

## $\alpha$ -, $\gamma$ -, and $\varepsilon$ -Muurolene, Major Sesquiterpenes of the Wood of *Pinus silvestris* L. and of Swedish Sulphate Turpentine \*, \*\*

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The major sesquiterpene of the wood of *Pinus silvestris* L. and of Swedish sulphate turpentine,  $\alpha$ -muurolene, has been shown by spectral studies and chemical transformations to possess structure (1). Similarly,  $\gamma$ -muurolene obtained from the same sources has been proved to be represented by structure (2). The structure of the hydrocarbon previously known as  $\varepsilon$ -cadinene has been revised and the name has been changed to  $\varepsilon$ -muurolene (3).

The nature of the neutral high-boiling wood constituents of Scots pine (*Pinus silvestris* L.) and of Swedish sulphate turpentine has been studied in this laboratory. The sesquiterpenes and the neutral diterpenes, which are the main neutral high-boiling components, have been investigated in detail. Isolation and characterization of the sesqui- and diterpenes has been described.<sup>1,2</sup> This paper deals with the structure elucidation of three of the major sesquiterpenes,  $\alpha$ -muurolene (1),  $\gamma$ -muurolene (2), and  $\varepsilon$ -muurolene (3).

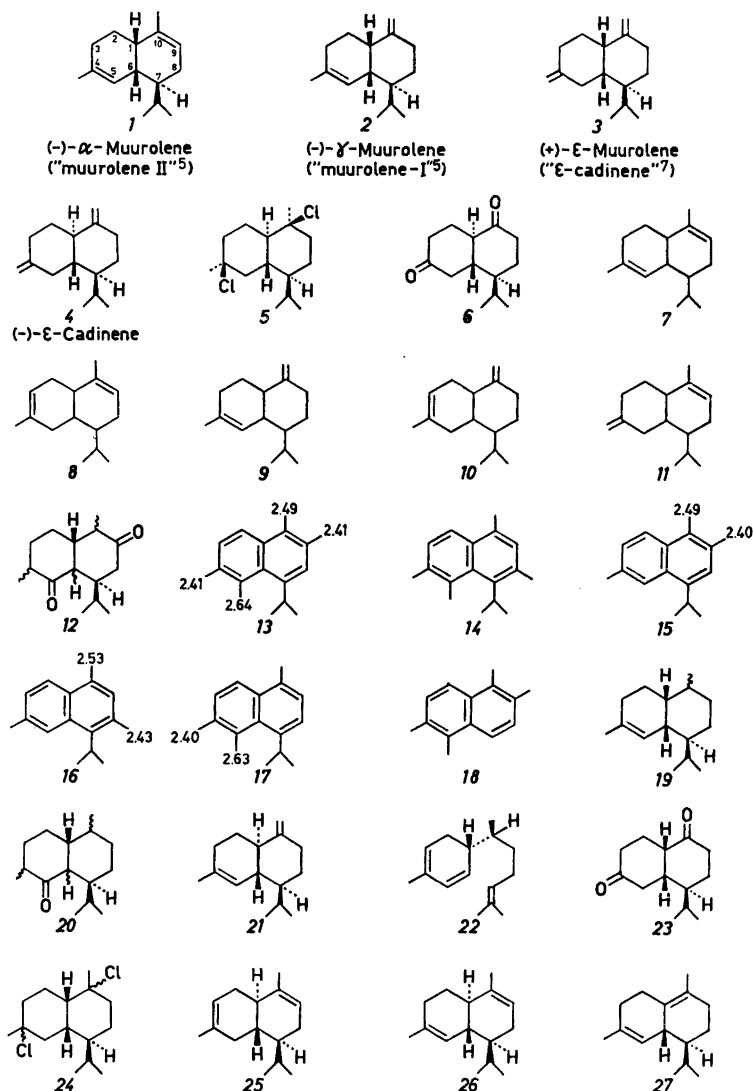
In 1929 Aschan found that an industrial extract of pine stumps (*Pinus silvestris*) contained "cadinene" and "muurolene".<sup>3</sup> With hydrogen chloride the fraction investigated yielded two different hydrochlorides, one of which was identical with the known cadinene dihydrochloride, the other being a new compound, the dihydrochloride derived from what Aschan called muurolene.

Recently, Pentegova and Lebedova<sup>4</sup> investigated Russian tall oil obtained from *Pinus silvestris* and reported the isolation of "muurolene".

The major sesquiterpene hydrocarbon isolated from *Pinus silvestris* wood and sulphate turpentine possesses the structure and absolute configuration shown in formula (1). In a preliminary report<sup>5</sup> the compound was referred to as "muurolene-II". It should now be called  $\alpha$ -muurolene by analogy with the cadinene nomenclature.<sup>6</sup> "Muurolene-I"<sup>5</sup> has been found to be represented by the  $\gamma$ -muurolene formula (2).  $\varepsilon$ -Muurolene (3)<sup>5</sup> has previously been considered to possess the  $\varepsilon$ -cadinene structure (4) by Sykora, Herout and Šorm.<sup>7</sup>

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*Determination of the basic skeleton of the muurolenes.*  $\alpha$ -,  $\gamma$ -, and  $\epsilon$ -Muurolene (all  $C_{15}H_{24}$ ) consumed two moles of hydrogen on hydrogenation over platinum in acetic acid, and were thus bicyclic. All three hydrocarbons gave cadalene on dehydrogenation.

When the muurolenes were treated with hydrogen chloride, mixtures containing (—)-muurolene dihydrochloride\* and (—)-cadinene dihydrochloride

\* In the preliminary report<sup>5</sup> this compound was incorrectly referred to as (+)-muurolene dihydrochloride.

were obtained.  $\alpha$ -Muurolene gave a product containing the two dihydrochlorides in the ratio 7:1,  $\gamma$ -muurolene in a ratio higher than 20:1 and  $\varepsilon$ -muurolene in the ratio 3:1.

If the crude hydrochlorides from  $\alpha$ - and  $\varepsilon$ -muurolene are recrystallized from methanol or ethanol, pure cadinene dihydrochloride will ultimately be obtained. The presence of muurolene dihydrochloride might then be overlooked, and this must obviously have contributed to the previous erroneous statement<sup>7</sup> that  $\varepsilon$ -muurolene was a cadinene.

The presence of muurolene dihydrochloride can, however, be easily detected in mixtures of the two hydrochlorides. Its crystals have the form of irregular polygonal plates, while cadinene dihydrochloride crystallizes as needles. Furthermore muurolene dihydrochloride shows characteristic IR absorptions at 1132 (medium) and 810  $\text{cm}^{-1}$  (strong). At the latter frequency cadinene dihydrochloride absorbs only very weakly. Fortunately, muurolene dihydrochloride absorbs very weakly at 852  $\text{cm}^{-1}$ , which is the position of one of the strongest absorption bands of cadinene dihydrochloride. Thus IR spectroscopy not only may serve in revealing the presence of muurolene dihydrochloride, but permits a quantitative estimation of both compounds. Separation of the two dihydrochlorides can be accomplished either by reversed phase partition chromatography (*cf.* Ref. 8) or mechanically.

On hydrogenation  $\alpha$ -,  $\gamma$ -, and  $\varepsilon$ -muurolene each gave a mixture of stereoisomers consisting mainly of two components. These were isolated by prepar-

Table 1. Hydrogenation products of  $\alpha$ -,  $\gamma$ -, and  $\varepsilon$ -muurolene.

Saturated product	from	Retention time min		$n_D$	$[\alpha]_D$	Percent of crude product
		anal. <sup>a</sup>	prep. <sup>b</sup>			
<i>a</i>	$\alpha$ -muurolene	7.5	7.3	1.4807	+28.4° ( <i>c</i> 1.8)	29
<i>b</i>		8.2	8.0	1.4809	+6.4° ( <i>c</i> 2.3)	11
<i>c</i>		9.9	9.4			58
<i>a</i> <sup>c</sup>	$\gamma$ -muurolene	7.5	7.3	1.4799	+25° ( <i>c</i> 0.6)	83
<i>b</i>		8.2	8.0	1.4802	+6.6° ( <i>c</i> 1.4)	3
<i>c</i> <sup>d</sup>		9.9	9.4			13
<i>a</i>	$\varepsilon$ -muurolene	7.5	7.3	1.4815	+23.6° ( <i>c</i> 1.3)	68
<i>b</i>		8.2	8.0	1.4791	+7° ( <i>c</i> 0.3)	6
<i>c</i>		9.9	9.4			24

<sup>a</sup> Column 1 % E 301 on Gas-Chrom P,<sup>25</sup> temperature 101°, gas flow 53 ml/min.

<sup>b</sup> Column 1 % SE 30 on Chromosorb W (60–80 mesh), temperature 135°, gas flow 210 ml/min.

<sup>c</sup> (Found: C 86.2; H 13.8.  $\text{C}_{15}\text{H}_{28}$  requires C 86.4; H 13.6).

<sup>d</sup> (Found: C 85.9; H 13.6.  $\text{C}_{15}\text{H}_{28}$  requires: C 86.4; H 13.6).

ative gas-liquid chromatography (GLC). Comparison of their retention times on three different GLC columns, their IR spectra and optical rotations showed that the same two saturated hydrocarbons had been formed from each muurolene (see Table 1). The two muurolane isomers and the product obtained on hydrogenation of  $\gamma$ - or  $\delta$ -cadinene<sup>2,21d</sup> were all readily distinguishable by IR and GLC.

Cadinene dihydrochloride (5) has been synthesized *via* the diketone (6).<sup>10,11</sup> This diketone has also been obtained<sup>9</sup> by ozonolysis of  $\varepsilon$ -muurolene.

These results show that, regardless of configuration,  $\alpha$ -,  $\gamma$ -, and  $\varepsilon$ -muurolene have the same basic skeleton as the cadinenes.

*Location of the double bonds in the three muurolenes.* By quantitative ozonolysis  $\varepsilon$ -muurolene has been shown<sup>9</sup> to contain two vinylidene groups. This was supported by its IR<sup>21c</sup> and NMR data (see Table 2).

The IR spectra indicated that  $\alpha$ - and  $\gamma$ -muurolene contained trisubstituted double bonds and  $\gamma$ -muurolene a vinylidene group. The UV spectra indicated that in both compounds the double bonds were non-conjugated.

According to the NMR data (characteristic data see Table 2)  $\alpha$ - and  $\gamma$ -muurolene both contained an isopropyl group.  $\alpha$ -Muurolene had two methyl groups linked to unsaturated carbon atoms and two olefinic protons.  $\gamma$ -Muurolene contained only one methyl group attached to an unsaturated

Table 2. NMR data of  $\alpha$ -,  $\gamma$ -, and  $\varepsilon$ -muurolene.

Structural unit	$\delta$ ppm	$J$ cps	Signal pattern	Number of protons
<i><math>\alpha</math>-Muurolene</i>				
Isopropyl	0.80	7	doublet	6
	0.86	7	doublet	
Methyl on double bond	1.65		singlet, broad	6
Olefinic proton	5.40		singlet, broad	1
	5.43	4	doublet, broad	1
<i><math>\gamma</math>-Muurolene</i>				
Isopropyl	0.78	7	doublet	6
	0.90	7	doublet	
Methyl on double bond	1.63	0.5	doublet, broad	3
Olefinic proton	4.58		multiplet, unres.	2
	5.50	4	doublet, broad	1
<i><math>\varepsilon</math>-Muurolene</i>				
Isopropyl	0.71	7		6
	0.90	7		
Olefinic proton	4.60		multiplet, unres.	4

carbon atom but three olefinic protons, two of which could be attributed to those of a vinylidene group.

The spectral data described above indicated that  $\alpha$ -muurolene could be represented by either of structures (7) or (8) and that  $\gamma$ -muurolene possesses one of the structures (9), (10), or (11).

The final location of the double bonds in  $\alpha$ - and  $\gamma$ -muurolene was achieved by introduction of methyl groups and dehydrogenation of the products to give alkylnaphthalenes. These were identified by comparison with synthetic samples. This method was first introduced into cadinene chemistry by Campbell and Soffer,<sup>12</sup> and has since been used frequently to determine the structure of compounds based on the cadinene skeleton (*cf. e.g.*, Ref. 13–15). In the present case hydroboration-oxidation was used to introduce a functional group onto the monosubstituted carbon of the trisubstituted ethylenic linkages of  $\alpha$ - and  $\gamma$ -muurolene.

*Determination of the positions of the double bonds in  $\alpha$ -muurolene.*  $\alpha$ -Muurolene was hydroborated in ethereal solution. Without isolation the product was oxidized by heating with an aqueous chromic acid solution<sup>16</sup> to give the diketone (12), m.p. 63°. This diketone was then treated with excess methylmagnesium iodide. The reaction sequence was completed in the usual manner by dehydration and dehydrogenation. Dehydrogenation under mild conditions (chloranil in xylene) gave a dimethylcadalene, m.p. 64°, which was dissimilar to any previously known dimethylcadalene. As concluded above,  $\alpha$ -muurolene is most probably represented by either of the structures (7) or (8). The fact that the dimethylcadalene obtained from  $\alpha$ -muurolene was different from the known<sup>12</sup> 2,7-dimethylcadalene, m.p. 102°, provides indirect evidence in favour of assigning structure (7) to the sesquiterpene. From a compound possessing the alternative structure (8) 2,7-dimethylcadalene should have been obtained.

The NMR spectrum of the new dimethylcadalene showed signals at  $\delta$  1.31 (6 protons, doublet,  $J$  7 cps),  $\delta$  2.41 (6 protons, singlet),  $\delta$  2.49 (3 protons, singlet),  $\delta$  2.64 (3 protons, singlet),  $\delta$  7.14 (1 proton, doublet,  $J$  9 cps),  $\delta$  7.72 (1 proton, doublet,  $J$  9 cps) and  $\delta$  7.21 (1 proton, singlet). According to these data the new dimethylcadalene should possess structure (13) or (14).

The assignments of the chemical shifts to the methyl protons as indicated in formula (13) were based on a comparison with the chemical shift data<sup>17</sup> of 2-, 3-, and 5-methylcadalene given in formulas (15), (16), and (17).

The coupling constant shown by two of the low-field hydrogens in the NMR spectrum of the new dimethylcadalene was large (9 cps). This indicated that two of the nuclear hydrogens of the hydrocarbon were vicinal as in structures (13) and (14).

Final proof for the assignment of structure (7) to  $\alpha$ -muurolene was obtained by converting it to 1,2,5,6-tetramethylnaphthalene (18). Except for the conditions of the dehydrogenation step this was accomplished by using the reaction sequence described above for conversion of  $\alpha$ -muurolene to the dimethylcadalene, m.p. 63°. When selenium at 280° was used for the dehydrogenation, the main product obtained was 1,2,5,6-tetramethylnaphthalene. This proved that  $\alpha$ -muurolene possessed structure (7) and also that the dimethylcadalene, m.p. 63°, was represented by structure (13).

The synthesis of 1,2,5,6-tetramethylnaphthalene described by Ružicka *et al.*<sup>18</sup> comprises several steps. A simple two-step synthesis of this compound from 2,6-dimethylnaphthalene has been accomplished. 2,6-Dimethylnaphthalene was chloromethylated to give 1,5-dichloromethyl-2,6-dimethylnaphthalene, which was reduced by zinc dust in glacial acetic acid. The fairly low over-all yield of *ca.* 15 % was quite sufficient for the present purpose of obtaining an authentic sample for comparison with the dehydrogenation product of  $\alpha$ -muurolene.

*Determination of the positions of the double bonds in  $\gamma$ -muurolene.* Ozonolysis of  $\gamma$ -muurolene yielded formaldehyde, showing that a vinylidene group was present in the sesquiterpene.

When  $\gamma$ -muurolene was hydrogenated using a nickel-boron catalyst of high selectivity<sup>19</sup> it consumed only one mole of hydrogen to give a dihydro- $\gamma$ -muurolene (19). The IR spectrum showed that the vinylidene group of  $\gamma$ -muurolene had been reduced selectively.

The dihydro- $\gamma$ -muurolene (19) was converted to a methylcadalene *via* the ketone (20) using the procedure described above for the conversion of  $\alpha$ -muurolene to 2,5-dimethylcadalene. The methylcadalene obtained was compared to samples (synthesized as in Refs. 12, 20) of 2-, 5-, and 7-methylcadalenes by GLC. It was found that the methylcadalene derived from  $\gamma$ -muurolene had the same retention time as 5-methylcadalene (17). The identity was confirmed by comparison of UV and IR spectra and by preparation of picrates. Thus  $\gamma$ -muurolene possesses structure (9).

*Configuration of the muurolenes.* The configurations at carbon atoms 1, 6, and 7 must be the same in all three muurolenes as the same products of hydrogenation and hydrochlorination were obtained. The formation of (–)-cadinene dihydrochloride (5) from  $\alpha$ - and  $\varepsilon$ -muurolene requires that at least the configurations at carbon atoms 6 and 7 in the muurolenes are the same as in the cadinenes. This, and the fact that  $\gamma$ -muurolene (9) and  $\gamma$ -cadinene (21) are different compounds, proves indirectly that the hydrocarbons are C-1 epimers. Accordingly, the configuration of  $\gamma$ -muurolene should be as shown in formula (2).

On hydrogenation  $\varepsilon$ -muurolene and isozingiberene have been reported to give the same tetrahydroderivative, "isocadinane".<sup>21a,b</sup> The isozingiberene used for the hydrogenation (IR spectrum, see Ref. 21c) was obtained by acid catalyzed cyclization of (–)-zingiberene (22).<sup>22</sup> The cyclization of zingiberene and the hydrogenations would be expected to leave the configuration at C-1 intact. Consequently, the configuration at C-1 in (–)-zingiberene and  $\varepsilon$ -muurolene should be the same, this being in accordance with structure (3) for  $\varepsilon$ -muurolene.

The muurolenes have been proved to be 1-*epi*-cadinenes by a series of experiments, which have been described briefly in the previously mentioned short communication.<sup>5</sup> On ozonolysis  $\varepsilon$ -muurolene gave a new, dextrorotatory non-crystalline diketone (23),  $[\alpha]_D +73.8^\circ$ . Acid catalyzed epimerization of the new diketone gave the levorotatory crystalline diketone (6),  $[\alpha]_D -42.6^\circ$ . The configurations of the two diketones were definitely established by converting (–)-muurolene dihydrochloride (24)\* and (–)-cadinene dihydrochloride (5)

\* See footnote p. 2853.

to the diketones (23) and (6), respectively. These transformations involved dehydrochlorinations to (+)- $\epsilon$ -muurolene (3) and to a new hydrocarbon, (-)- $\epsilon$ -cadinene (4), respectively. Ozonolysis of these hydrocarbons gave the expected diketones. By using potassium triethyl carbinolate for the dehydrochlorinations it was possible to obtain fairly high yields of  $\epsilon$ -muurolene (ca. 20 %) and  $\epsilon$ -cadinene (ca. 40 %) from muurolene dihydrochloride and cadinene dihydrochloride, respectively.\*

The correlation of the crystalline diketone (6) with cadinene dihydrochloride (5) in the way described (cf. also Ref. 11) establishes its configuration. The oily diketone must then possess the configuration shown in formula (23). Hence the stereostructure of  $\epsilon$ -muurolene must be (3). As the three muurolenes investigated have the same configuration,  $\alpha$ -muurolene must possess structure (1) and  $\gamma$ -muurolene structure (2).

Formula (5) represents the absolute configuration of (-)-cadinene dihydrochloride.<sup>7</sup> As (-)-cadinene dihydrochloride has been converted into the (-)-diketone (6), the formula drawn must represent the absolute configuration of the levorotatory form of this diketone (cf. also Ref. 11). The absolute configuration of the muurolenes follows from the correlation of the same levorotatory diketone (6) with (-)-muurolene dihydrochloride.\*\* (-)- $\alpha$ -Muurolene (1), (-)- $\gamma$ -muurolene (2) and (+)- $\epsilon$ -muurolene (3) isolated from *Pinus silvestris* all yielded levorotatory\* muurolene dihydrochloride and thus the formulas drawn represent the absolute configuration of these sesquiterpenes.

## EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. IR spectra were recorded on a Perkin-Elmer No. 21 instrument (NaCl prism, sample as liquid film, or, for solids, in KBr unless otherwise stated), UV spectra on a Beckman DK 2 recording spectrophotometer (solvent ethanol) and NMR spectra on a Varian A 60 instrument operating at 60 Mc/s (solvent carbon tetrachloride, internal standard tetramethylsilane). For analytical gas-liquid chromatography (GLC) a PYE argon chromatograph (column length 1.2 m, inner diameter 4 mm) and for preparative GLC an Aerograph A-700 "Autoprep" instrument (column length 20', outer diameter 3/8") were used.

Identifications were made by comparison with authentic samples, when applicable, by mixed melting point determinations, by GLC and thin layer chromatography (TLC) and by comparison of IR spectra, UV spectra and optical rotations.

The procedures used to prepare columns for GLC, plates for argentative TLC (Ag-TLC) and adsorbent (Ag-silica) for argentative column chromatography have been described previously.<sup>25</sup>

Rotations were taken in chloroform. Light petroleum refers to the fraction b.p. 40–60°.

\* The products obtained on elimination of hydrogen chloride from cadinene dihydrochloride by heating with sodium acetate in acetic acid are  $\beta$ -cadinene (25)<sup>12</sup>,  $\alpha$ -cadinene (26)<sup>23</sup> and, probably,  $\delta$ -cadinene (27).<sup>23</sup> These are expected products, as the direction of elimination under the conditions used should be controlled by the relative stabilities of the olefinic products formed (Saytzeff-type elimination). The Hofmann-type elimination observed on treatment of cadinene dihydrochloride with potassium triethyl carbinolate is in accordance with the results of Brown *et al.*<sup>24</sup> These authors demonstrated that it is possible to shift the direction of elimination of halides from Saytzeff-type to Hofmann-type by increasing the steric requirement of the attacking base.

\*\* See footnote p. 2853.

The isolation of  $\alpha$ -,  $\gamma$ -, and  $\varepsilon$ -muurolene from the wood of *Pinus silvestris* and from Swedish sulphate turpentine has been described previously.<sup>1,2</sup> Physical constants and IR and UV spectral data for  $\alpha$ - and  $\gamma$ -muurolene have also been reported.<sup>2</sup>

**Hydrogenation of  $\alpha$ -muurolene.** A mixture of the sesquiterpene (0.31 g), platinum (from platinum oxide, 0.11 g) and glacial acetic acid (15 ml) was shaken under hydrogen. The amount of hydrogen consumed corresponded to the uptake of 1.9 moles of  $H_2$ . After dilution with water (50 ml) the mixture of saturated hydrocarbons was isolated by extraction with ether. The organic layer was dried with sodium sulphate and the ether and part of the acetic acid were evaporated off. The residue was chromatographed on alumina (basic, activity I, 10 g). Light petroleum (25 ml) eluted a colourless oil (0.26 g).

GLC using a 1% E 301 column (conditions, see Table 1) revealed the presence of three components *a*, *b*, and *c*. The two main components (*a* and *c*) were isolated by preparative GLC (for conditions, see Table 1). The physical constants of the isolates as well as the retention times and relative amounts of all three components are also given in Table 1.

The IR spectra of compounds *a* and *c* differed considerably from each other. Characteristic absorption bands, which may be used to distinguish these muurolane isomers from each other and from "cadinane" (cf. Ref. 21d) are for compound *a* 1302 and 1295 (equal intensities), 1155, 1085, 947 and 917  $cm^{-1}$  (carbon tetrachloride) and for compound *c* 1287, 1177 (sharp, strong), 1037 and 937  $cm^{-1}$  (carbon tetrachloride).

**Dehydrogenation of  $\alpha$ -muurolene.** On selenium dehydrogenation *cadalene* (picrate, m.p. 115–116.5°) was obtained in 32% yield.

**Addition of hydrogen chloride to  $\alpha$ -muurolene.** A solution of the hydrocarbon (0.20 g) in dry ether (0.2 ml) was saturated with dry hydrogen chloride at  $-18^\circ$  and then left in the refrigerator for 20 h. The solvent and excess hydrogen chloride was evaporated off at room temperature under reduced pressure. The residue was a semi-crystalline mass, which was crystallized once from a small amount of light petroleum. The crystalline product obtained (0.13 g), consisted of a mixture of muurolene dihydrochloride (plates), m.p. 67–75°, and cadinene dihydrochloride (needles),  $r_p$  80–105°. The muurolene dihydrochloride/cadinene dihydrochloride ratio was about 7:1 as found by IR spectroscopy utilizing the absorption bands in the spectra of muurolene dihydrochloride and cadinene dihydrochloride at 810 and 852  $cm^{-1}$ , respectively.

The two hydrochlorides were separated by reversed phase partition chromatography of the mixture (0.13 g). Hexane on polyvinyl chloride powder was used as the stationary phase and methanol/water 9:1 as the mobile phase.<sup>8</sup> The column (from polyvinyl chloride powder, 15 g) was prepared as described by Wickberg.<sup>8</sup> 5-Millilitre fractions were collected, and the course of the separation was followed by paper chromatography using hexadecane impregnated glass fibre paper.<sup>8</sup> With methanol/water 19:1 as the eluent, cadinene dihydrochloride had  $R_F$  0.31 and muurolene dihydrochloride  $R_F$  0.23. Accordingly, fractions 4–12 (0.018 g) contained almost pure cadinene dihydrochloride, m.p. 110–116°, fractions 13–15 (0.010 g) mixtures of the two hydrochlorides and fractions 16–19 (0.087 g) almost pure muurolene dihydrochloride, m.p. 78–84°. One recrystallization of the appropriate fractions from light petroleum and one from methanol gave (–)-muurolene dihydrochloride\* (0.060 g), m.p. 84–86°,  $[\alpha]_D^{22} -13.9^\circ$  (*c* 1.3) and (–)-cadinene dihydrochloride (0.015 g), m.p. 117–118°,  $[\alpha]_D^{22} -36.0^\circ$  (*c* 2.3).

**Hydroboration-oxidation of  $\alpha$ -muurolene (1).**  $\alpha$ -Muurolene (5.0 g) was mixed with a solution (1.25 M, 38 ml) of lithium borohydride in ether. Boron trifluoride etherate (1.75 ml) was added dropwise with stirring under  $N_2$  over a period of 0.5 h. The mixture was stirred at room temperature for 2 h. The excess hydride was destroyed by slow addition of water (10 ml). An aqueous dichromate solution (67 ml, prepared from a mixture of potassium dichromate, 44.0 g, and sulphuric acid, conc., 33.0 ml, by dilution with water to 180 ml) was slowly added. The mixture was heated for 2 h under vigorous stirring at such a temperature that the ether refluxed.<sup>16</sup> After cooling, the aqueous phase was extracted with two portions of ether, the ether phases were combined and washed successively with water, aqueous sodium bicarbonate and water. After drying (sodium sulphate) the ether was evaporated to give an oil (4.8 g).

\* See footnote p. 2853.



Chromatography on silica gel (210 g) deactivated with water (14 ml) using ether (50 %) in light petroleum as the eluent gave the following fractions: (1), eluted with 200 ml, 0.03 g; (2), 100 ml, 0.89 g; (3) 100 ml, 1.18 g; (4) 200 ml, 1.86 g; (5), 200 ml, 0.20 g. Fraction (4) consisted of a crystalline compound (pure according to TLC), which was recrystallized from light petroleum to give the diketone (12), m.p. 60–63°,  $[\alpha]_D^{22} + 58^\circ$  (c 1.9), IR band at 1706  $\text{cm}^{-1}$ . (Found: C 76.2; H 10.4.  $\text{C}_{15}\text{H}_{24}\text{O}_2$  requires C 76.2; H 10.2). The *mono-2,4-dinitrophenylhydrazone* had m.p. 144–145° and showed an IR band at 1702  $\text{cm}^{-1}$  (carbonyl).

The IR spectrum of fraction (3) (homogeneous according to TLC) was very similar to that of the crystalline diketone. As fraction (3) could be converted to a dimethylcadalene identical with that obtained (see below) from the crystalline diketone (fraction 4) it contained probably a stereoisomer (or a mixture of stereoisomers) of the crystalline diketone.

*Conversion of the diketone (12) to 2,5-dimethylcadalene (13).* The crystalline diketone (0.18 g) in dry ether (2 ml) was added to a stirred solution of methylmagnesium iodide prepared from magnesium (0.15 g), methyl iodide (0.85 g) and ether (2 ml). The mixture was refluxed for 18 h. After cooling in ice, ice-cold dilute hydrochloric acid was added. The layers were separated and the aqueous phase was extracted with ether. The ether solution was washed with aqueous sodium bicarbonate and with water and then dried (sodium sulphate).

Evaporation of the solvent gave an oil which, without purification, was treated with formic acid (85 %, 3 ml) at 90° for 15 min. After cooling, water was added and the mixture was extracted with ether. Most of the formic acid was removed by washing with aqueous sodium bicarbonate. The solvent was evaporated and the residue was filtered through alumina (basic, activity I, 20 g). Light petroleum (50 ml) eluted a colourless oil (0.12 g).

The oil was added to a solution of tetrachloro-*p*-benzoquinone (chloranil, 0.3 g) in xylene (2 ml) and the mixture was refluxed for 23 h. After cooling, the reaction mixture was added to an alumina column (basic, activity I, 15 g). Light petroleum (60 ml) eluted an oil (0.10 g), which, according to GLC, contained a dimethylcadalene as the main component. It was purified by preparative GLC to give a crystalline compound (0.030 g), m.p. 59–62°. Sublimation *in vacuo* gave 2,5-dimethylcadalene (13) m.p. 63–64°. (Found: C 90.6; H 9.5.  $\text{C}_{17}\text{H}_{22}$  requires C 90.2; H 9.8).

*Conversion of the diketone (12) to 1,2,5,6-tetramethylnaphthalene (18).* Treatment of the diketone (0.32 g) with methylmagnesium iodide followed by dehydration as described above gave an oil (0.19 g), which was heated with selenium (0.25 g) at 280° for 28 h. The crystalline product (0.09 g) was isolated by extraction with light petroleum and filtration through alumina. Recrystallization from methanol and sublimation *in vacuo* gave 1,2,5,6-tetramethylnaphthalene, m.p. 112–114° identical with the synthesised compound (see below).

*Synthesis of 1,2,5,6-tetramethylnaphthalene (18).* A mixture of 2,6-dimethylnaphthalene (Fluka, 18 g), paraformaldehyde (9 g), phosphoric acid (85 %, 14 ml), hydrochloric acid (conc., 28 ml) and glacial acetic acid (25 ml) was heated on a steam bath with stirring for 5 h. The product was isolated by filtration and recrystallization from dimethyl sulphoxide to give 1,5-dichloromethyl-2,6-dimethylnaphthalene (12 g), m.p. 144–145°. (Found: C 66.6; H 5.6.  $\text{C}_{14}\text{H}_{14}\text{Cl}_2$  requires C 66.4; H 5.6).

1,5-Dichloromethyl-2,6-dimethylnaphthalene (7 g) and zinc dust (14 g) was added to glacial acetic acid (200 ml) and the mixture was refluxed for 12 h. The excess zinc dust was removed by filtration and washed with light petroleum. To the combined filtrate and washings water was added and the mixture was extracted with light petroleum. The organic layer was washed with aqueous sodium bicarbonate and the solvent was evaporated. The residue was filtered through alumina (basic, activity I, 200 g) to give almost pure 1,2,5,6-tetramethylnaphthalene (1.9 g), m.p. 110–113°. Purified by sublimation *in vacuo* the hydrocarbon had m.p. 113–114° (lit. <sup>18</sup> m.p. 116°).

*Hydrogenation of  $\gamma$ -muurolene (platinum, acetic acid).* The compound was hydrogenated and the product was worked up in the manner described above for  $\alpha$ -muurolene. The hydrogen consumed corresponded to 1.8 mole  $\text{H}_2$ . The two main saturated stereoisomers present in the product were isolated by preparative GLC as described for hydrogenated  $\alpha$ -muurolene. They were identical with compounds *a* and *c*, respectively, from hydrogenated  $\alpha$ -muurolene as indicated by comparison of IR spectra and GLC patterns. Three columns were used, (1) 1 % E 301 (see Table 1), (2) 1 % Reoplex 470 on Chromo-

sorb W at 90°, and (3) 15% 2,4-dinitrophenyl-2-naphthyl ether + 0.75% dibenzylpyridine on Silocel (firebrick type) at 150°. The properties of the saturated products are given in Table 1.

*Dehydrogenation of  $\gamma$ -muurolene.* Selenium dehydrogenation gave *cadalene*, identified as the *picrate*, m.p. 115–116°, in 36% yield.

*Addition of hydrogen chloride to  $\gamma$ -muurolene.* The compound (1.2 g) was treated with dry hydrogen chloride in ether as described for  $\alpha$ -muurolene. The crude product (0.37 g) had m.p. 78–86° after one crystallization from a small amount of light petroleum indicating that it consisted of impure muurolene dihydrochloride. The product appeared not to be contaminated with cadinene dihydrochloride. In its IR spectrum the absorption at 852  $\text{cm}^{-1}$  was very weak, not stronger than that of pure muurolene dihydrochloride, indicating that the muurolene dihydrochloride/cadinene dihydrochloride ratio was at least 20:1. Recrystallization from light petroleum and from methanol gave pure (–)-*muurolene dihydrochloride*,\* m.p. 87–88°,  $[\alpha]_{\text{D}}^{22} - 13.2$  (c 2.7).

*Ozonolysis of  $\gamma$ -muurolene.*  $\gamma$ -Muurolene (0.15 g) was ozonised in methylene chloride (2 ml) at –80° until a stable blue colour appeared. Excess ozone was removed and the solvent was evaporated off at room temperature under reduced pressure. A semisolid product was obtained, to which water (2 ml) was added. The mixture was boiled, and the formaldehyde formed was isolated as the dimedone adduct, m.p. 189–190°.

*Selective hydrogenation of  $\gamma$ -muurolene (2) to dihydro- $\gamma$ -muurolene (19).* To a stirred solution of  $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$  (5.00 g) in ethanol (95%, 150 ml), through which hydrogen was bubbled, a solution of sodium borohydride (0.74 g) in ethanol (95%, 20 ml) was added over a period of 1 min.<sup>19</sup>  $\gamma$ -Muurolene (3.42 g) was added to the catalyst suspension and the mixture was shaken under hydrogen until about one mole  $\text{H}_2$  had been consumed, which required ca. 60 h. The catalyst was removed by filtration, the solution was diluted with water and extracted with light petroleum. The organic layer was washed with water and the solvent was evaporated off. Filtration through alumina gave a colourless oil (3.17 g), which was chromatographed on Ag-silica (100 g). Light petroleum (1000 ml) eluted the *dihydro- $\gamma$ -muurolene (19)* (2.28 g),  $[\alpha]_{\text{D}}^{24} - 35^\circ$  (c 0.6), IR bands at 1665, 872, and 827  $\text{cm}^{-1}$ , no absorption band at 1649 and only weak absorption at 883  $\text{cm}^{-1}$ . (Found: C 87.1; H 12.3.  $\text{C}_{15}\text{H}_{26}$  requires C 87.3; H 12.7). Elution with ether (5%) in light petroleum (500 ml) gave unchanged  $\gamma$ -muurolene (0.63 g).

*Hydroboration-oxidation of dihydro- $\gamma$ -muurolene (19).* To a stirred mixture of dihydro- $\gamma$ -muurolene (1.50 g), lithium aluminum hydride (0.21 g) and dry ether (20 ml) under  $\text{N}_2$ , a solution of boron trifluoride etherate (0.93 ml) in dry ether (50 ml) was added over a period of 0.5 h. After stirring at room temperature for 1.5 h the excess hydride was destroyed by slow addition of water. A solution of sodium hydroxide (2.5%, 4.5 ml) in ethanol/water (9:1) was added followed by hydrogen peroxide (30%, 2.0 ml) over a period of 1 min. Most of the ether was evaporated and the residue was refluxed on the steambath for 0.5 h. After cooling, the mixture was diluted with water and extracted with ether (three portions, 10 ml each). The ethereal extract was washed with water and then treated with an aqueous dichromate solution (10.0 ml) as described above for the oxidation of hydroborated  $\alpha$ -muurolene. The product was chromatographed on silica gel (70 g). Benzene was used as the eluent and 70 ml fractions were collected. Fractions 2–4 (1.10 g) were pure according to TLC and consisted of the *ketone (20)*,  $[\alpha]_{\text{D}}^{22} + 33.9^\circ$  (c 2.0). The IR spectrum showed an absorption band at 1710  $\text{cm}^{-1}$  but no band at about 1420  $\text{cm}^{-1}$ . (Found: C 81.1; H 11.8.  $\text{C}_{15}\text{H}_{26}\text{O}$  requires C 81.0; H 11.8). The *2,4-dinitrophenylhydrazone* had m.p. 153–155°.

*Conversion of the ketone (20) to 5-methylcadalene (17).* The ketone (0.30 g) in dry ether was treated with excess methylmagnesium iodide in the manner described above for the diketone (12) from  $\alpha$ -muurolene. Dehydration and dehydrogenation of the crude product were carried out as for the conversion of  $\alpha$ -muurolene to 2,5-dimethylcadalene. The final product obtained (0.14 g) consisted mainly of 5-methylcadalene as indicated by GLC using a Reoplex column (1% on Chromosorb W) at 140°, gas flow 61 ml/min. Under these conditions 2-, 5-, and 7-methylcadalene had the retention times 5.7, 7.3, and 6.5 min, respectively. Authentic samples of these hydrocarbons were obtained by the syntheses described by Campbell and Soffer<sup>12</sup> (for 2-methylcadalene) and by Sukh Dev<sup>20</sup>

\* See footnote p. 2853.

(for 5- and 7-methylcadalene). Chromatography of the crude methylcadalene from  $\gamma$ -muurolene on silica gel (15 g) using light petroleum as the eluent gave pure 5-methylcadalene (17), identical with synthetic 5-methylcadalene. The *picrate* had m.p. 101–102° (lit.<sup>20</sup> m.p. 103°).

**Hydrogenation of  $\epsilon$ -muurolene.** On catalytic hydrogenation as for  $\alpha$ -muurolene (see above) 2.0 moles  $H_2$  were consumed. The two main saturated stereoisomers formed were isolated by preparative GLC. They were identical with compounds *a* and *c*, respectively, from hydrogenated  $\alpha$ -muurolene as indicated by comparison of IR spectra and GLC patterns. The same three columns were used as for comparison of the hydrogenation products of  $\alpha$ - and  $\gamma$ -muurolene (see above). The properties of the saturated products are given in Table 1.

**Addition of hydrogen chloride to  $\epsilon$ -muurolene.** The compound (0.065 g) was treated with hydrogen chloride under the same conditions as for  $\alpha$ - and  $\gamma$ -muurolene. The muurolene dihydrochloride/cadinene dihydrochloride ratio in the crude crystalline product was about 3:1 (IR). (–)-*Muurolene dihydrochloride*\* (0.026 g), m.p. 85–87°,  $[\alpha]_D -12.9^\circ$  (*c* 0.8) and (–)-*cadinene dihydrochloride* (0.013 g), m.p. 116–118°,  $[\alpha]_D -35.5^\circ$  (*c* 0.9) were isolated by partition chromatography and recrystallization as described for the same products from  $\alpha$ -muurolene.

**Ozonolysis of  $\epsilon$ -muurolene.**  $\epsilon$ -Muurolene (1.45 g) was ozonised in methylene chloride (10 ml) and the ozonides were decomposed as described above for  $\gamma$ -muurolene. The non-volatile reaction products were isolated by extraction with ether. The neutral fraction (aqueous sodium bicarbonate) was an oil (0.93 g), which was rapidly chromatographed (over a period of about one hour) on silica gel (30 g) deactivated with water (2 ml) using ether (50 %) in light petroleum as the eluent. The first portion (100 ml) eluted an oil (0.28 g), which, according to TLC using silica gel G, was a mixture of relatively non-polar compounds. The next portion (50 ml) eluted the *diketone* (23) (oil, 0.19 g),  $[\alpha]_D^{22} +73.8^\circ$  (*c* 0.9), showing IR bands at 1707 and 1426  $cm^{-1}$ . According to TLC as above (eluent isopropyl ether) it was a pure compound with  $R_F$  0.17. The last fraction collected (200 ml) was, according to TLC, a mixture (0.33 g) of the above *diketone* (23) and its epimer (6) (see below). TLC of the eluted fractions revealed that partial epimerization of the *diketone* (23) to give the *diketone* (6) had occurred during the chromatography.

**Epimerization of the *diketone* (23).** A mixture of the *diketone* (0.016 g), acetic acid (2 ml), water (1 ml), and sulphuric acid (conc., 0.05 ml) was heated at 90° for 1.5 h. The mixture was diluted with water and extracted with ether. The ethereal solution was shaken with aqueous sodium bicarbonate and then with water. After drying with sodium sulphate, evaporation of the ether gave a crystalline product, m.p. 90–100°. Vacuum sublimation gave the *diketone* (6) (0.013 g), m.p. 100–101°,  $[\alpha]_D^{22} -42.6^\circ$  (*c* 0.5). The IR spectrum (carbon tetrachloride) was identical with that<sup>9</sup> of the *diketone*, m.p. 103°, obtained<sup>9</sup> from “ $\epsilon$ -cadinene”. TLC (silica gel G, eluent isopropyl ether) showed that the crude reaction product contained only a trace of the original *diketone* (23),  $R_F$  0.17. The crystalline *diketone* (6) had  $R_F$  0.10.

On GLC using a Reoplex 470 column (1 %) on Chromosorb W (80–100 mesh) at 158° (gas flow 86 ml/min) the oily and the crystalline *diketones* had the retention times 9.1 and 11.1 min, respectively. Under these conditions they were partially equilibrated. Thin layer chromatographically pure oily *diketone* (23) gave a mixture of (23) and (6) in the ratio 7:10 and the crystalline *diketone* (6) a mixture of the same *diketones* in the ratio 1:10.

**Dehydrochlorination of (–)-muurolene dihydrochloride (24).**\* Potassium (0.32 g) was dissolved in dry triethyl carbinol (4.5 ml) under nitrogen. After heating to 55° the dihydrochloride (0.83 g) was added and the solution was stirred at this temperature for 16 h. During this time the solution became cloudy. After cooling, the reaction mixture was poured into water and ice (50 ml). The mixture was extracted with ether, the ether extract was washed with water and dried (sodium sulphate). The residue (ca. 4 g) after evaporation of the ether contained triethyl carbinol and was rapidly filtered through alumina (120 g) using light petroleum (300 ml) as the eluent.

\* See footnote p. 2853.

The eluted oil (0.63 g) was chromatographed on Ag-silica (40 g). Elution with the solvents indicated gave the following fractions: (1) 1 % ether (E.) in light petroleum (L.P., 175 ml), 0.02 g; (2) 1 % E. in L.P. (175 ml), 0.27 g; (3) 1 % E. in L.P. (150 ml), 0.05 g; (4) 1 % E. in L.P. (300 ml), 0.04 g; (5) 2 % E. in L.P. (300 ml), 0.02 g; (6) 5 % E. in L.P. (500 ml), 0.11 g. The IR spectra of fractions (2), (4), and (6) indicated that they consisted mainly of  $\alpha$ -,  $\gamma$ -, and  $\epsilon$ -muurolene, respectively. Fraction (6) was identified as (+)- $\epsilon$ -muurolene (3)  $[\alpha]_D^{22} +48.0^\circ$  (c 1.5).

*Dehydrochlorination of (-)-cadinene dihydrochloride (5).* Cadinene dihydrochloride (0.83 g) was treated with potassium triethyl carbinolate in the manner described above for muurolene dihydrochloride. The mixture of olefins (0.55 g) obtained after filtration of the reaction product through alumina was chromatographed on Ag-silica (30 g). After a mixture of hydrocarbons (0.25 g) had been eluted using ether (2 %) in light petroleum (400 ml) the major reaction product (-)- $\epsilon$ -cadinene (4) (0.19 g) was eluted with ether (5 %) in light petroleum (500 ml). The hydrocarbon was pure according to GLC and Ag-TLC. The  $R_F$ -value (eluent benzene) was 0.06, while that of  $\epsilon$ -muurolene was 0.16. (-)- $\epsilon$ -Cadinene had  $[\alpha]_D^{22} -15.9^\circ$  (c 1.5) and  $n_D^{22} 1.5032$ . (Found: C 88.0; H 11.8.  $C_{15}H_{24}$  requires C 88.2; H 11.8). The IR spectrum showed characteristic bands at 3075, 1775 (overtone), 1645, 1185, 1137, 1077, and 880  $cm^{-1}$ .

*Ozonolysis of (-)- $\epsilon$ -cadinene.* The hydrocarbon (0.140 g) was ozonised in methylene chloride (3 ml) and the ozonides were decomposed as described for  $\gamma$ -muurolene. The neutral fraction of the products (0.090 g) was crystalline. Vacuum sublimation gave the diketone (6), m.p. 99–101°,  $[\alpha]_D^{22} -40.2^\circ$  (c 1.5), identical with the diketone obtained by ozonolysis of  $\epsilon$ -muurolene followed by epimerization.

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*Added in proof.* The same structure of  $\alpha$ - and  $\gamma$ -muurolene have recently been proposed by Zabza *et al.*<sup>26</sup> but on different evidence.

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