and 154, respectively. Compound (A) was not obtained pure, but analysis of the mass spectrum suggested that the material was not 2,6-dimethyloctan-4-one, the saturated ketone derived from dihydrotagetone, but rather an ester (C<sub>9</sub>H<sub>16</sub>O<sub>2</sub>). But-2-enyl isovalerate (10), which could have been formed by a fragmentation-recombination reaction, would fit this molecular formula, and synthesis of this ester<sup>10</sup> from the appropriate acid and alcohol gave a material which indeed appeared to be identical (g.l.c. and mass spectrum) with compound (A).

With regard to compound (B), Teisseire, in his study of the Carroll reaction,<sup>11</sup> has pointed out that the allylic alcohol used is capable of rearrangement during the course of the transesterification reaction. Thus but-2-en-1-ol could isomerise to but-3-en-2-ol, which on treatment with ethyl 5-methyl-3-oxohexanoate (8) would yield 1-methylallyl 5-methyl-3-oxohexanoate (2). Pyrolysis would then yield 2-methylnon-7-en-4-one (6) which, when prepared by this method, was indeed found to be identical with compound (B).

<sup>6</sup> J. Dreux and J. Cologne, *Bull. Soc. chim. France*, 1955, 1312.

<sup>7</sup> B.P. 829,620; 948,752; 948,755 (*Chem. Abs.*, 1960, 54, 19,598h; 1964, 60, 13,147b, 15,738a).

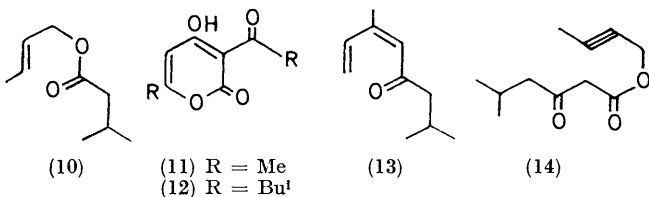
<sup>8</sup> R. Levine and C. R. Hauser, *J. Amer. Chem. Soc.*, 1944, 66, 1768.

<sup>9</sup> W. B. Renfrow, *J. Amer. Chem. Soc.*, 1944, 66, 144.

<sup>10</sup> E. Charon, *Ann. Chim. (France)*, 1899, [7] 17, 255.

<sup>11</sup> P. Teisseire, *Recherches*, 1957, 7, 29.

From the residue of the dihydrotagetone preparation was successfully distilled a compound (C), b.p. 150—154° at 3 mmHg. By analogy with other Carroll reactions, where the pyrone (11) can be formed by dimerisation of a substituted acetoacetic ester, the corresponding product from either ethyl 5-methyl-3-oxohexanoate (8) or but-enyl 5-methyl-3-oxohexanoate (1) would be 4-hydroxy-6-isobutyl-3-isovaleryl-2-pyrone (12). To verify this assumption, the  $\beta$ -keto-ester (8) was treated under the conditions described for the dimerisation of acetoacetic ester;<sup>12</sup> the dimeric product obtained had the same physical properties as compound (C), and spectroscopic analyses confirmed their identity.



The yield of dihydrotagetone in the pyrolysis experiments (30—38%) is similar to that obtained in other Carroll reactions where the carbinyl carbon is unsubstituted (4); substitution on this carbinyl carbon atom will usually result in an improved yield.<sup>5b,13</sup> This is probably a consequence of the geometry of the transition state of this rearrangement, which has a cyclohexane chair-like conformation.<sup>14</sup> In the case of the substituted compounds, the stability of an equatorial alkyl group over an axial one forces the substituted compound to adopt a much more rigid transition state and hence promotes the desired reaction to a greater extent than is possible in the unsubstituted molecule.

An attempt to synthesise tagetone (2,6-dimethylocta-5,7-dien-4-one) (13)<sup>15</sup> by a Carroll reaction from but-2-ynyl 5-methyl-3-oxohexanoate (14) [prepared from ethyl 5-methyl-3-oxohexanoate (8) and but-2-yn-1-ol<sup>16</sup>] produced isobutyl methyl ketone, the starting alcohol, and carbon dioxide as the main recognisable components. This seems to substantiate the work of Lacey,<sup>17</sup> who has found that the pyrolysis of acetylenic  $\beta$ -keto-esters is hampered when the carbinyl carbon atom is unsubstituted. Alkyl-oxygen fission appears the preferred mode of reaction in such cases.

#### EXPERIMENTAL

I.r. spectra were determined for liquid films with a Unicam SP 100 instrument, n.m.r. spectra with a Varian A-60A, for solutions in carbon tetrachloride, and mass spectra with an A.E.I. MS 902 instrument at 70 eV; g.l.c. analyses were performed with a Pye 104 instrument [9 ft glass column packed with 3% FFAP on Chromosorb G (100—120 mesh)].

*Ethyl 5-Methyl-3-oxohexanoate* (8).—Sodium hydride (50% suspension; 144 g, 3.0 mol) and sodium-dried benzene

\* (Hardman and Holden Ltd.): a 1 : 1 mixture of aluminium isopropoxide and *s*-butoxide.

<sup>12</sup> F. Arndt, *Org. Synth.*, 1955, Coll. Vol. 3, p. 231.

<sup>13</sup> U.S.P. 2,795,617 (*Chem. Abs.*, 1958, 52, 2,050i).

(500 ml) were placed in a flask (3 l) fitted with stirrer, nitrogen inlet, dropping funnel, and reflux condenser with drying tube. The suspension was stirred for 10 min, the solid was allowed to settle, and the benzene-paraffin mixture was syphoned off. Further dry benzene (1.5 l) was then run in, followed by diethyl carbonate (354 g, 3.0 mol), added during 30 min. The mixture was heated to reflux temperature and isobutyl methyl ketone (200 g, 2.0 mol) was added dropwise with stirring during 3.0 h. The mixture was then refluxed with stirring for a further 1 h.

The mixture was set aside at room temperature overnight, and acetic acid (100 ml) was then added slowly to decompose the excess of sodium hydride. The heavy slurry thus formed was poured into ice-cold water (2 l). The organic layer was separated and the aqueous phase extracted with ether (3  $\times$  500 ml); the combined organic layers were washed thoroughly with brine, dried (MgSO<sub>4</sub>), and concentrated to yield a golden-yellow oil (574 g). On distillation, after a forerun of diethyl carbonate, ethyl 5-methyl-3-oxohexanoate (8) was obtained as a liquid, b.p. 116—117° at 30 mmHg,  $n_D^{20}$  1.4298 (268 g, 1.56 mol, 78%).

*Pyrolysis Reaction*.—Ethyl 5-methyl-3-oxohexanoate (172.0 g, 1.0 mol), but-2-en-1-ol (79.2 g, 1.1 mol) and Aliso B\* (224 mg, 1.0 mmol) were placed in a flask fitted with a small Vigreux column; the flask was heated to 110°, and the ethanol formed was removed by fractional distillation. The pot temperature was raised to 180—190° and maintained there until the evolution of carbon dioxide was negligible (*ca.* 15 h). The red-brown pyrolysate was directly distilled and separated into three fractions:

Fraction (i), b.p. 90—105° at 40 mmHg (46.2 g), was largely dihydrotagetone (5). Fractionation gave material of b.p. 97—98° at 40 mmHg,  $n_D^{20}$  1.4293,  $\nu_{\max}$  918m, 998m, 1175m, 1277m, 1377m, 1394m, 1419m, 1478m, 1650m, 1721s, 2875s, 2960s, 3020m, and 3085m cm<sup>-1</sup>,  $\delta$  (p.p.m.) 0.89 (d, *J* 6 Hz, Me<sub>2</sub>CH), 1.00 (d, *J* 6 Hz, MeCH), *ca.* 2.1—2.4 (CH<sub>2</sub>·CO·CH<sub>2</sub>), *ca.* 2.7 (m, MeCH·C·C), 4.87 (H<sub>A</sub>), 4.92 (H<sub>B</sub>), and 5.74 (H<sub>C</sub>) (*J*<sub>AC</sub> *ca.* 9.5, *J*<sub>BC</sub> *ca.* 17.5,

*J*<sub>AB</sub> *ca.* 1, *J*<sub>CD</sub> *ca.* 6 Hz)  $\left( \begin{array}{c} \text{H}_A \\ \text{H}_B \end{array} \right) \text{C}=\text{C} \begin{array}{c} \text{H}_C \\ \text{CH}_D \end{array} \right)$ ; *m/e* 57 (100%),

85 (98), 69 (55), 55 (55), 41 (55), 43 (34), 97 (25), and 154 (5).

The semicarbazone was repeatedly crystallised from aqueous ethanol to give colourless needles, m.p. 95—96° (lit.<sup>3</sup> 92.5°). The remaining material, compound (A), which was not obtained pure, was shown to be but-2-enyl isovalerate (10) by comparison with authentic material.<sup>10</sup>

Fraction (ii), b.p. 105—120° at 40 mmHg (12.3 g), contained a mixture of dihydrotagetone and compound (B). Fractional distillation allowed the isolation of pure (B), b.p. 113—115° at 40 mmHg, identical with 2-methylnon-7-en-4-one (6) (see later).

Fraction (iii) b.p. 145—160° at 3 mmHg (75.6 g) was redistilled to give a pale yellow liquid, compound (C), b.p. 150—154° at 3 mmHg, having structure (12) (see later).

An alternative procedure allowed the isolation of but-

<sup>14</sup> N. Wakabayashi, R. M. Waters, and J. P. Church, *Tetrahedron Letters*, 1969, 3253; D. J. Faulkner, *Synthesis*, 1971, 175; J. Reucroft and P. G. Sammes, *Quart. Rev.*, 1971, 25, 135.

<sup>15</sup> E. E. Boehm, V. Thaller, and M. C. Whiting, *J. Chem. Soc.*, 1963, 2535.

<sup>16</sup> L. F. Hatch and V. Chiola, *J. Amer. Chem. Soc.*, 1951, 73, 360.

<sup>17</sup> R. N. Lacey, *J. Chem. Soc.*, 1954, 827.

2-enyl 5-methyl-3-oxohexanoate (1). After the removal of the ethanol, the remaining material was distilled under reduced pressure to yield compound (1) as a liquid, b.p. 145—147° at 30 mmHg (146 g, 0.74 mol, 74%),  $n_D^{20}$  1.4494,  $v_{\max}$  972s, 1160s, 1234s, 1270s, 1325s, 1376m, 1421m, 1461m, 1477m, 1728s, 1756s, 2878s, 2961s, and 3030w  $\text{cm}^{-1}$ ;  $\delta$  (p.p.m.) 0.92 (d,  $J$  6.8 Hz,  $\text{Me}_2\text{CH}$ ), 1.71 (dm,  $J$  5.5 and ca. 1 Hz,  $\text{MeCH:C}$ ), ca. 2.03 (m,  $\text{CHMe}_2$ ), ca. 2.38 ( $\text{CH}_2\cdot\text{CHMe}_2$ ), 3.34 ( $\text{CO}\cdot\text{CH}_2\cdot\text{CO}$ ), 4.51 (dm,  $J$  5.5 and ca. 1 Hz,  $\text{CO}_2\cdot\text{CH}_2\cdot\text{CH:C}$ ), 5.31—6.1 (complex m,  $\text{CH:CH}$ ), and 4.91 (enol  $\text{CH:C}\cdot\text{OH}$ );  $m/e$  57 (100%), 43 (73), 41 (49), 85 (29), 55 (29), 58 (27), and 72 (22). The  $\beta$ -keto-ester (1) was then pyrolysed in the usual way to yield dihydrotagetone. There was no improvement in yield using this two-stage procedure.

*2-Methylnon-7-en-4-one* (6).—Ethyl 5-methyl-3-oxohexanoate (43 g, 0.25 mmol), but-3-en-2-ol (22.5 g, 0.31 mol), and Aliso B (56 mg, 0.25 mol), were heated in a flask fitted with a Vigreux column. When the pot temperature reached 100—105°, the ethanol produced began to distill off and was collected during 3 h (7.0 g). The pot temperature was then raised to 200° and kept at this level until no further carbon dioxide was evolved (8 h).

The crude product was fractionally distilled to yield 2-methylnon-7-en-4-one, b.p. 113—115° at 40 mmHg,  $d_D^{20}$  1.4355 (22.3 g, 0.14 mol, 56%),  $v_{\max}$  970s, 1150m, 1175m, 1270m, 1376s, 1417m, 1462m, 1478m, 1723s, 2878s, 2960s, and 3020m  $\text{cm}^{-1}$ ,  $\delta$  (p.p.m.) 0.91 (d,  $J$  7 Hz  $\text{Me}_2\text{CH}$ ), 1.62 ( $\text{MeCH:C}$ ), ca. 2.15—2.4 ( $\text{CH}_2\cdot\text{CO}\cdot\text{CH}_2\cdot\text{CH}_2$ ), and 5.39 (m,  $\text{CH:CH}$ ),  $m/e$  57(100%), 85(98), 41(64), 69(61), 55(48), 97(33), 43(33), and 154(9). This material was identical with compound (B).

*4-Hydroxy-6-isobutyl-3-isovaleryl-2-pyrone* (12).—To a 250 ml flask containing ethyl 5-methyl-3-oxohexanoate (86 g, 0.5 mol) and sodium hydrogen carbonate (0.05 g) was fitted a modified Hahn condenser<sup>18</sup> (filled with toluene), the side-arm being arranged for downward distillation. The mixture was heated (pot temperature 180—240°, head temperature 76—78°) until no further ethanol was collected (24.0 g). After cooling, the partial condenser

was removed and replaced by a Vigreux column. Fractional distillation yielded the pyrone (12), b.p. 147—148° at 2 mmHg (25.0 g, 0.1 mol, 40%),  $n_D^{20}$  1.5167,  $v_{\max}$  710m, 815m, 843m, 883m, 939m, 1005s, 1110m, 1123m, 1172m, 1218m, 1271m, 1290m, 1335s, 1388s, 1462s, 1570s, 1620s, 1650s, 1747s, 2875s, 2964s, and 3100w  $\text{cm}^{-1}$ ,  $\delta$  (p.p.m.) 1.00 and 1.02 (12H, each d,  $J$  6.8 Hz  $\text{Me}_2\text{CH}$ ), ca. 1.8—2.5 (complex m,  $\text{Me}_2\text{CH}\cdot\text{CH}_2\cdot\text{CO}$  and  $\text{Me}_2\text{CH}\cdot\text{CH}_2\cdot\text{C:C}$ ), 2.87 (d,  $J$  6.8 Hz  $\text{Me}_2\text{CH}\cdot\text{CH}_2\cdot\text{C:C}$ ) 5.84 ( $\text{CH:C}$ ), and 16.91 (H-bonded OH),  $m/e$  43 (100%), 41 (99), 195 (96), 57 (87), 168 (82), 237 (72), 69 (70), 85 (62), 153 (50), 252 (35), 67 (35), and 201 (33). This material was identical with compound (C).

*But-2-ynyl 5-Methyl-3-oxohexanoate* (14).—Ethyl 5-methyl-3-oxohexanoate (59.3 g, 0.34 mol), but-2-yn-1-ol<sup>16</sup> (26.5 g, 0.38 mol), and Aliso B (76 mg, 34 mmol) were heated in a flask fitted with a Vigreux column. The pot temperature was raised to 130°, and the ethanol produced was removed by fractional distillation. Distillation under reduced pressure gave but-2-ynyl 5-methyl-3-oxohexanoate (14) as a pale yellow liquid, b.p. 134—136° at 10 mmHg (42.2 g, 0.216 mol, 64%),  $n_D^{20}$  1.4597,  $v_{\max}$  989m, 1160s, 1230s, 1278m, 1322s, 1378s, 1418m, 1728s, 1760s, 2248w, 2876s, and 2962s  $\text{cm}^{-1}$ ,  $\delta$  (p.p.m.) 0.94 (d,  $J$  6.8 Hz,  $\text{Me}_2\text{CH}$ ), 1.85 (t,  $J$  2.5 Hz,  $\text{MeC:C}$ ), ca. 1.9—2.5 (complex m,  $\text{Me}_2\text{CH}\cdot\text{CH}_2$ ), 3.36 ( $\text{CO}\cdot\text{CH}_2\cdot\text{CO}$ ), 4.61 (q,  $J$  2.5 Hz,  $\text{C:C}\cdot\text{CH}_2$ ), 4.63 (q,  $J$  2.5 Hz, enol  $\text{C:C}\cdot\text{CH}_2$ ), 4.92 (enol  $\text{CH:C}\cdot\text{OH}$ ), and 11.89 (enol H-bonded OH),  $m/e$  69 (100%), 57 (76), 53 (70), 85 (65), 41 (62), 43 (54), 42 (46), and 84 (27). Pyrolysis of this material in the presence of a wide range of catalysts failed to yield tagetone; isobutyl methyl ketone, but-2-yn-1-ol, and carbon dioxide were the principal products among a large number present in trace amounts.

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<sup>18</sup> A. I. Vogel, 'Practical Organic Chemistry,' Longmans, London, 3rd edn., p. 885.