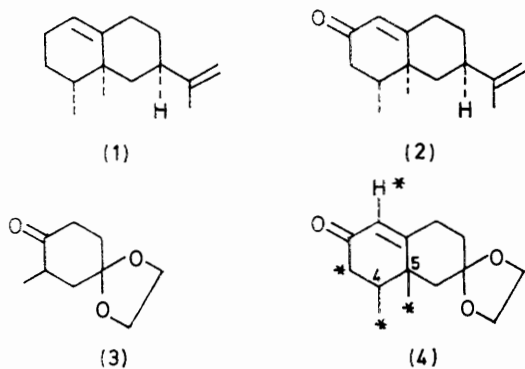


## Further Synthetic Studies in the Nootkatane Sesquiterpene Group. A New Total Synthesis of ( $\pm$ )-Valencene and ( $\pm$ )-Nootkatone

By H. Michael McGuire, H. Clyde Odom, (jun.), and A. Reginald Pinder,\* Department of Chemistry, Clemson University, Clemson, South Carolina 29631, U.S.A.

A new stereospecific synthesis of racemic valencene [ $4\beta H,5\alpha$ -eremophila-1(10),11-diene] (1) and nootkatone [ $4\beta H,5\alpha$ -eremophila-1(10),11-dien-2-one] (2), starting from 4,4-ethylenedioxy-2-methylcyclohexanone, is described.

SEVERAL syntheses of the racemic varieties of valencene (1) and nootkatone (2) have been described recently.<sup>1</sup> We record here a further successful synthetic approach to these compounds, which are the principles responsible for the flavour of grapefruit juice.<sup>2</sup>



Our starting point was the acetal (3) of 2-methylcyclohexane-1,4-dione. It has been claimed<sup>3</sup> that this compound results from a regiospecific condensation between 2-methylcyclohexane-1,4-dione and ethylene glycol (1 mol), but in our hands this reaction gave a mixture, separable by g.l.c. into the two possible isomeric monoacetals, the diacetal, and unchanged diketone. The desired acetal (3) was therefore synthesized from furfuraldehyde by the sequence described by Sarett and his co-workers.<sup>4</sup> Annulation of it with *trans*-pent-3-en-2-one afforded the crystalline octalone (4) in 56% yield, based on unrecovered (3). There was reason to believe, from a study of the annulation step using models,<sup>5</sup> that the methyl groups in the product (4) would be *cis*, as depicted. That this was very probably so was supported by a study of the effect of the  $\text{Eu}(\text{fod})_3$  shift reagent † on the n.m.r. spectrum of the product. Comparison of the downfield shifts experienced by four sets of protons [asterisked in (4)] at various concentrations of the shift reagent, with those of analogous sets of protons in nootkatone (2), of known relative configuration,<sup>6</sup> showed

† Tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato)europium(III).

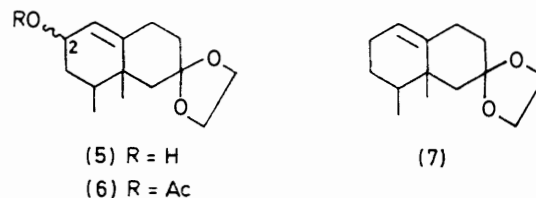
‡ Many of the structures drawn here, including (4), represent racemates, only one enantiomer being shown.

<sup>1</sup> J. A. Marshall and R. A. Ruden, *Tetrahedron Letters*, 1970, 1239; *J. Org. Chem.*, 1971, **36**, 594; K. P. Dastur, *J. Amer. Chem. Soc.*, 1973, **95**, 6509; R. M. Coates and J. E. Shaw, *J. Org. Chem.*, 1970, **35**, 2597. See also ref. 20.

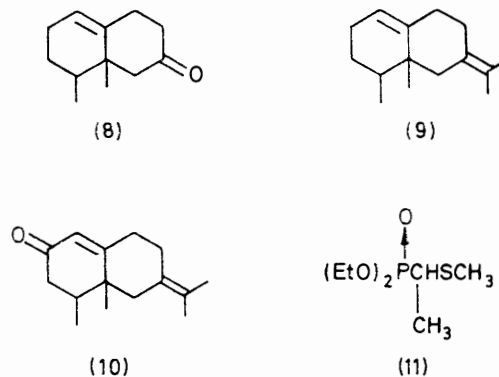
<sup>2</sup> H. Erdtman and Y. Hirose, *Acta Chem. Scand.*, 1962, **16**, 1311. See also ref. 6.

<sup>3</sup> R. K. Mathur and A. S. Rao, *Tetrahedron*, 1967, **23**, 1259.

them to be almost identical, leading to the conclusion that (4) almost certainly has the  $4\beta,5\beta$ -dimethyl configuration.‡



Reduction of enone (4) with lithium aluminium hydride generated the allylic alcohol (5), of unspecified stereochemistry at C(2). Acetylation then afforded the corresponding acetate (6), reduction of which with lithium and ethylamine<sup>7</sup> furnished, in high yield, the octalin (7). Hydrolysis with dilute acid under mild conditions provided the octalone (8). Considerable effort was devoted to causing this ketone to react with isopropylidene-triphenylphosphorane, in a Wittig reaction, with a view to converting it into the diene (9); the latter substance would presumably be easily oxidizable to  $\alpha$ -vetivone (isonootkatone) (10).<sup>8</sup> However, reaction did



not take place, presumably owing to the very strongly basic character of the ylide, which simply deprotonated the ketone in one of the  $\alpha$ -positions. It is noteworthy that, as far as we are aware, a successful reaction between

<sup>4</sup> R. M. Lukes, G. I. Poos, and L. H. Sarett, *J. Amer. Chem. Soc.*, 1952, **74**, 1401; S. A. Narang and P. C. Dutta, *J. Chem. Soc.*, 1960, 2842.

<sup>5</sup> Cf. J. A. Marshall, H. Faubl, and T. M. Warne, *Chem. Comm.*, 1967, 753; H. C. Odom and A. R. Pinder, *ibid.*, 1969, 26.

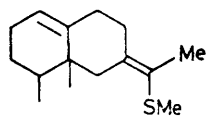
<sup>6</sup> W. D. MacLeod, *Tetrahedron Letters*, 1965, 4779.

<sup>7</sup> A. S. Hallsforth, H. B. Henbest, and T. I. Wrigley, *J. Chem. Soc.*, 1957, 1969.

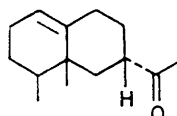
<sup>8</sup> K. Endo and P. de Mayo, *Chem. Comm.*, 1967, 89; J. A. Marshall and N. H. Andersen, *Tetrahedron Letters*, 1967, 1611.

this ylide and a ketone has not been reported, although it has reacted successfully with the more reactive carbonyl group of aldehydes.<sup>9</sup>

The ketone (8) was therefore subjected to a Wadsworth-Emmons reaction<sup>10</sup> with diethyl (1-methylthioethyl)phosphonate (11), which gave the thioenol ether (12) in high yield.<sup>11</sup> Hydrolysis then provided the methyl ketone (13), which was converted entirely into the 7 $\alpha$ -

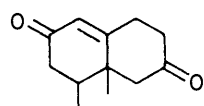


(12)

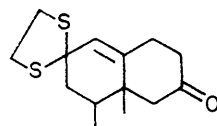


(13)

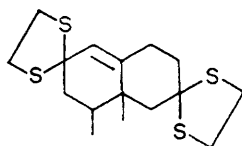
acetyl (equatorial) conformer by brief treatment with base. A Wittig reaction of this conformer with methylenetriphenylphosphorane yielded ( $\pm$ )-valencene identical in every respect (except optical rotation) with an authentic sample of natural (+)-valencene (1). The formation of valencene, of known relative configuration,<sup>6,12</sup> confirms the 7 $\alpha$ -configurational assignment of the acetyl group in (13), and also the 4 $\beta$ ,5 $\beta$ -configuration of the methyl groups. A sample of the synthetic valencene was oxidized with *t*-butyl chromate to ( $\pm$ )-nootkatone (2), identical with an authentic specimen.



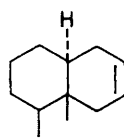
(14)



(15)



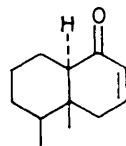
(16)



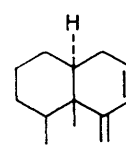
(17)

Other attempts to make the octalin (7) included a Kishner reduction of the semicarbazone of enone (4), which resulted in much pyrolytic decomposition. Acid hydrolysis of acetal (4) led to the diketone (14); however, in spite of a report<sup>13</sup> that ethanedithiol reacts with  $\alpha\beta$ -unsaturated ketones more readily than with saturated, efforts to convert the diketone into the dithioacetal (15) were attended by the formation of substantial amounts of the bisdithioacetal (16), and unchanged diketone. The desired product was separable, in poor yield, by chromatography, but was later found to be more accessible by dithioacetalization of (4), followed by acid hydrolysis. Attempts to desulphurize (15) with Raney

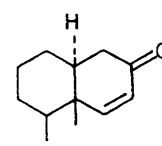
nickel were accompanied by reductive attack on the double bond, with formation of a mixture of products. Efforts to effect a Wittig reaction between ketone (15) and isopropylidene-triphenylphosphorane were unrewarding, probably for the reason advanced to explain the failure of enone (8) to react under the same circumstances (see above).



(18)

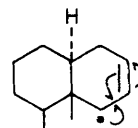


(19)

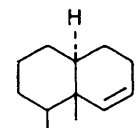


(20)

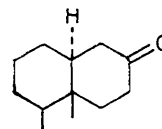
The possible synthetic use of the octalin (17) was next considered. The hydrocarbon was synthesized as outlined by Djerassi and his co-workers,<sup>14</sup> and oxidized with sodium dichromate, in the hope of generating the enone (18), perhaps accompanied by the isomeric enone (19). The oxidation product, obtained in *ca.* 20% yield, was homogeneous on t.l.c. and g.l.c., and had  $\lambda_{\text{max}}$  229 nm ( $\epsilon$  10,500), but its n.m.r. spectrum, in which the olefinic proton signals appeared as a well-resolved AB quartet at  $\delta$  5.95 and 7.20 (2H, *J* 10 Hz), showed that it was not to be formulated as (18) or (19), but as the rearranged enone (20). The formation of the latter can be rationalized in terms of a rearrangement of the initial radical (21), produced by the oxidation, to (22), as shown.<sup>15</sup> The structure (20) was confirmed by catalytic hydrogenation



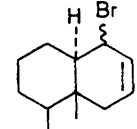
(21)



(22)



(23)



(24)

of the enone to (23), identical with an authentic sample synthesized from the same hydrocarbon by a different, unequivocal route.<sup>14</sup> Another attempt to prepare (18) *via* the bromide (24) was thwarted by the finding that the hydrocarbon (17) on treatment with *N*-bromosuccinimide gave a mixture of bromides. If bromide (24) had been secured, it was proposed to attempt its oxidation to (18) with, for example, dimethyl sulphoxide.<sup>16</sup>

<sup>13</sup> J. W. Ralls and B. Riegel, *J. Amer. Chem. Soc.*, 1954, **76**, 4479.

<sup>14</sup> L. H. Zalkow, F. X. Markley, and C. Djerassi, *J. Amer. Chem. Soc.*, 1960, **82**, 6354.

<sup>15</sup> W. G. Dauben, M. Lorber, and D. S. Fullerton, *J. Org. Chem.*, 1969, **34**, 3587.

<sup>16</sup> W. W. Epstein and F. W. Sweat, *Chem. Rev.*, 1967, **67**, 247, and references cited therein.

<sup>9</sup> G. Wittig and D. Wittenberg, *Annalen*, 1957, **606**, 1.

<sup>10</sup> W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, 1961, **83**, 1733.

<sup>11</sup> Cf. E. J. Corey and J. Shulman, *J. Org. Chem.*, 1970, **35**, 777.

<sup>12</sup> G. L. K. Hunter and W. B. Brogden, *J. Food. Sci.*, 1965, **30**, 1, 876.

## EXPERIMENTAL †

**2-Methylcyclohexane-1,4-dione.**—This diketone was obtained in 70% yield by Birch reduction of 2,5-dimethoxytoluene, as described by Turner and his co-workers,<sup>17</sup> b.p. 129—136° at 25 mmHg, m.p. 48°;  $\nu_{\max}$  (film) 1705  $\text{cm}^{-1}$ .

**Reaction of 2-Methylcyclohexane-1,4-dione with Ethylene Glycol.**—A mixture of the diketone (2.52 g, 0.02 mol), ethylene glycol (1.24 g, 0.002 mol), toluene-*p*-sulphonic acid monohydrate (0.17 g), and dry benzene (150 ml) was refluxed in a Dean and Stark apparatus until the separation of water was complete (6 h). The solution was cooled, washed with saturated aqueous sodium hydrogen carbonate and water, and dried ( $\text{Na}_2\text{SO}_4$ ). The solvent was removed *in vacuo*, and the residue distilled, b.p. 132—150° at 25 mmHg (2.6 g). G.l.c. of the product showed four components which were, in order of increasing retention time, 2-methylcyclohexane-1,4-dione (15%), 4,4-ethylenedioxy-2-methylcyclohexanone (3) (37%), the isomeric 4,4-ethylenedioxy-3-methylcyclohexanone (20%), and 1,1:4,4-bisethylenedioxy-2-methylcyclohexane (28%).

**4,4-Ethylenedioxy-2-methylcyclohexanone (3).**—This ketone was synthesized from furfuraldehyde by the sequence described by Sarett and his collaborators,<sup>4</sup> b.p. 134° at 26 mmHg;  $\nu_{\max}$  (film) 1710 and 1125  $\text{cm}^{-1}$ . The product crystallized from pentane in irregular prisms, m.p. 50—51°.

**Annulation of 4,4-Ethylenedioxy-2-methylcyclohexanone.**—Sodium hydride (57% dispersion in mineral oil) (20 g) was washed thrice by decantation with dry pentane, covered with dry ether (100 ml), and stirred at ambient temperature under dry nitrogen during the gradual addition (few min) of the foregoing ketone (34 g, 0.2 mol) in dry ether (100 ml). Stirring was continued for 2 h, then a solution of *trans*-pent-3-en-2-one<sup>18</sup> (20 g, 0.24 mol) in dry ether (250 ml) was added during 4 h, at room temperature, under nitrogen. The mixture was stirred for a further 18 h, then cooled in ice and decomposed cautiously with ice-water. The organic layer was separated and the aqueous layer extracted twice with ether. The combined extracts were washed twice with water, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated. The residue was distilled fractionally *via* a 6 in Vigreux column, to give two fractions: (a) b.p. <125° at 0.2—0.3 mmHg (23.8 g; unchanged cyclohexanone), and (b) b.p. 123—130° at 0.15—0.2 mmHg (11.7 g). The second fraction crystallised partially on keeping. It was taken up in light petroleum (100 ml; b.p. 60—90°) and chromatographed on Merck alumina (100 g), with elution by the same solvent (100 ml portions). Fractions 2—10 yielded a pale yellow oil (11.2 g), which solidified readily and crystallized from hexane or ether to give 7,7-ethylenedioxy-4 $\beta$ ,5 $\beta$ -dimethyl- $\Delta^{1(10)}$ -octalin-2-one (4) in prisms, m.p. 105—106° (8.0 g; 56% based on unrecovered cyclohexanone) (Found: C, 71.0; H, 8.4.  $\text{C}_{14}\text{H}_{20}\text{O}_3$  requires C, 71.2; H, 8.5%),  $\lambda_{\max}$  (EtOH) 237 nm ( $\epsilon$  15,700),  $\nu_{\max}$  ( $\text{CHCl}_3$ ) 1661 (conjugated C=O), 1618 (C=C), and 1087  $\text{cm}^{-1}$  (cyclic ether),  $\delta$  ( $\text{CDCl}_3$ ) 0.88 (3H, d, *J* 6.5 Hz,  $\text{CHCH}_3$ ), 1.10 (3H, s, angular  $\text{CH}_3$ ), 2.0 (2H, poorly resolved t,  $\text{CH}_2\text{CO}$ ), 3.7 (4H, s,  $\text{OCH}_2\text{CH}_2\text{O}$ ), and 5.45 (1H, s, =CH); the *cis* stereochemistry of the methyl groups was supported by use of a shift reagent in the n.m.r. spectrum (see above). The *semicarbazone* separated from methanol in prisms, m.p. 222° (decomp.),  $\lambda_{\max}$  (EtOH) 270 nm ( $\epsilon$  25,700),  $\delta$  ( $\text{CDCl}_3$ ) 0.83 (3H, d, *J* 5.5 Hz,  $\text{CHCH}_3$ ), 1.05

(3H, s, angular  $\text{CH}_3$ ), 3.67 (4H, s,  $\text{OCH}_2\text{CH}_2\text{O}$ ), and 5.45 (1H, s, =CH) (Found: C, 61.3; H, 8.0; N, 14.3.  $\text{C}_{15}\text{H}_{23}\text{N}_3\text{O}_3$  requires C, 61.4; H, 7.9; N, 14.35%). Attempts to use this semicarbazone in a Kishner reduction were unsuccessful owing to extensive pyrolytic decomposition.

**Lithium Aluminium Hydride Reduction of the Foregoing Ketone.**—The octalone (4) (0.472 g) in dry ether (25 ml) was added during 15 min to a stirred solution—suspension of lithium aluminium hydride (0.08 g) in dry ether (25 ml), maintained at 0°. The mixture was stirred at 0° for a further 5 h, then kept in the refrigerator overnight. It was decomposed by the cautious addition of ice-water, in the presence of Celite. The organic layer was separated, the residue washed several times with ether, and the combined organic layers dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The residue of 7,7-ethylenedioxy-4 $\beta$ ,5 $\beta$ -dimethyl- $\Delta^{1(10)}$ -octalin-2-ol (5) (0.48 g, 100%) solidified readily, and separated from ether in prisms, m.p. 134°,  $\nu_{\max}$  (film) 3401 (OH), 1647 (C=C), and 833  $\text{cm}^{-1}$  (CH=C), no C=O band (Found: C, 70.3; H, 9.3.  $\text{C}_{14}\text{H}_{22}\text{O}_2$  requires C, 70.55; 9.3%).

**2-Acetoxy-7,7-ethylenedioxy-4 $\beta$ ,5 $\beta$ -dimethyl- $\Delta^{1(10)}$ -octalin (6).**—The octalol (5) (1.2 g) in dry pyridine (15 ml) was cooled in ice and acetic anhydride (1.5 ml) added. After being kept 3 days at 0°, the solution was poured into a large volume of ice-water and the product isolated by three-fold extraction with ether. The combined extracts were washed with water, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated, leaving the acetate (6), b.p. 125—130° (bath) at 0.02 mmHg (1.09 g),  $\nu_{\max}$  (film) 1730 (C=O), 1664 (C=C), and 837  $\text{cm}^{-1}$  (C=CH), no OH band (Found: C, 68.5; H, 8.7.  $\text{C}_{16}\text{H}_{24}\text{O}_4$  requires C, 68.5; H, 8.6%).

**7,7-Ethylenedioxy-4 $\beta$ ,5 $\beta$ -dimethyl- $\Delta^{1(10)}$ -octalin (7).**—The acetate (6) (1.09 g) in dry ether (10 ml) was added to distilled ethylamine (100 ml) and the mixture was stirred during the gradual addition of metallic lithium (0.4 g) in small portions during 30 min. At the half-way point a permanent blue colour developed. Stirring was continued for a further 15 min, then a few drops of methanol were added until the colour was discharged. The whole was poured into a large excess of ice-water, and the product isolated by three extractions with ether. The dried ( $\text{Na}_2\text{SO}_4$ ) extract was concentrated *via* a short Vigreux column, the residue taken up in light petroleum (b.p. 30—60°), and the solution filtered through a short column of alumina. Evaporation of the solvent gave the octalin (7), b.p. (bath) 155—160° at 17.5 mmHg, 90—95° at 0.05 mmHg (0.76 g, 88%),  $\nu_{\max}$  (film) 1667 (C=C) and 1083  $\text{cm}^{-1}$  (cyclic ether),  $\delta$  ( $\text{CDCl}_3$ ) 0.80 (3H, d, *J* 4.5 Hz,  $\text{CHCH}_3$ ), 0.95 (3H, s, angular  $\text{CH}_3$ ), 3.67 (4H, poorly resolved t,  $\text{OCH}_2\text{CH}_2\text{O}$ ), and 5.05 (1H, m, =CH) (Found: C, 75.4; H, 9.9.  $\text{C}_{14}\text{H}_{22}\text{O}_2$  requires C, 75.6; H, 10.0%).

**4 $\beta$ ,5 $\beta$ -Dimethyl- $\Delta^{1(10)}$ -octalin-7-one (8).**—The preceding acetal (7) (3.7 g), methanol (25 ml), water (5 ml), and conc. HCl (0.5 ml) were mixed and kept at room temperature overnight. Water was added and the product isolated by ether extraction. Evaporation of the dried ( $\text{Na}_2\text{SO}_4$ ) extract *via* a short Vigreux column afforded the octalone (8), b.p. (bath) 140° at 17—18 mmHg (2.21 g, 82%),  $\nu_{\max}$  (film) 1721 (saturated C=O), 1667 (C=C), and 806  $\text{cm}^{-1}$  (=CH) (Found: C, 80.9; H, 10.0.  $\text{C}_{12}\text{H}_{18}\text{O}$  requires C, 80.85; H, 10.2%). The 2,4-dinitrophenylhydrazones separated from ethyl acetate in orange needles, m.p. 171°

† G.l.c. data were obtained on an F and M 810 instrument, using SE30 and FFAP columns. N.m.r. measurements were made on  $\text{CDCl}_3$  or  $\text{CCl}_4$  solutions, with a Varian A60 instrument, using tetramethylsilane as internal standard.

<sup>17</sup> R. Anliker, A. S. Lindsey, D. E. Nettleton, and R. B. Turner, *J. Amer. Chem. Soc.*, 1957, **79**, 220.

<sup>18</sup> H. C. Odom and A. R. Pinder, *Org. Synth.*, 1971, **51**, 115.

(Found: C, 60.3; H, 6.1; N, 15.5.  $C_{18}H_{22}N_4O_4$  requires C, 60.3; H, 6.2; N, 15.6%).

**4 $\beta$ ,5 $\beta$ -Dimethyl-7-(1-methylthioethylidene)- $\Delta^{1(10)}$ -octalin (12).**—Diethyl (1-methylthioethyl)phosphonate (11) was prepared by methylation of diethyl methylthiomethylphosphonate<sup>10</sup> as described by Corey and Shulman.<sup>11</sup> This compound (2.70 g) was dissolved in 1,2-dimethoxyethane-hexamethylphosphoramide (4:1) (60 ml). The solution was stirred under nitrogen and treated with a hexane solution of n-butyl-lithium (6.6 ml of 2.27M), then stirred at 0° for 4 h. A solution of the preceding octalone (8) (1.11 g) in dimethoxyethane (5 ml) was added and stirring continued at 0° overnight under nitrogen. The mixture was diluted with ice-water (30 ml) and saturated aqueous ammonium chloride (30 ml), and extracted thrice with ether. The combined extracts were washed with aqueous sodium hydrogen carbonate and brine, dried ( $Na_2SO_4$ ), and concentrated. The residue was fractionally distilled *via* a 3 in Vigreux column. A small fore-run was obtained, followed by a main fraction, b.p. (bath) 100–110° at 0.02 mmHg (1.22 g, 83%) of the desired *thioenol ether* (12),  $\nu_{max}$  (film) 1639, 1613 (C=C), and 835  $cm^{-1}$  (=CH) (Found: C, 76.2; H, 10.2.  $C_{15}H_{24}S$  requires C, 76.2; H, 10.2%).

**7 $\alpha$ -Acetyl-4 $\beta$ ,5 $\beta$ -dimethyl- $\Delta^{1(10)}$ -octalin (13).**—The foregoing thioether (12) (0.5 g) was dissolved in acetonitrile-water (3:1) (25 ml) and mixed with a solution of mercuric chloride (1.125 g) in the same solvent combination (25 ml). The mixture was refluxed gently on a water-bath for 6.5 h. After a short time, a precipitate of the mercury thiolate began to separate. The system was cooled, filtered, and the residue washed with ether. Excess of ice-water was added to the filtrate, which was separated, and the aqueous layer was extracted twice more with ether. The combined extracts were washed with water and aqueous sodium hydrogen carbonate, dried ( $Na_2SO_4$ ), and concentrated. The residue was taken up in light petroleum (b.p. 30–60°) and the solution filtered through a short column of Merck alumina. Evaporation gave the desired *methyl ketone* (13), b.p. (bath) 100–105° at 0.02 mmHg (0.23 g, 53%),  $\nu_{max}$  (film) 1706 (C=O), 1658 (C=C), and 807  $cm^{-1}$  (=CH) (Found: C, 81.6; H, 10.6.  $C_{14}H_{22}O$  requires C, 81.5; H, 10.75%). T.l.c. revealed that the product was virtually a single epimer, but before use in the next step the product (0.23 g) in methanol (4 ml) was mixed with a solution of sodium methoxide (10 ml) made by dissolving sodium metal (1.0 g) in methanol (25 ml), and kept at room temperature for 5 h. Dilution with water and ether extraction afforded the methyl ketone (0.20 g), homogeneous on t.l.c. [development with light petroleum (b.p. 30–60°)-ethyl acetate, 15:1]. The *2,4-dinitrophenylhydrazone* separated from ethanol in yellow needles, m.p. 172° (Found: C, 62.4; H, 6.75; N, 14.5.  $C_{20}H_{26}N_4O_4$  requires C, 62.2; H, 6.8; N, 14.5%).

**( $\pm$ )-Valencene (1).**—A hexane solution of n-butyl-lithium (0.66 ml of 2.27M) was added to dry ether (25 ml) under nitrogen, and the solution stirred during the gradual addition (5 min) of methyltriphenylphosphonium bromide (0.535 g). Stirring was continued for 2 h. The preceding methyl ketone (13) (0.175 g) in dry ether (25 ml) was then added all at once and the mixture stirred at ambient temperature overnight. Solid material was removed by filtration and the filtrate shaken with ice-water, dried ( $Na_2SO_4$ ), and concentrated *via* a short Vigreux column. The semi-

crystalline residue was dissolved in light petroleum (b.p. 30–60°) and chromatographed on Merck alumina, with elution by the same solvent. Evaporation of the combined eluates on a rotary evaporator yielded an oil (0.15 g), b.p. 73–75° at 0.03 mmHg. The product was identical in all respects (except optical rotation) (i.r., n.m.r., and t.l.c. comparison) with an authentic sample of natural valencene. A sample of the product on oxidation with t-butyl chromate, as described by Hunter and Brogden,<sup>6,12</sup> afforded ( $\pm$ )-nootkatone (2), which crystallized from a small volume of light petroleum (b.p. 30–60°) in hard prisms, m.p. 46°. It was identical in all respects with an authentic sample of ( $\pm$ )-nootkatone.<sup>20</sup>

**4 $\beta$ ,5 $\beta$ -Dimethyl- $\Delta^{1(10)}$ -octalin-2,7-dione (14).**—A mixture of the annulation product (4) (2.87 g), water (10 ml), conc. HCl (5 ml), and methanol (50 ml) was kept at 0° for 28 h. Some of the methanol was removed *in vacuo*, and the residue diluted with ice-water. The *diketone* was isolated by several ether extractions, yielding an oil, b.p. 120–125° at 0.08 mmHg (2.3 g, 100%), which solidified on keeping, and separated from light petroleum (b.p. 60–90°) in very pale yellow hexagonal prisms, m.p. 105–106°,  $\nu_{max}$  (film) 1705 (saturated CO), 1642 (conjugated CO), and 1608  $cm^{-1}$  (C=C),  $\lambda_{max}$  (EtOH) 236 nm ( $\epsilon$  15,000) (Found: C, 75.0; H, 8.7.  $C_{12}H_{16}O_2$  requires C, 75.0; H, 8.4%).

**Reaction of Dione (14) with Ethanedithiol.**—The foregoing diketone (14) (1.92 g, 0.01 mol) and ethanedithiol (0.94 g, 0.01 mol) in methanol (40 ml) were cooled in ice and treated with boron trifluoride-ether complex (5 ml). After 30 h at 0° the mixture was poured into ice-water and extracted four times with ether. The combined extracts were washed with aqueous sodium hydrogen carbonate and water, dried ( $Na_2SO_4$ ), and concentrated. The residue showed four spots on t.l.c.; it was dissolved in light petroleum (b.p. 60–90°) and chromatographed on Baker acid-washed alumina (60 g). Elution with the same solvent yielded *2,2:7,7-bisethylenedithio-4 $\beta$ ,5 $\beta$ -dimethyl- $\Delta^{1(10)}$ -octalin* (16) (0.30 g), which showed no carbonyl absorption in the i.r. and crystallized from methanol in prisms, m.p. 117–118° (Found: C, 55.7; H, 7.1; S, 37.1.  $C_{16}H_{24}S_4$  requires C, 55.8; H, 7.0; S, 37.2%). Continued elution with light petroleum (b.p. 60–90°)-benzene (3:1) yielded *2,2-ethylenedithio-4 $\beta$ ,5 $\beta$ -dimethyl- $\Delta^{1(10)}$ -octalin-7-one* (15) (0.36 g), prisms from light petroleum (b.p. 60–90°), m.p. 104°,  $\nu_{max}$  ( $CHCl_3$ ) 1712  $cm^{-1}$  (saturated CO); no intense u.v. absorption. Further elution with benzene-ether (4:1) gave a small amount of a crystalline product which, on spectral evidence [ $\lambda_{max}$  (EtOH) 237 nm ( $\epsilon$  15,800),  $\nu_{max}$  ( $CHCl_3$ ) 1645  $cm^{-1}$  (conjugated CO)], is assigned the structure of the isomeric *7,7-ethylenedithioacetal*. Finally, elution with ether yielded unchanged diketone (14).

The 2,2-ethylenedithioacetal (15) was also prepared by reaction of the 7,7-ethylenecetal (4) with ethanedithiol, to give the mixed acetal-dithioacetal, which on mild, acid hydrolysis yielded (15). Attempts to desulphurize (15) by heating with different varieties of Raney nickel under different conditions were accompanied by extensive attack on the double bond.

**Oxidation of 4 $\beta$ ,5 $\beta$ -Dimethyl-trans- $\Delta^7$ -octalin (17).**—The required hydrocarbon (17) was synthesized by a well-documented procedure.<sup>14,21,22</sup> A sample (5.0 g) was mixed

<sup>21</sup> A. J. Speziale, J. A. Stephens, and Q. E. Thompson, *J. Amer. Chem. Soc.*, 1954, **76**, 5011; L. B. Barkley, M. W. Farrar, W. S. Knowles, H. Raffelson, and Q. E. Thompson, *ibid.*, p. 5014.

<sup>22</sup> L. H. Zalkow, F. X. Markley, and C. Djerassi, *J. Amer. Chem. Soc.*, 1959, **81**, 2914. See also A. K. Torrence and A. R. Pinder, *J. Chem. Soc. (C)*, 1971, 3410.

<sup>19</sup> M. Green, *J. Chem. Soc.*, 1963, 1324.

<sup>20</sup> M. Pesaro, G. Bozzato, and P. Schudel, *Chem. Comm.*, 1968, 1152.

with a solution of sodium dichromate dihydrate (18.2 g, 3 mol) in glacial acetic acid (90 ml) and the whole heated on a water-bath for 8 h, then kept at room temperature overnight. The mixture was diluted with water and rendered almost neutral by the addition of aqueous sodium hydroxide [NaOH (60 g) in water (200 ml)], and the product isolated with ether. The extracts were washed with sodium hydrogen carbonate and water, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated. An oil (2.66 g) remained, which was taken up in light petroleum (b.p. 30—60°; 100 ml) and subjected to chromatography on Baker acid-washed alumina (60 g). Elution with the same solvent yielded unchanged hydrocarbon (1.19 g), followed by 4 $\beta$ ,5 $\beta$ -dimethyl-trans- $\Delta^6$ -octalin-8-one (20) (0.81 g, 20% based on unrecovered hydrocarbon), eluted with benzene-ether (1 : 1), b.p. 155—160° (bath) at 32 mmHg,  $\lambda_{\text{max}}$  (EtOH) 229 nm ( $\epsilon$  10,500),  $\nu_{\text{max}}$  (film) 1667 (conjugated CO), 1613 (C=C), and 680  $\text{cm}^{-1}$  (*cis*-CH=CH),  $\delta$  ( $\text{CDCl}_3$ ) 0.79 (3H, s, angular  $\text{CH}_3$ ), 0.95 (3H, d,  $J$  10 Hz,  $\text{CHCH}_3$ ), 5.95 and 7.20 (2H, ABq,  $J$  10 Hz, CH=CH) (Found: C, 80.9; H, 10.3.  $\text{C}_{12}\text{H}_{18}\text{O}$  requires C, 80.85; H, 10.2%).

The 2,4-dinitrophenylhydrazone separated from methanol in orange-red needles, m.p. 188—189° (Found: C, 60.25; H, 6.2; N, 15.8.  $\text{C}_{18}\text{H}_{22}\text{N}_4\text{O}_4$  requires C, 60.3; H, 6.2; N, 15.6%).

Hydrogenation of the octalone (0.11 g) in methanol (15 ml) in the presence of palladized carbon (5%) gave, after the usual work-up, 5 $\beta$ ,6 $\beta$ -dimethyl-trans-decalin-2-one (0.11 g), which was converted into its 2,4-dinitrophenylhydrazone, yellow needles from ethyl acetate, m.p. and mixed m.p. with an authentic sample <sup>22</sup> 172—173°.

We thank Dr. O. J. Jacobus of this Department for the n.m.r. shift reagent measurements, Drs. Q. E. Thompson and W. S. Knowles (Monsanto Chemical Co., St. Louis) for gifts of chemicals, Dr. G. L. K. Hunter (Coca-Cola Co., Atlanta) for gifts of nootkatone and valencene, and Dr. P. Schudel (Givaudan-Esrolko, Zürich) for a sample of racemic nootkatone. One of us (H. C. O.) is grateful for the award of a NASA traineeship.

[4/365 Received, 25th February, 1974]