Tetrahedron, 1965, Vol. 21, pp. 115 to 138. Pergamon Press Ltd. Printed in Northern Ireland

TERPENOIDS—LXII

THE CONSTITUTION OF AGAROSPIROL, A SESQUITERPENOID WITH A NEW SKELETON*

K. R. VARMA, M. L. MAHESHWARI and S. C. BHATTACHARYYA
National Chemical Laboratory, Poona, India

(*Received* 24 *August* 1964; *in revised form* 14 *September* 1964)

Abstract—Degradative studies and physical measurements supported by an unambiguous synthesis of the derived ketone (XVa) have led to the assignment of a novel spiro-skeleton to agarospirol (Ia), a sesquiterpene alcohol isolated from the essential oil of infected agarwood (*Aquilaria agallocha* Roxb.). The corresponding carbon skeleton (VI) has been named agarospirane. Agarospirol is the second spiro-terpenoid to be isolated from Nature. The most probable stereochemistry of agarospirol appears to be as in XXXIX.

WORK from this Laboratory on the constituents of agarwood oil† (*Aquilaria agollocha* Roxb.) has been recorded in previous papers.[1–4] Investigations of the alcoholic constituents has led to the isolation of a new monoethenoid, bicyclic, sesquiterpene alcohol, $C_{15}H_{26}O$, as a major component. Chemical and spectroscopic studies supported by the synthesis of one of the derived ketones (XVa) indicates that this alcohol possesses a novel spiro-bicyclodecane structure (Ia). It is the second spiro-terpenoid to be isolated from Nature, the first, acorone (XVIII), was isolated from the oil of sweet flag (*Acorus calamus* Linn.) and studied[5] by Sorm *et al.* We propose to name this alcohol agarospirol and the corresponding carbon skeleton (VI) agarospirane.‡

Agarospirol was isolated as such in the pure state (GLC) free from other related constituents by column chromatography, or preferably, as the acetate, which forms only under energetic conditions (NaOAc—Ac_2O_{20}). The acetate, $C_{17}H_{28}O_2$ (Ib), on saponification with cold alcoholic potash gives pure agarospirol, $C_{15}H_{26}O$ (Ia), which may be reconverted to the same acetate. The acetate is resistant to LAH in refluxing tetrahydrofuran.

Agarospirol, $C_{15}H_{26}O$ (Ia), $(\alpha)_D^{27}$ $-5{\cdot}7°$, an oil, b.p. 90–91°/0·1 mm, ν_{max} 3472, 1149 cm^{-1} (t—OH), does not give a solid ester derivative, but a crystalline monoepoxide, $C_{15}H_{26}O_2$ (II), m.p. 109–110°; the presence of another liquid epimeric epoxide

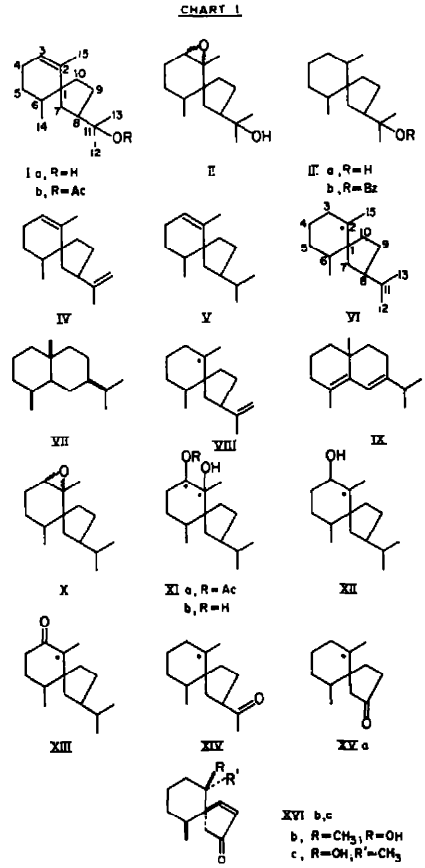
* Communication No. 715 from the National Chemical Laboratory, Poona-8, India.

† The oil studied was obtained by solvent extraction from the infected wood.

‡ The numbering of the carbon skeleton is analogous with that of acorone (XVIII) and does not follow the I.U.P.A.C. Rule, *J. Amer. Chem. Soc.* **82**, 5545 (1960).

[1] T. C. Jain and S. C. Bhattacharyya, *Tetrahedron Letters* No. 9, 13 (1959).
[2] M. L. Maheshwari, T. C. Jain, R. B. Bates and S. C. Bhattacharyya, *Tetrahedron* **19**, 1079 (1963).
[3] M. L. Maheshwari, T. C. Jain and S. C. Bhattacharyya, *Perf. & Ess. Oil Rec.* **53**, 294 (1962).
[4] M. L. Maheshwari, K. R. Varma and S. C. Bhattacharyya, *Tetrahedron* **19**, 1519 (1963).
[5] J. Vrkot, J. Jonas, V. Herout and F. Šorm, *Coll. Czech. Chem. Comm.* **29**, 539 (1964) and earlier papers.

CHART 1



was indicated but this was not further purified. The NMR spectrum* of the solid epoxy alcohol (II, Fig. 4) shows a split doublet at 9·13 and 9·25 τ (J = 7 c/s, 3H) for one methyl group in the environment $\begin{matrix} R \\ R \end{matrix}\!\!>\!\!CH\cdot CH_3$, a signal at 8·77$\tau$ (very slightly split, 6H) for a hydroxyisopropyl group[6] and a singlet at 8·69τ (3H) for a methyl group attached to a carbon atom bearing one oxygen atom (epoxy) and no proton, and a triplet centered at 7·1τ (J = 5 c/s, 1H) for the proton on the epoxide ring. The NMR spectrum of agarospirol (Fig. 3) shows a broad doublet centred at 8·33τ (J = 3 c/s) attributable to a methyl group on a double bond and the presence of such a system is confirmed by the singlet at 8·69τ shown by the epoxy alcohol at the expense of the signal at 8·33τ.

Agarospirol gives a positive reaction towards tetranitromethane and the presence of only one double bond is indicated by hydrogenation and oxidimetric titrations. The double bond is trisubstituted as indicated by ν_{max} 1654 and 813 cm^{-1} (Fig. 1)

* NMR spectra were run on a Varian A–60 spectrometer at 60 m/c for dilute solutions in CCl_4 using tetramethyl silane as internal reference standard. The chemical shifts are reported in τ units and the splitting constants in c/s.

[6] L. M. Jackmann, *Application of NMR spectroscopy in organic chemistry* p. 97. Pergamon Press, London (1959).

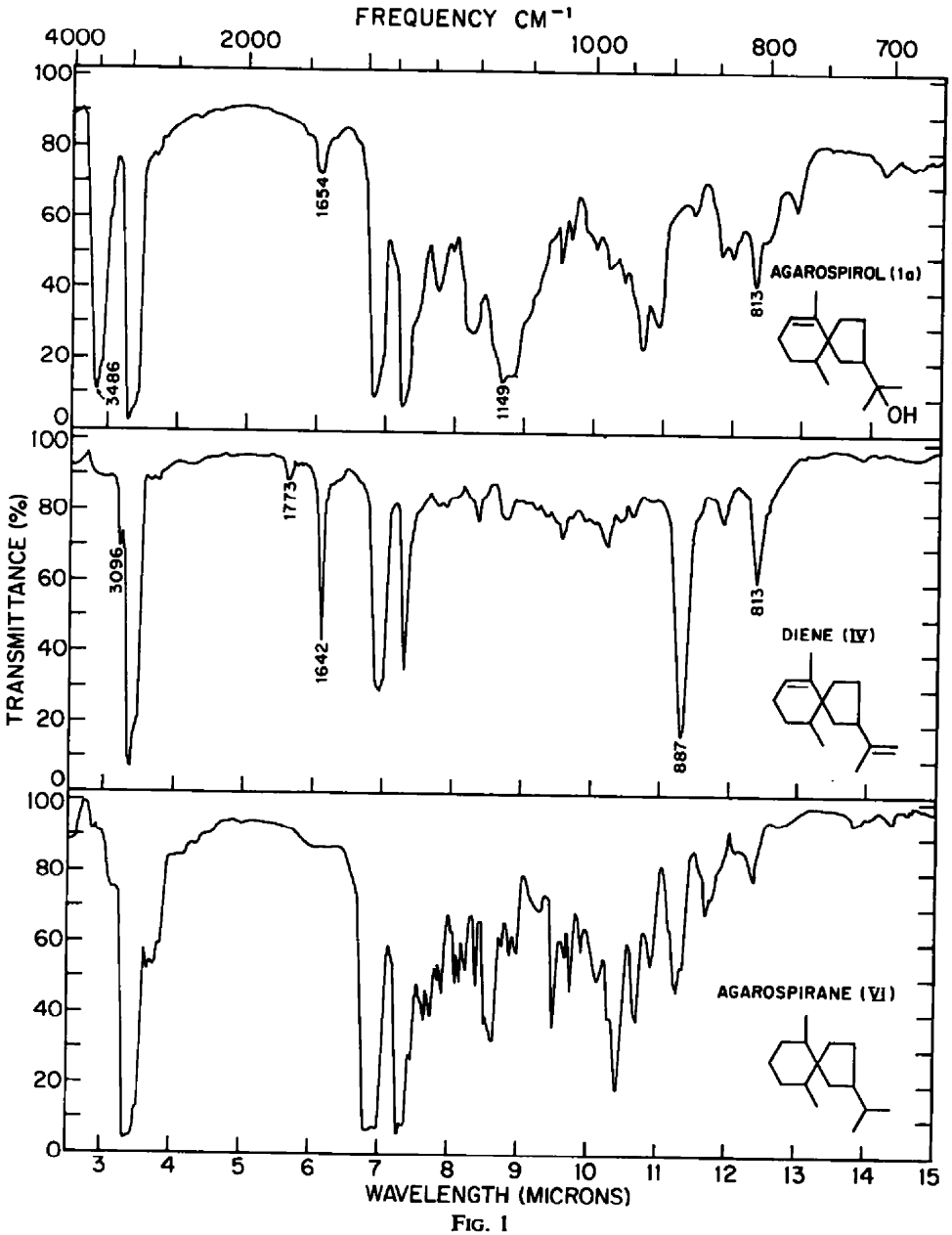


FIG. 1

and confirmed by the broad signal at 4·85τ (one H). Hydrogenation of agarospirol using Pd-C (10%) or Adams' catalyst results in each case in the absorption of one equivalent of hydrogen to give the saturated dihydro alcohol, $C_{15}H_{28}O$ (IIIa), which is a mixture of epimers in the approximate ratio 45:55 (GLC). Formation of any hydrogenolysis product could not be detected. The IR spectrum of dihydroagarospirol (IIIa) does not show the peaks at 1654 and 813 cm^{-1} shown by agarospirol and it does not give any colouration with tetranitromethane. The NMR spectrum shows a doublet at 8·91 and 8·87τ (J = 3 c/s, 6H) for a 2-hydroxy-isopropyl group[6] and a

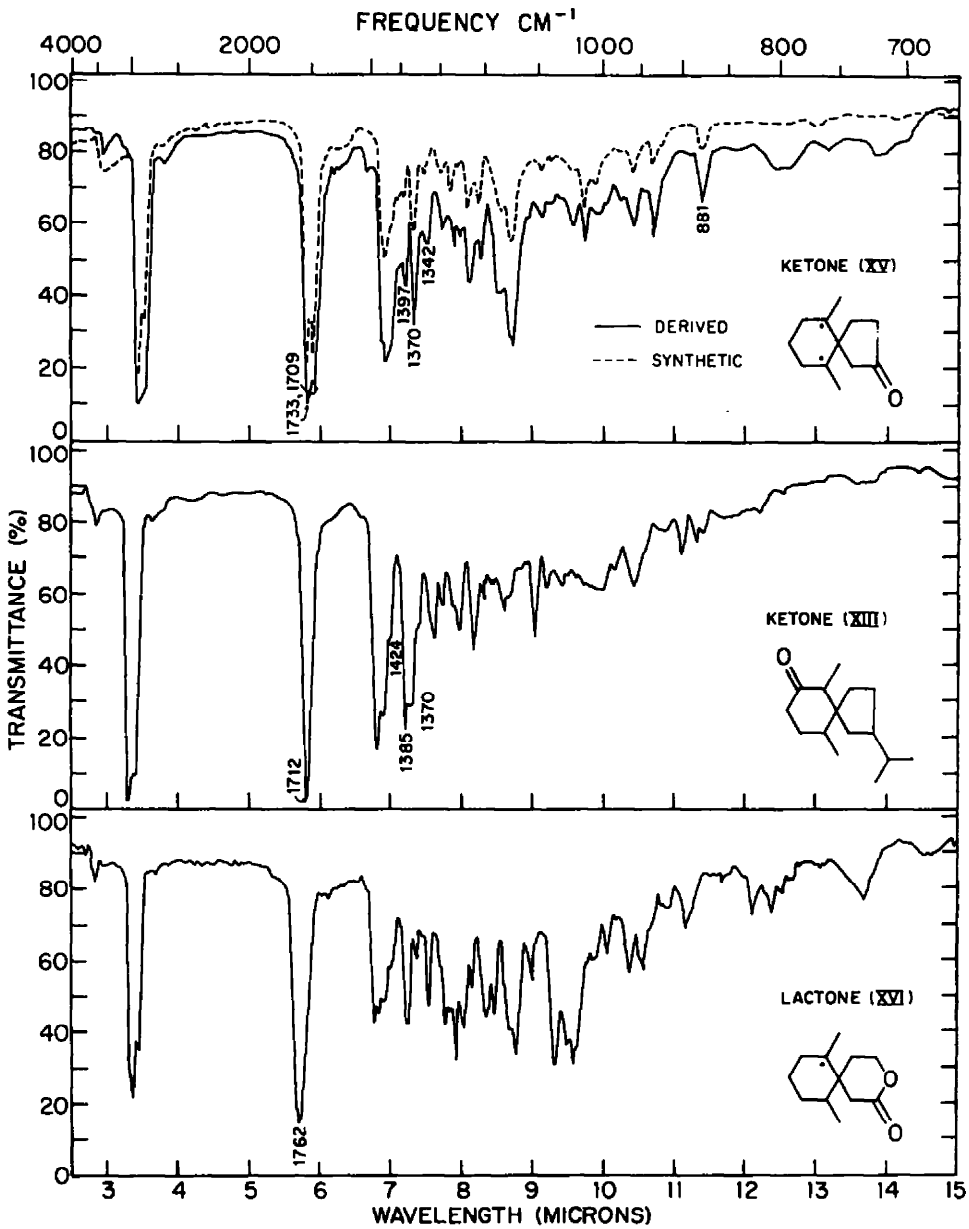


FIG. 2

triplet at 9·30, 9·18 and 9·10τ (6H) due to two partly superimposed methyls of the type $\begin{matrix} R \\ R \end{matrix}\!\!>\!CH\cdot CH_3$. It gives only liquid ester derivatives.

The tertiary nature of the hydroxyl group in agarospirol is shown by its resistance to chromic oxide–pyridine complex[7] or that of the dihydro alcohol towards chromic oxide in acetic acid. This is further supported by the IR bands at 3472 and 1149 cm^{-1}

[7] G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *J. Amer. Chem. Soc.* **75**, 422 (1953).

and confirmed by the NMR doublet at 8·88 and 8·83τ (J = 2 c/s) characteristic of a hydroxy-isopropyl group shown by agarospirol (Fig. 3).

Agarospirol benzoate on pyrolysis gives a homogeneous (GLC) diene $C_{15}H_{24}$ (IV), which shows ν_{max} 3096, 1770 (overtone), 1639 and 888 cm^{-1} (Fig. 1), in addition to the peak at 813 cm^{-1} for the trisubstituted double bond originally present, thus indicating the end methylene nature of the newly formed double bond, which is to be expected

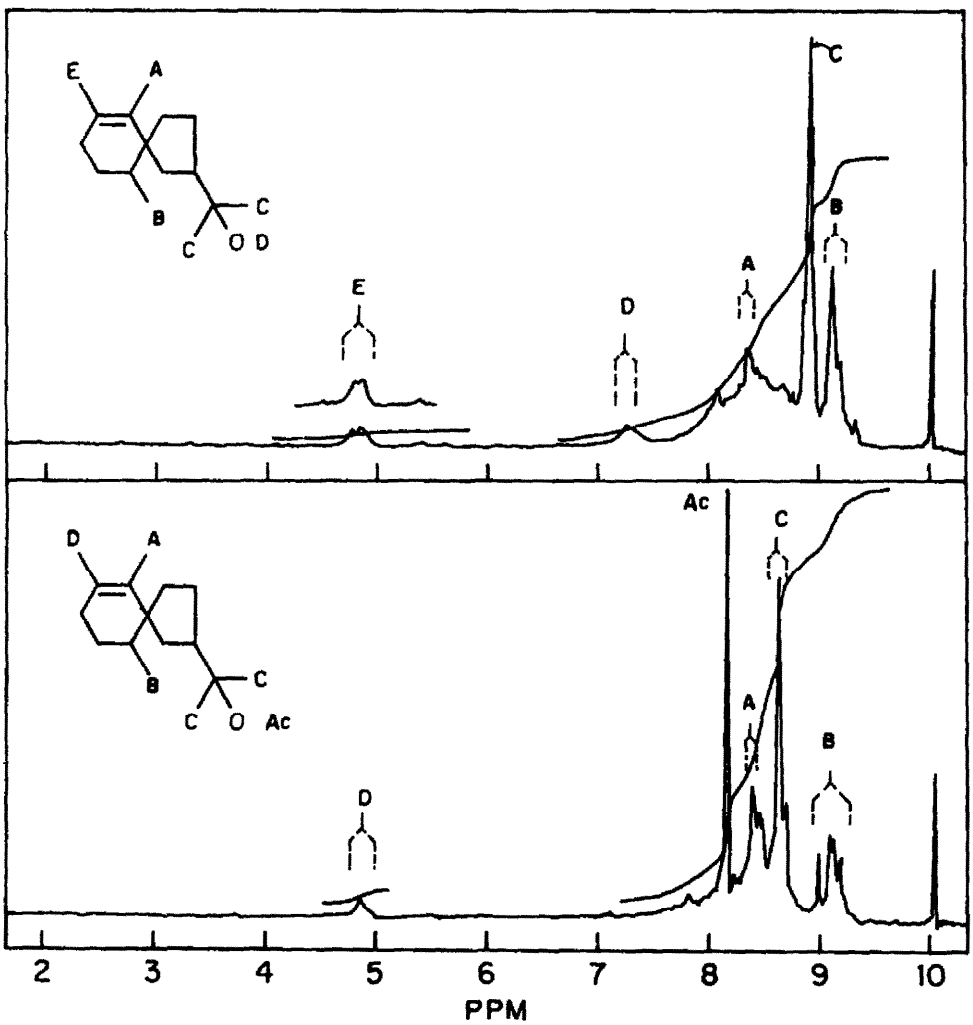


FIG. 3

from a hydroxy-isopropyl side chain. This is further confirmed by the broad signal at 4·78τ (one H) and the sharp signal at 5·37τ (2H) in the NMR spectrum of the diene. In addition, a signal at 8·27τ (6H) accounts for two methyl groups on double bonds and the C_8 methyl group is a clear doublet at 9·06 and 9·16τ (3H). This observation is important as it shows that no isomerization of the skeleton has taken place during the pyrolysis. The two double bonds in the diene are not conjugated as shown by the absence of any characteristic absorption in the 230–350 mμ region (end absorption

ε 210,3880). Attempted isomerization of the diene with N-lithioethylenediamine[8] or of the diene or agarospirol as such with perchloric acid in acetic acid[2] failed to furnish any appreciable quantity of conjugated isomer as checked by UV. This is relevant, as the presence of a selinanic skeleton in agarospirol was suspected and selinanic compounds of similar type are known to give under the above conditions the hetero-annular diene[2,8] (IX), easily characterized by its high optical rotation and characteristic spectra. This evidence indicates the inability of the two double bonds to conjugate suggesting the presence of an uncommon ring system of the spiro-type in agarospirol.

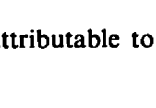
Catalytic hydrogenation of the diene (IV) results in the uptake of two equivalents of hydrogen to give a saturated epimeric hydrocarbon mixture $C_{15}H_{28}$ (VI; 45:55, GLC), which was freed of traces of unsaturated impurity by peracid treatment and chromatography. The same saturated hydrocarbon is also obtained by dehydration of agarospirol with thionyl chloride in pyridine followed by complete hydrogenation. Though the physical constants of the saturated hydrocarbon are similar to those of selinane (VII; prepared from authentic dihydroeudesmol), its IR spectrum (Fig. 1) is strikingly different from those of selinane or any other saturated skeletal hydrocarbon reported in the literature.[9] The NMR spectrum fully substantiates this view. As expected it does not show the presence of an angular methyl group which is characteristic of selinane and many other saturated sesquiterpene hydrocarbons. Instead, it shows two methyl groups of the type —CH·CH_3 one of which appears as a clear doublet at 9·32 and 9·20τ (J = 7 c/s, 3H) while the other remains partly merged with the isopropyl protons which appear down field at 9·12 and 9·08τ (J = 2 c/s). In accordance with this assignment the integral upfield from 9·0τ accounts for 12 protons.

Selective hydrogenation of the diene (IV), removes the end methylene double bond in the side chain to afford the monoene, $C_{15}H_{26}$ (V), which is obtained in 98% purity (GLC) by column chromatography. The trisubstituted double bond originally present in the monoene is indicated by ν_{max} 1656 and 811 cm^{-1} and end absorption, ε 215 mμ, 2200. Its NMR spectrum exhibits an apparently unsplit signal at 9·17τ (part of —CH—CH_3). The isopropyl methyl protons appear at 9·12 and 9·09τ (J = 2 c/s). The broad signal at 8·45τ (3H) attributable to one methyl group on a double bond is fully supported by the NMR spectra of the epoxide (X) and the diol (XIb), both of which show unsplit signals for methyls of the type $O{<}C{<}CH_3$. Hydroboration–oxidation of the monoene (V)[10] gives the monol (XII), which is oxidized with chromic oxide to the ketone (XIII). The IR spectrum of the ketone (Fig. 2) shows the carbonyl stretching frequency at 1712 cm^{-1} and also an inflexion at 1429 cm^{-1} attributable to a CH_2—CO— grouping in a six-membered ring. GLC analysis shows it to be a mixture of two epimers in the ratio 70:30 indicating that the reaction sequence is followed by partial epimerization. This is normal, as a methyl group in the α-position can easily epimerize. Equilibration with potassium t-butoxide in t-butyl alcohol gives an almost pure epimer (90%, GLC), 2,4-DNP m.p. 179–180°. Part of the methyl group α- to the carbonyl appears in the NMR spectrum of the epimeric mixture of ketones

[8] B. S. Tyagi, B. B. Ghatge and S. C. Bhattacharyya, *Tetrahedron* **19**, 1189 (1963).

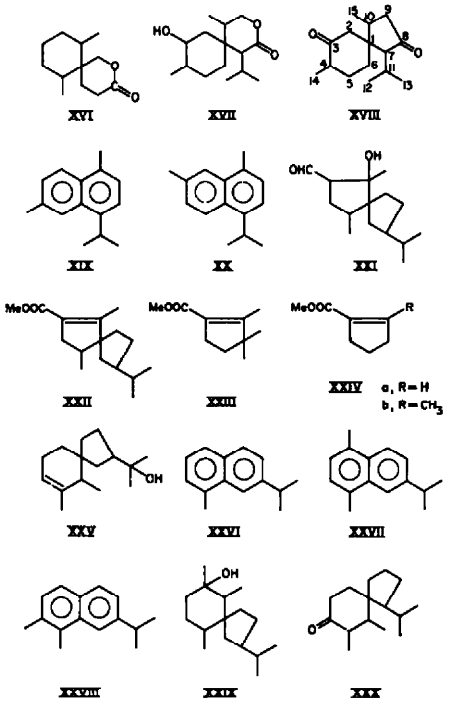
[9] J. Pliva, M. Horak, V. Herout and F. Sorm, *Terpeneskeptren* (1960); M. Suchy, V. Herout and F. Sorm, *Russ. Chem. Revs.* (English translation) **31**, 474 (1962).

[10] H. C. Brown and G. Zwiefel, *J. Amer. Chem. Soc.* **81**, 247 (1959).

(Fig. 6) as a characteristic sharp signal at 9·37τ (while part of it remains merged with the other methyl signals downfield ($J > 11$ c/s). This assignment is only tentative. The methylene and methine protons α- to the carbonyl appear as a triplet centred around 7·83τ (3H). The same ketone may be obtained in lower yield (~40%) together with other products by BF_3 ethereate isomerization of the epoxide (X). The epoxide (X) prepared by peracid treatment of the monoene and purified by chromatography (95%, GLC) shows a doublet at 7·20 and 7·26τ ($J = 4$ c/s, one H) for one proton in the epoxide ring and a signal at 8·88τ attributable to the grouping  .

The epoxide is stable to LAH in refluxing tetrahydrofuran. However, small yields (~15%) of an alcohol may be isolated by chromatography which when pyrolysed in the form of benzoate afford a mixture of hydrocarbons whose IR spectrum exhibit bands at 888 and 815 cm^{-1} in accordance with expectations.

CHART 2



Although this evidence indicates the presence of a methyl group positioned on a double bond, further chemical evidence was deemed necessary. Ozonolysis of the monoene (V) followed by hydrogenation of the ozonide, yields a product with indications of a positive iodoform test. The same product is obtained by periodate oxidation of the *cis*-diol* (XIb) obtained by osmylation of the monoene. The presence of an

* It is interesting to note that the *trans*-diol (XIb) obtained by acetic acid cleavage of the epoxide (X) followed by saponification of the resulting acetoxy alcohol (XIa) was comparatively stable to sodium metaperiodate.

aldehyde function in the product was proved by a +ve Fehling's test, by the NMR signal at 0·2τ (about one H) and ν_{max} 2770 and 1730 cm^{-1}. Hydrogen bonding is suggested by the broad nature of the carbonyl stretching band and the strong hydroxyl frequency which appears around 3530 cm^{-1}. Oxidation with silver oxide followed by careful esterification of the acid with diazomethane affords an ester, $C_{16}H_{26}O_2$ (90%, GLC), whose spectral properties are in accordance with the structure, XXII. The ester grouping is shown by ν_{max} 1722 and 1178 (split) cm^{-1} and a shoulder at 1663 cm^{-1} can be attributed to a tetrasubstituted double bond in conjugation with an ester carbonyl. The UV spectrum, λ_{max} 229 mμ (ε 7,800), is strikingly similar to those of 1-carbomethoxy-2-methylcyclopent-1(2) ene[11] (XXIVb; λ_{max} 232 mμ, ε 11,000) and methyl-isolauranolate[12] (XXIII λ_{max} 229 mμ, ε 9,850), but different from that of 1-carbomethoxy-cyclopent-1(2) ene[11] (XXIVa; λ_{max} 222 mμ, ε 11,500). This structure is further supported by the NMR spectrum which does not show olefinic protons but indicates the presence of a methyl group on a double bond and carbomethoxy protons(6·39τ, 3H). These data suggest structure XXI for the hydroxy aldehyde.*

After this evidence regarding the presence of a trisubstituted double bond on a six-membered ring, the position of the hydroxy-isopropyl side chain and the nature of the other ring was ascertained experimentally. The epimeric mixture of dihydroalcohol (IIIa) affords a benzoate (IIIb), pyrolysis of which furnishes a hydrocarbon, $C_{15}H_{26}$ (VIII), ν_{max} 1642, 887 cm^{-1} (>=CH_2), which is also a mixture of epimers in the ratio (45:55, GLC). Ozonolysis in chloroform at 0° followed by decomposition with hot water gives formaldehyde (~70%), acetone (~15%) and a mixture of ketones. Chromatography of the ketone mixture yields as the less polar fraction (~80%) a mixture of two epimeric ketones, $C_{14}H_{24}O$, which is a methyl ketone (XIV) as suggested by a +ve iodoform test, ν_{max} 1709, 1370 and 1348 cm^{-1} and confirmed by the NMR signal (slightly split) at 7·86τ (3H) (Fig. 6). The mixture of 2,4-dinitrophenylhydrazones may be separated by fractional crystallization and have m.ps 147–149° and 118–122°. The more polar constituent (XVa), $C_{12}H_{22}O$, may be separated from the methyl ketone by column chromatography. The IR spectrum of this ketone (Fig. 2), which is also a mixture of epimers (45:55, GLC), taken for a thin film and for chloroform solution show split bands of almost equal intensity at ν_{max} 1733 and 1709 cm^{-1}, thus indicating a keto group on a five membered ring. The presence of at least one methylene group flanking the carbonyl is indicated by the inflexion at 1422 cm^{-1}. Many cyclopentanones and cyclopentenones are known to give split carbonyl bands and in the absence of other structural features which justify such an observation, these doublet bands in the carbonyl stretching region have been attributed to Fermi Resonance.[13] Cyclopentanone itself gives two carbonyl bands at 1746 and 1728 cm^{-1} and

* For similar cyclizations see N. L. Wendler and H. L. Slates, *J. Amer. Chem. Soc.* **80**, 3937 (1958) and K. Tanabe and Y. Morisawa, *Chem. & Pharm. Bull., Japan* **11**, 536 (1963).

[11] E. R. H. Jones, G. H. Mansfield and M. C. Whiting, *J. Chem. Soc.* 4077 (1956); A. T. Nielson, *J. Org. Chem.* **22**, 1546 (1957).

[12] Prepared according to B. Shive, J. T. Horeczy and H. L. Lochte, *J. Amer. Chem. Soc.* **62**, 2744 (1940) and carefully esterified with diazomethane.

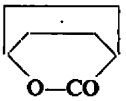
[13] [a] R. N. Jones, C. L. Angell, T. Ito and R. J. D. Smith, *Canad. J. Chem.* **37**, 2007 (1960);
[b] R. N. Jones and C. Sandorfy in *Techniques of Organic Chemistry* (Edited by A. Wiessberger) Vol. IX; pp. 487 and 444. Interscience, London, New York (1956).

has been extensively studied.[14] 3-Isopropenylcyclopentanone is reported[15] to give two bands at 1744 and 1724 cm^{-1} and a C_{17}-keto steroid showing doublets carbonyl bands at 1745 and 1742 cm^{-1} is also known.[16a,b] On the strength of these reports in the literature the above bands are attributed to a cyclopentanone moiety. Apart from proving the presence of a cyclopentane ring in agarospirol, the above series of reaction also prove the position of the hydroxy-isopropyl side chain. The derived epimeric ketones (XVa) from agarospirol have been characterized as to epimeric 2,4-dinitrophenylhydrazones, m.p. 194–196° and 201–203° and have been independently obtained via Baeyer–Villiger oxidation of the methyl ketone (XIV). An unambiguous synthesis of the ketone (stereochemistry unknown) fully substantiates the structure (XVa) assigned. The NMR spectrum of the derived ketone is also in accordance with the structure (XVa) and shows the presence of six cyclopentanone protons which appear as a triplet at 7·77, 7·89 and 8·06 (J = 17 c/s). The other ring protons appear around 8·63τ. The two methyl groups remain partly superimposed and appear at 9·08, 9·19 and 9·33τ.*

Before the synthesis of the ketone (XV; Chart 3) was initiated in order to confirm the presence of a five membered ring, we attempted Baeyer–Villiger oxidation of the derived ketone with the expectation of getting a normal δ-lactone. The IR spectrum of the lactone (XVI) does not show the normal δ-lactone frequency[18a] but a single band at 1762 cm^{-1}, too high for a δ-lactone in normal environments. Such high frequencies have been reported for spiro-δ-lactones in cardanolides[16a,b] and in certain tricyclic δ lactones[19] and is a consequence of ring strain.[18a] This observation suggests the presence of an abnormal ring fusion in the ketone and consequently in agarospirol and a spiro juncture appears to be the only possibility.† A closer examination of the IR spectrum of the ketone (XVa) confirms this view. Chiurdoglu and Tursch[20] and Dixon and Naro[21] have studied a number of a spiro compounds and indicate that a doublet in the region 7·30 to 7·66 μ is probably characteristic of spiro compounds. These bands are not of general applicability in the terpenoid field as isopropyl and

* Signals for tertiary methyl groups in such spiro compounds appear to show up at unusually high field, i.e. around 9·3τ. Cf. the two epimeric spiro compounds (XVIb,c) reported by Kropp and Erman[18b] where the tertiary methyl groups appear as doublets centered around 9·30 and 9·38τ respectively, positions too high for tertiary methyl groups in other compounds.

† The lactone (XVII) derived from acorone (XVIII) is reported[a] to show carbonyl frequency at



1730 cm^{-1}. This low value is probably the effect of the alkyl substituent. The lactone is reported[17] to absorb at 1754 cm^{-1}.

[14] C. L. Angell, P. J. Kreuger, R. Lanzon, L. C. Leitch, K. Noack, R. J. D. Smith and R. N. Jones *Spectrochim. Acta* **11**, 926 (1959); and Refs cited therein; [b] C. Castinel, G. Chiurdoglu, M. L. Josien, L. Lascombe and E. Vanlanduyf, *Bull. Soc. Chim. Fr.* 807 (1958); [c] for a recent related study see H. Minato, *Bull. Chem. Soc., Japan* **38**, 1020 (1963).

[15] Y. R. Naves, *Bull. Soc. Chim. Fr.* 1372 (1958).

[16a] R. N. Jones and F. Herling, *J. Org. Chem.* **19**, 1252 (1954);

[b] R. N. Jones and B. S. Gallagher, *J. Amer. Chem. Soc.* **81**, 5242 (1959).

[17] T. J. Perun, L. Zetfel, R. G. Nelb and D. S. Tarbell, *J. Org. Chem.* **28**, 2937 (1963).

[18a] L. J. Bellamy *The Infrared spectra of complex molecules.* Methuen, London (1960);

[b] P. J. Kropp and W. F. Erman, *J. Amer. Chem. Soc.* **85**, 2456 (1963).

[19] P. Wilder and A. Winston, *J. Amer. Chem. Soc.* **76**, 5598 (1955).

[20] C. Chiurdoglu and B. Tursch, *Bull. Soc. Chim., Belges* **66**, 600 (1957).

[21] J. A. Dixon and P. A. Naro, *J. Org. Chem.* **25**, 2094 (1960).

gem-dimethyl groups also absorb in the same region. However, the derived ketone (XVa) which does not contain any such grouping shows a clear *triplet* in the region 7·10 to 7·55 μ [1397 (w), 1370 (m), 1342 (w) cm^{-1}], further supporting the presence of a spiro juncture. The triplet nature is evidently due to the additional methyl groups in the ketone (XVa).

The relative disposition of the alkyl substituents in agarospirol is established by dehydrogenation. Spiro compounds are known to give the corresponding naphthalenes under dehydrogenation conditions.[22] Dehydrogenation of the diene (IV) and the monoene (V), under conditions used for agarospirol (Ia), gives in comparable yields (28–35%) of eudalene (XXVI), characterized by UV and IR spectra and as the sym—TNB and picric acid adducts. As only traces of azulenes were discernible, the perhydroazulene skeleton is ruled out. The presence of naphthalenes other than eudalene could not be detected. Contrary to the ease with which the above compounds undergo dehydrogenation, the dihydro alcohol (IIIa), the monoene (VIII) or the skeletal hydrocarbon (VI) give under similar conditions poor yields (6–10%) of eudalene, detectable only by UV. These experiments clearly indicate the special part played by the trisubstituted double bond in facilitating dehydrogenation of Ia, IV and V. The dehydrogenation to the corresponding naphthalene can be rationalized on the basis of a spiro-(4,5)-decane structure for agarospirol. Isomerization to the naphthalene precursor, greatly fascilitated by the presence of a double bond in a convenient position, followed by dehydrogenation, explains the formation of the eudalene. In this respect, agarospirol is reminiscent of acorone (XVIII), the corresponding diol from which gives a mixture of cadalene and 1,7-dimethyl-4-isopropylnaphthalene (daucalin).[23]

In accordance with these results, only two structures (Ia and XXV) are possible for agarospirol. As *only* eudalene would result from either Ia or XXV, differentiation between these structures was obtained by labelling followed by dehydrogenation and also by an unambiguous synthesis of the ketone (XV) starting from 2,6-dimethylcyclohexanone (*vide infra*).

Treatment of the derived six membered ring ketone (XIII) with methyl-lithium yields the carbinol (XXIX) which may be purified and dehydrogenated with selenium to furnish a substituted naphthalene identified as 1,4-dimethyl-6-isopropyl-naphthalene (XXVII). The m.p. of the picrate (101–102°), agrees with that reported for 1,4-dimethyl-6-isopropylnaphthalene picrate (102–103°).[24a] The sym-TNB adduct which analyses satisfactorily has a m.p. 135–136° after four crystallizations, though it is reported to melt at 144·5–146°.[24a] However, its identity as the derivative of 1,4-dimethyl-6-isopropylnaphthalene is confirmed by its NMR spectrum.* The mutual shielding and deshielding affects exerted by alkyl substituents has been used to assess the relative disposition of the alkyl substituents in the naphthalene nucleus.[25] The methyl protons in 1,4-dimethyl-6-isopropylnaphthalene are expected to give a signal at 158 c/s which is in good agreement with the observed values (156 and 158 c/s). If the structure (XXV) is correct these reactions through the corresponding derived ketone (XXX) should give 1,2-dimethyl-7-isopropylnaphthalene (XXVIII picrate m.p. 92–93·5°, sym.

* Measured in dil. CS_2 solution.

[22] P. Linstead, *Ann. Rep. Chem. Soc.* 33, 295 (1936).

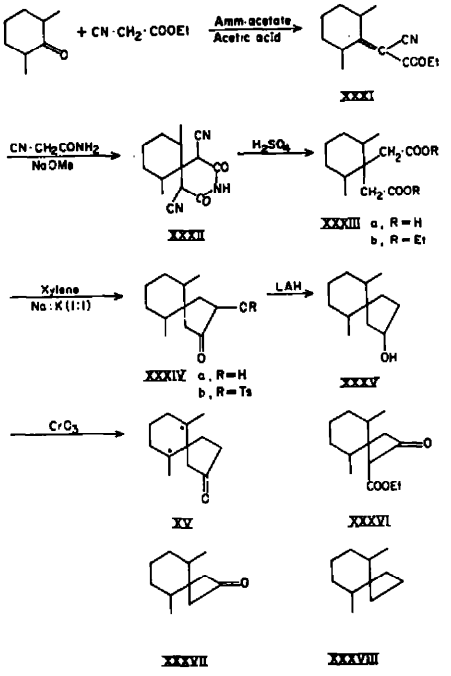
[23] V. Sykora, V. Herout, J. Pliva and F. Sorm, *Coll. Czech. Chem. Commun.* 23, 1072 (1958).

[24a] G. Krishna Rao and S. Dev, *J. Ind. Chem. Soc.* 33, 561 (1956);

[b] A. E. Bradfield, B. H. Hegde, B. S. Rao, J. L. Simonsen and A. E. Gillam, *J. Chem. Soc.* 668 (1936).

TNB adduct m.p. 108–110°)[24b] and the methyl signals should appear at 144 and 151 c/s.[25] These observations support Ia as the only possible structure for agarospirol and confirmed by an unambiguous synthesis of the derived ketone (XV) as detailed below:

CHART 3



The easiest route to the ketone (XV) is an approach through the diacid (XXXIIIa). As a trial experiment, the Guareschi condensation[26] of 2,6-dimethylcyclohexanone, was unsuccessful. Use of a stronger base (NaOMe)[27] also failed to furnish the Guareschimide (XXXII) as o-methyl groups are known to hinder this condensation.[26,38] However, Knoevenagel condensation of 2,6-dimethylcyclohexanone with cyanacetic ester to the alkylidene derivative (XXXI) was achieved by the Cope[28] procedure, though a large amount of the catalyst (NH_4OAc-HOAc) was necessary.

Michael addition of sodiocyanacetamide to the alkylidene ester using McElvain's procedure[27] gave 38% yield of the required β-(2,6-dimethylcyclohexyl)-α,α'-dicyanoglutarimide (XXXII), m.p. 254–55° which was hydrolysed with sulfuric acid to furnish a nearly quantitative yield of β-spiro-(2,6-dimethylcyclohexyl)-glutaric acid (XXXIIIa), m.p. 189°. As acyloin condensation of the diester (XXXIIIb) using a large excess of finely pulverized sodium in a dry inert atmosphere in boiling xylene, does not give the acyloin, the latter was obtained in good yield by using instead of sodium an alloy of sodium and potassium (1:1).[29] Quick chromatography of the

[25] B. A. Nagasampagi, R. C. Pandey, V. S. Pansare, J. R. Prahlad and S. Dev, *Tetrahedron Letters* **8**, 411 (1964).

[26] G. J. Handley, E. R. Nelson and T. C. Somevs, *Austr. J. Chem.* **13**, 127 (1960).

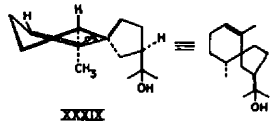
[27] S. M. McElvain and D. H. Clemens, *J. Amer. Chem. Soc.* **80**, 3917 (1958).

[28] A. C. Cope and E. M. Hancock, *Organic Syntheses* **25**, 46 (1945).

[29] For a similar case, see B. Eisert, G. Bock, K. Kosch, and F. Spalink, *Chem. Ber.* **93**, 1451 (1960).

reaction product on neutral alumina, deactivated with acetic acid, gave the pure acyloin (XXXIVa), though there was some loss of material. From the earlier fraction of chromatography the keto-ester (XXXVI) and the spiro-butanone (XXXVII), formed via Dieckmann condensation were isolated and characterized.

The IR spectrum of the acyloin shows strong split carbonyl bands of almost equal intensity at 1751 and 1703 cm^{-1} apart from the hydroxyl (3509 cm^{-1}) and spiro absorptions [1402 (w), 1346 (m), 1376 (w)] cm^{-1}. The presence of a band at 1439 may be attributed to the —CH_2—CO grouping. Lithium aluminium hydride reduction of the keto-tosylate (XXXIVb) gives the monol (XXXV) which on oxidation with chromic oxide* and chromatography furnishes small amounts of a hydrocarbon which appears to be XXXVIII together with the ketone (XV) as the major component. The IR spectrum of the synthetic ketone (XV) is almost superimposable on that of the ketone derived from agarospirol (Fig. 2), the difference being due to the stereochemical non homogenity of the derived product. The pure synthetic product shows the expected fine structure and unambiguously proves the correctness of structure (Ia) for agarospirol. Work on the stereochemistry and synthesis of agarospirol is in progress. However, based on the information now available, the most probable stereochemistry of agarospirol is depicted by XXXIX. In the NMR spectrum, the doublet for the tertiary methyl group in agarospirol shows a normal pattern. In the acetate this methyl group appears as five closely spaced signals whose total area corresponds to 3 protons. It is also remarkable that in the spectrum of the acetate all other features are retained with the exception of the shielding effect produced in the methyl protons of the side chain. The explanation for this abnormal splitting may be sought in some steric factor, which leads to congestion on passing from the alcohol to the acetate. The possibility of any rearrangement during the interconversion of agarospirol to the acetate and *vice versa* can be unequivocally ruled out even from the NMR spectra themselves and has been confirmed by saponifying pure agarospirol acetate to agarospirol; agarospirol thus generated on acetylation reforms the same acetate as above, as confirmed by their identical physical properties and spectral data.

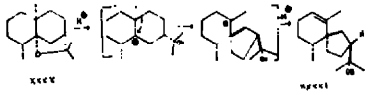


XXXIX

Studies with Dreiding models indicate that only one conformation is possible where the acetoxy-isopropyl side chain and the tertiary methyl group come unusually close together. In all the other possible models the two groups are too far apart to account for the above phenomenon of abnormal splitting. It would thus appear that agarospirol has the stereochemistry as in XXXIX. Such a geometry can also explain the difficulty encountered in acetylation in contrast to the facile saponification brought about by cold alcoholic alkali, a property not in accordance with the behaviour of tertiary alcoholic groups in many other molecules. The positive rotation of agarospirol acetate (+11·32°) as compared with the negative rotation (−5·7°) of agarospirol also supports the steric restriction imposed on the side chain of agarospirol acetate, readily explained by the geometry (XXXIX).

* This composite method of reduction of acyloin to the corresponding monoketone is the unpublished work of V. V. Dhekne of our laboratory.

The suggested structure for agarospirol does not represent a true isoprenoid. In view of the difference observed in the NMR spectra (Fig. 5) of the derived (XVa) and synthetic ketone further work is being undertaken to separate the two epimers from the derived ketone and also to collect additional evidences to substantiate the proposed structure and stereochemistry of agarospirol. Agarospirol may be biogenetically related to dihydroagarofuran (XXXX) another constituent isolated and studied from the same oil.[2] This view is strengthened by the presence in large amounts of alcoholic components *only* in the fungus infected wood. The following mechanism may be visualized:



The resulting stereochemical formulation (XXXXI), like the previously indicated

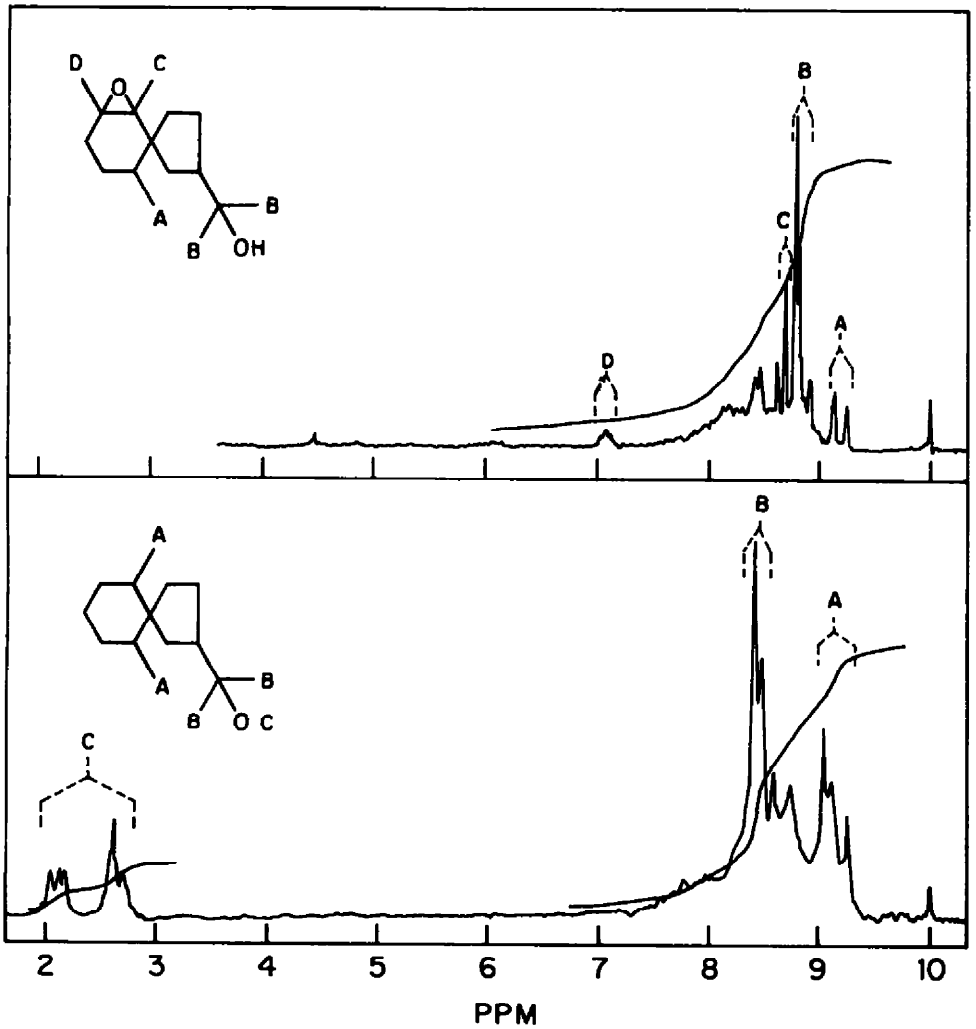


FIG 4

sterio formula (XXXIX), would also explain the abnormal NMR spectrum of agarospirol acetate. The formation of (XXXXI) involves a flipping of the six-membered ring to relieve 1:3-di-axial interaction of the two methyl groups at C_2 and C_6 to give the intermediate spiro carbonium ion.

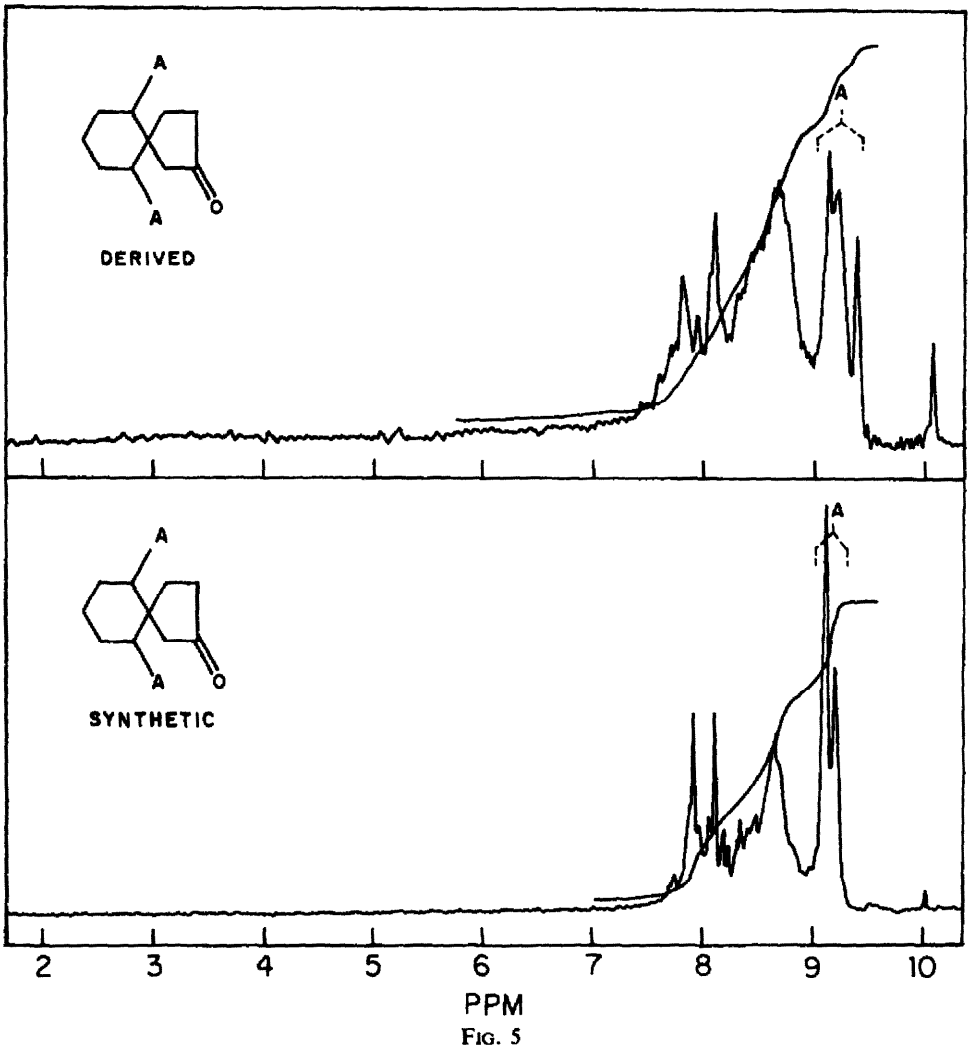


FIG. 5

EXPERIMENTAL

All m.ps are uncorrected, b.ps indicate the bath temp. Rotations were taken in chloroform solutions. The IR spectra were taken in liquid cells or as liquid films for liquids and as nujol mulls for solids on a Perkin-Elmer 137B Infracord spectrophotometer. UV spectra are recorded for ethanol solution on a Beckman DK2 instrument. The GLC analyses were carried out using polyester columns on a Perkin-Elmer model or a Griffin-George instrument operating under press. using H_2 as carrier gas. Pet. ether indicates the fraction b.p. 60–80°. Neutral alumina graded according to the Brockman scale[30] was used for chromatography.

[30] E. Lederer and M. Lederer, *Chromatography* p. 26 Elsevier, N.Y. (1957); H. Brockmann and H. Schödder, *Ber. Dtsh. Chem. Ges.* 74, 73 (1941).

Agarospirol acetate (Ib)

The alcoholic fractions of agarwood oil from the infected wood[3] were chromatographed over fifty-fold alumina (gr. II). The earlier fractions eluted with benzene were a mixture of ketonic and other oxygenated constituents studied earlier.[4] The latter fraction having comparable properties

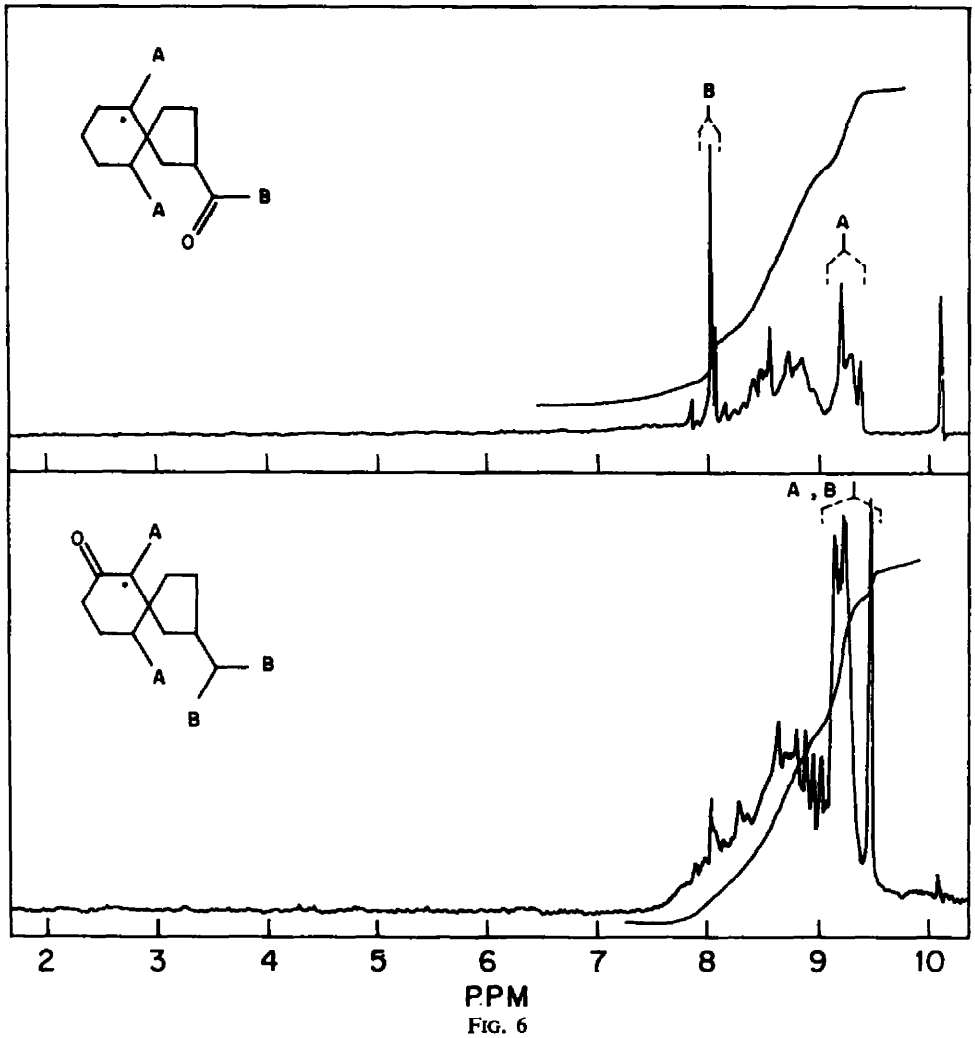


FIG. 6

(15 g) were mixed with freshly fused sodium acetate (15 g) and acetic anhydride (75 ml) and refluxed in an oil bath at 150–60° for 6 hr and worked up to give the crude acetate (17·7 g) which was chromatographed over alumina (gr. II, 160 fold). The material (1·7 g) eluted with pet. ether was identified as IV. The earlier fractions eluted with pet. ether–benzene (85:15) and showing comparable physical characteristics were mixed and distilled to furnish pure (GLC) agarospirol acetate (Ia, 10 g), b.p. 130°/0·5 mm, $(\alpha)_D^{28}$ +11·33° (*c*, 9·52), n_D^{28} 1·4892, mol.wt. 266·4 (saponification); ν_{max} 1730, 1253 cm^{-1} (ester); 813 cm^{-1} (trisubstituted double bond). NMR signals: 9·16, 9·1, 9·09, 9·06, 8·94 (3H, C_6 methyl), 8·57 (d, 6H, 1·5; C_7 side chain methyl protons), 8·37 (d, 3H, 2; C_2 methyl), 8·08 (S, 3H, acetoxy protons), 4·82 (broad, 1H, C_3 (3 proton). (Found: C, 77·3; 77·13; H, 10·8, 10·48. $C_{17}H_{28}O_2$ requires: C, 77·27; H, 10·6%). Attempted reduction with LAH in refluxing tetrahydrofuran gave back the starting material. The later fractions of chromatography (ν_{max} 1645, 888 cm^{-1}) are under investigation.

Agarospirol (Ia)

Agarospirol acetate (28·82 g) was mixed with alcoholic potash (110 ml, 10%) and left at room temp for 17 hr. The product was diluted with water (600 ml) and extracted with ether (3 × 150 ml) and the combined ether extracts washed with water, dried over Na_2SO_4 and the solvent removed to give the crude alcohol (24·5 g) which was freed from traces of unsaponified material (300 mg) by chromatography over alumina (gr. II, 500 g). The alcoholic fraction eluted with ether was distilled to furnish pure (GLC) agarospirol (Ia), as a colourless oil, b.p. 90–91°/0·1 mm, $(\alpha)_D^{27}$ −5·7° (*c*, 28·7), n_D^{27} 1·5080, d_{25}^{25} 0·9797; +ve tetranitromethane test, ν_{max} 1654, 813 cm^{-1} (trisubstituted double bond), 3472, 1149 cm^{-1} (t —OH); NMR signals:[21] 9·16, 9·06 (d, 3H, 6; C_6 methyl); 8·89, 8·83 (d, 6H, 3; C_8 side chain); 8·33 (broad d, 3H, 2; C_2 methyl), 4·85 (broad S, one H; C_3 proton). (Found: C, 80·67; H, 11·34. $C_{15}H_{26}O$ requires: C, 81·08; H, 11·71%). It did not give any solid hydroxy derivative. Attempted oxidation with chromic oxide–pyridine complex[7] yielded only the starting material. It resisted acetylation with acetic anhydride–pyridine; even under reflux only poor yields of acetate could be realized.

Dihydroagarospirol (IIIa)

Agarospirol (2·56 g) in glacial acetic acid (60 ml), containing PtO_2 (150 mg, pre-reduced) on stirring at 22° in an H_2 atm absorbed in the course of 5 hr H_2 (300 ml) equivalent to one double bond. The catalyst was filtered off, diluted with water (250 ml) and extracted with ether (3 × 75 ml). The combined ether extracts were washed with dil. Na_2CO_3 aq and water, dried over $NaSO_4$ and the solvent removed to furnish the crude product (2·57 g) which was chromatographed over alumina (gr. III, 40 g). Elution with pet. ether failed to elute any hydrogenolysis product. Total elution with benzene (200 ml) followed by distillation furnished dihydroagarospirol (IIIa, 2·49 g) as a viscous oil, b.p. 118°(bath)/0·4 mm, $(\alpha)_D^{27}$ +18·94° (*c*, 12·98), n_D^{26} 1·4962, ν_{max} 3490, 1146 cm^{-1} (t —OH); −ve tetranitromethane test; NMR signals: 9·30, 9·18, 9·10 (t, 6H; superimposed C_2 and C_6 methyls); 8·87, 8·91 (d, 6H, 3; C_8 side chain). GLC analysis showed it to be a mixture of two epimers (56:44). Attempted oxidation with chromic oxide in glacial acetic acid yielded the starting material. It did not give any solid ester derivative. (Found: C, 80·17; H, 12·51. $C_{15}H_{28}O$ requires: C, 80·37; H, 12·50%).

Hydrogenation of agarospirol using PtO_2 in ethanol or ethyl acetate and with Pd-C (10%) in the same solvents gave comparable results.

Epoxy agarospirol (II)

Agarospirol (1·0 g) in chloroform (10 ml) was cooled in ice and mixed with a chloroform solution of perbenzoic acid (0·92N; 1·2 mole) and left in the cold for 24 hr. The chloroform solution was washed with dil. Na_2CO_3 aq and water, dried over Na_2SO_4 and the solvent removed under red. press. to furnish the epoxide (0·95 g) whose IR spectrum exhibited weak ν_{max} 1712 cm^{-1}, due to partial isomerization to the ketone. Crystallization from pet.ether gave shining cylindrical rods of epoxy agarospirol (II, 300 mg), m.p. 109–110°, $(\alpha)_D^{28}$ +44·78°; ν_{max} 1113, 1117, 1073, 860 cm^{-1} (epoxide), 3540 cm^{-1} (—OH); NMR signals 9·13, 9·25 (d, 3H, 7; C_6 methyl); 8·77 (s, 6H; C_8 side chain), 8·69 (s, 3H; C_2 methyl); 7·1 (t, one H, 5; C_3 proton). (Found: C, 75·54; H, 10·76. $C_{15}H_{26}O_2$ requires: C, 75·58; H, 11·00%).

The monoene (VIII)

(a) Dihydroagarospirol was benzoylated under the conditions used for agarospirol benzoate (*vide infra*) and the crude benzoate purified by chromatography over alumina and distilled to furnish pure dihydroagarospirol benzoate (IIIb) as a viscous oil, b.p. 180°/0·2 mm, $(\alpha)_D^{28}$ +0·72° (*c*, 5·6), n_D^{28} 1·5240. NMR signals: (Fig. 4) 9·03, 9·07, 9·12, 9·26 (6H, partly superimposed C_6 and C_2 methyls); 8·40, 8·48 (d, 6H, 4; C_7 side chain); 2·63 and 2·07 (5 aromatic protons). It could not be induced to crystallize. (Found: C, 80·58; H, 9·96. $C_{22}H_{32}O_2$ requires: C, 80·48; H, 9·754%).

(b) Pyrolysis of dihydroagarospirol benzoate under the conditions used for agarospirol benzoate (*vide infra*) followed by chromatography over alumina (gr. I, 70 fold) and distillation over Na gave in 90% yield the monoene (VIII), $(\alpha)_D^{27}$ +15·39° (*c*, 10·47), n_D^{20} 1·4920, ν_{max} 1642, 887 cm^{-1} (>C=CH_2).

[21] s, singlet; d, doublet; t, triplet. In the parenthesis, the nature of the signals (τ) corresponding number of protons, the splitting constant J (c/s) and the assignments follow in that order.

NMR signals: 9·25, 9·18, 9·10 (superimposed C_6 and C_2 methyls); 8·28 (d, 3H, 1·5; C_{11} methyl); 5·40 (S, 2H, C_{13} unsaturated methylene protons). (Found: C, 87·11; H, 12·53. $C_{15}H_{26}$ requires: C, 87·32; H, 12·69%). It could not be successfully resolved by GLC into the two epimers.

The ketones (XIV *and* XVa)

The monoene (VIII, 3·45 g) in dry chloroform (60 ml) was ozonized at ice temp for 6 hr (~120 mg of ozone/hr). The solvent was removed under red. press. and the residue heated with water (30 ml) for 3 hr on a water bath. The volatile vapours were collected in a cold water trap and divided into two portions. One portion gave formaldimedone, m.p. 188°, undepressed by an authentic sample. The weight of the crude formaldimedone corresponded to about 60% of isopropenyl moiety. The other portion gave iodoform, m.p. 119° (alc-water), the weight of the crude iodoform corresponding to about 15% of isopropylidene moiety.

The non-volatile portion was extracted with ether and worked up to give an oil (3·0 g) which was chromatographed over alumina (gr. III, 150 g). Elution with pet. ether (100 ml) furnished unreacted hydrocarbon (965 mg). Further elution with pet. ether (100 ml) furnished a mixture of the ketone (XIV; ν_{max} 1709 cm $^{-1}$) and an ester[32] (ν_{max} 1733, 1242 cm^{-1}) which were separated by saponification followed by chromatography (the ketonic portion was identified as XIV while the alcoholic portion on oxidation gave XVa). Further elution with pet. ether (900 ml) gave the ketone (XIV, 815 mg) which was further purified by rechromatography to furnish an analytical specimen, b.p. 140°(bath)/3·5 mm, $(\alpha)_D^{27}$ - 0·35° (*c*, 6·0); ν_{max} 1709, 1370, 1348 cm^{-1} (—$CO.CH_3$); +ve iodoform test; NMR signals: 9·27, 9·20, 9·1 (t, 6H; superimposed methyls at C_2 and C_6); 8·43 (s, one H; C_6 proton); 7·86 (S, 3H, —$CO.CH_3$). (Found: C, 80·26; H, 11·53. $C_{14}H_{24}O$ requires: C, 80·67; H, 11·61%). It gave a mixture of epimeric 2,4-dinitrophenylhydrazones which were separated by fractional crystallization (ethanol) and gave m.ps 147–149° and 118–123° (more soluble). Thin layer chromatography showed that both derivatives were fairly pure (Found: N, 14·53 and 14·28 respectively. $C_{20}H_{28}N_4O_4$ requires: N, 14·43%). The mixture of two epimeric semicarbazones showed m.p. 193–95° (alcohol) (Found: C, 68·92; H, 10·26; N, 15·82. $C_{15}H_{27}N_3O$ requires: C, 68·79; H, 10·28; N, 16·74%).

Further elution of the initial column with pet. ether–benzene (9:1) furnished a product (513 mg) which was purified by rechromatography over alumina to yield the ketone (XVa), b.p. 130°(bath)/3·5 mm, ν_{max} 1709, 1733 cm^{-1} (cyclopentanone); 1397 (w), 1370 (m), 1342 (w) cm^{-1} (spiro system). GLC analysis showed an approximate epimer ratio (45:55). Repeated fractional crystallization from ethanol gave two epimeric 2,4-dinitrophenylhydrazones, m.p. 194–196° and 201–203°. Both were fairly pure by TLC. (Found: N, 15·32; 15·80 respectively. $C_{15}H_{24}N_4O_4$ requires: N, 15·55%).

Baeyer-Villiger oxidation of the ketone (XIV)

To the ketone (XIV, 450 mg) in chloroform (5 ml), containing a catalytic amount of *p*-toluenesulfonic acid, was added in the cold, a chloroform solution of perbenzoic acid (6 ml, 0·9 N) and the mixture left ice cold for 48 hr. The product was found to be constituted mainly of the ester [ν_{max} 1740(s), 1242(s) cm^{-1}]. Saponification by refluxing for 1 hr with alcoholic potash (10 ml, 5%) followed by chromatography over alumina (gr. III, 7 g) furnished the pure alcohol (212 mg; ν_{max} 3356, 1020 cm^{-1}) free of the ketone. The alcohol, in glacial acetic acid (3 ml), was mixed with a solution of CrO_3 (150 mg) in acetic acid (3 ml) containing water (3 ml) and left at room temp for 3 hr. Excess of CrO_3 was decomposed with methanol, diluted with water (30 ml), extracted with ether (3 × 20 ml), the combined ether extracts washed with dil. Na_2CO_3 aq and water, dried over Na_2SO_4 and the solvent removed to furnish the crude ketone which was chromatographed over alumina (gr. III, 3 g). Elution with pet. ether–benzene (8:2, 30 ml) furnished the ketone (XVa), b.p. 130°(bath)/3·0 mm. The IR spectrum was superimposable on that of the ketone obtained by ozonolysis; the triplet at 1397, 1370 and 1342 cm^{-1} in the IR spectrum is attributable to a spiro system. It gave the same 2,4-dinitrophenylhydrazones mentioned above. (Found: C, 79·83; H, 11·35. $C_{15}H_{20}O$ requires: C, 80·0; H, 11·20%). NMR signals: 9·08, 9·19, 9·33 (two tertiary methyl groups), 8·63 (six-membered ring protons), 7·77, 7·89, 8·06 (6H, t, 17; five-membered ring protons).

[32] Formation of esters during ozonization is not without precedents. For example, see J. Pasero, L. Comeau and M. Naudet, *Bull. Soc. Chim., Fr.* 1794 (1963).

The lactone (XVI)

The ketone (XVa, 30 mg) in chloroform (2 ml) containing a catalytic amount of *p*-toluenesulfonic acid was mixed with a chloroform solution of perbenzoic acid (0·9 N, 3 ml) and left ice cold for 48 hr. The product was saponified by refluxing with alcoholic potash (5 ml, 5%) for 2 hr. It was diluted with water and extracted with ether (2 × 15 ml). The aqueous solution was acidified with HCl aq and extracted with ether (3 × 10 ml), the combined ether extracts washed with water, dried over Na_2SO_4 and the solvent removed to furnish the crude lactone which was passed over a column of alumina (gr. II, 500 mg) and eluted with benzene to furnish the pure lactone (XVI, 15 mg), ν_{max} 1762 cm^{-1} (Found: C, 74·25; H, 10·52. $C_{12}H_{20}O_2$ requires: C, 73·47; H, 10·21%).

The diene (IV)

(a) *Agarospirol benzoate.* To agarospirol (1·6 g) in pyridine (5 ml) was added benzoyl chloride (2 ml) and the mixture left at room temp for 24 hr. Water (30 ml) was added and the product heated on a water bath for 20 min cooled and extracted with ether. The combined ether extracts (100 ml) were washed with dil. Na_2CO_3 aq and water, dried over Na_2SO_4 and the solvent removed to furnish the crude benzoate whose IR spectrum showed absence of hydroxyl absorption. Chromatography over alumina (gr. II, 50 g) furnished the pure benzoate (Ic), b.p. 175°(bath)/0·2 mm, $(\alpha)_D^{27}$ +5·96°, n_D^{28} 1·5279. It could not be induced to crystallize (Found: C, 80·90; H, 9·52. $C_{22}H_{30}O_2$ requires: C, 80·91; H, 9·69%).

(b) Agarospirol benzoate (1·6 g) was pyrolysed by heating in an oil bath at 220–230° for 30 min at 100 ± 5 mm press. The material that distilled over was combined with the residue and filtered through a column of alumina (gr. I, 50 g) and eluted with pet. ether (150 ml) to furnish the pure diene (IV, 1·03 g). Distillation over Na gave an analytical specimen, b.p. 118°/3·0 mm, $(\alpha)^{27}$ −1·98° (*c*, 14·64%), n_D^{27} 1·5046, d_{25}^{25} 0·9156; ν_{max} 3096, 1777, 1639, 888 cm^{-1} (>C=CH$_2$), 813 cm^{-1} (trisubstituted double bond); ε 210 mμ 3880; NMR signals: 9·06, 9·16 (d, 3H, 6; C_6 methyl), 8·27 (S, 6H, C_2 and C_{11} methyls), 5·37 (S, 2H; C_{13} unsaturated methylene protons), 4·78 (broad S, one H; C_3 proton). GLC analysis showed it to be a pure product. (Found: C, 88·08; H, 12·06. $C_{15}H_{24}$ requires: C, 88·24; H, 11·77%).

Attempted isomerization with N-lithioethylenediamine, perchloric–acetic acid, BF_3 ethereate or formic acid did not give any appreciable amount of conjugated product as checked by UV absorption measurements. In all cases, shifting of the methylene double bonds from the side chain, without creating conjugation could be observed in the IR spectra.

The monoene (V)

The diene (IV, 1·34 g) stirred in absolute methanol (60 ml) containing Pd-C (200 mg, 5%) was allowed to absorb H_2 (185 ml) equivalent to 1·08 double bond. The catalyst was filtered off and solvent removed to furnish the crude hydrocarbon which was a mixture of VI, V and IV in the ratio 10:75:15 by GLC analysis. Elaborate column chromatography over 1000 fold alumina (gr. I) collecting fractions of 25 ml each in pet. ether gave in the middle fractions in a pure condition (98%, GLC) the monoene (V, 0·70 g) which was distilled over Na to furnish an analytical specimen, b.p. 118°(bath)/3·3 mm, $(\alpha)_D^{28}$ +4·8° (*c*, 5·0), n_D^{30} 1·4900; ν_{max} 1656, 811 cm^{-1} (trisubstituted double bond), 1379, 1362 cm^{-1} (Isopropyl group); ε 210 mμ 2,600; ε 215, 2,200. NMR signals: 8·43 (d, 3H, 2, C_3 methyl); 4·80 (broad, S, one H; C_2 methyl) (Found: C, 87·01; H, 12·78. $C_{15}H_{26}$ requires: C, 87·32; H, 12·69%).

Agarospirane (VI)

The diene (IV, 500 mg) stirred in glacial acetic acid (20 ml) with PtO_2 (50 mg, pre-reduced) in an H_2 atm absorbed in the course of 4 hr, H_2 (132 ml) equivalent to 2·03 double bonds. Thereafter no absorption was noticed. The catalyst was filtered off, the filtrate diluted with water (60 ml), extracted with pet. ether and the combined pet. ether fractions (50 ml) washed free of acid, dried and solvent removed to yield the saturated hydrocarbon (480 mg) which was left ice cold for 24 hr in a chloroform solution of perbenzoic acid (5·0 ml, 0·52 N). The product was filtered through a column of alumina (25 g, gr. I) and the skeletal hydrocarbon (VI) eluted with pet. ether (50 ml). An analytical specimen, distilled over Na, showed b.p. 112°(bath)/3·0 mm, $(\alpha)_D^{30}$ +19·88° (*c*, 10·5), n_D^{31} 1·4772; ν_{max} 1379, 1361 cm^{-1} (isopropyl group); · ve tetranitromethane test; NMR spectrum: 9·32, 9·2, 9·17, 9·12, 9·08

(superimposed C_3, C_6 and C_{11} methyls). GLC analysis showed that it was a mixture of two epimers in the ratio (45:55). (Found: C, 87·0; H, 12·90. $C_{15}H_{28}$ requires: C, 86·48; H, 13·52%). The IR spectrum was different in the finger print region from that of an authentic sample of selinane (VII), $(\alpha)_D^{30}$ +14·19° (*c*, 5·4), n_D^{30} 1·4795, prepared by a similar process from dihydroeudesmol. Attempted isomerization of VI with BF_3 etherate in dry benzene (room temp, 24 hr) yielded starting material, identical in IR, NMR and other physical constants.

The epoxide (X)

The monoene (V, 3·25 g) in dry chloroform (10 ml) was mixed in the cold with a chloroform solution of perbenzoic acid (42 ml, 1·0 N) and left ice cold for 24 hr. Titration of an aliquot portion after this interval indicated consumption of 0·98 mole equivalent of peracid. The product, the crude epoxide (3·23 g), showed weak ν_{max} 3560 and 1713 cm^{-1} indicating the presence of hydroxyl and ketonic impurities. Chromatography over alumina (gr. II, 130 g) and elution with pet. ether gave in the middle fractions the epoxide (X, 2·2 g) which was 98% pure by GLC. An analytical specimen showed b.p. 120°(bath)/1 mm, $(\alpha)_D^{27}$ −11·32° (*c*, 6·185), n_D^{28} 1·4845; ν_{max} 901 cm^{-1} (epoxide); NMR signals: 7·20, 7·26 (d, one H, 4; C_3 proton), 8·80τ (S, 3H; C_3 methyl). (Found: C, 80·71; H, 11·77. $C_{15}H_{26}O$ requires: C, 81·08; H, 11·71%).

Attempted reduction with LAH in refluxing tetrahydrofuran gave an alcohol (~15%), ν_{max} 3560 cm^{-1} which was purified by chromatography and pyrolysed as the benzoate to furnish an hydrocarbon mixture, ν_{max} 888 cm^{-1} (medium, exocyclic double bond) and 813 cm^{-1} (w, trisubstituted double bond). (Found: C, 86·93; H, 12·54. $C_{15}H_{26}$ requires: C, 87·32; H, 12·69%).

Isomerization of the epoxide

To the epoxide (730 mg) in dry benzene (10 ml), BF_3 ethereate (0·3 ml) was added with cooling and the product left at room temp for 1 hr. The light brown coloured solution was washed with dil. Na_2CO_3 aq and water, dried and the solvent removed to furnish the crude product, ν_{max} 3571, 1709 cm^{-1}. Chromatography on alumina (gr. II, 40 g) furnished on elution with pet. ether and pet. ether–benzene (8:2) respectively, unreacted-epoxide (90 mg) and a ketone (300 mg); ν_{max} 1710 (s), 1422 (sh) cm^{-1}, $(\alpha)_D^{27}$ +15·70 (*c*, 9·175), n_D^{29} 1·4860. (Found: C, 81·66; H, 11·71. $C_{15}H_{26}O$ requires: C, 81·08; H, 11·71%), whose IR spectrum was superimposed on that of ketone (XIII) obtained by hydroboration and oxidation of monoene (V). Further elution with pet. ether–benzene (6:4) furnished a viscous oil (225 mg; presumably an enolic α-ketol), b.p. 160°(bath)/0·2 mm, $(\alpha)_D^{30}$ +2·43° (*c*, 8·62;)λ_{max} 292 mμ (ε 124), 237 mμ (shoulder) ε 743); ν_{max} 3425 (s), 1706 (s) 1613 cm^{-1}. (Found: C, 75·91; H, 11·15. $C_{15}H_{26}O_2$ requires: C, 75·63; H, 10·92%). This product was not further investigated. Repetition of the isomerization under different conditions (using also ether as solvent) gave comparable results.

The monol (XII)

To the monoene (V, 620 mg) in purified tetrahydrofuran (20 ml), containing a trace of anhydrous Zn chloride and cooled in ice, was passed diborane generated[10] by the addition of a solution of $NaBH_4$ (1·2 g) in pure, dry diglyme (20 ml) to a solution of BF_3 ethereate (15 ml) in diglyme (30 ml). The addition of diborane was over in 1·5 hr. After another hr at room temp, NaOH aq (10 ml, 12%) was added under ice cooling followed by H_2O_2 (10 ml, 30%) in the course of 1 hr and the mixture left at 0° for 2 hr. The upper layer of tetrahydrofuran was separated and the aqueous layer extracted with ether (3 × 30 ml). The combined organic layers were washed with water, dried over Na_2SO_4 and solvent removed to yield the crude monol (580 mg) which was chromatographed over alumina (gr. II, 10 g). Pet. ether (50 ml) eluted unreacted hydrocarbon (100 mg). Benzene eluted the alcoholic material (470 mg) which was distilled to furnish an analytical specimen of the monol (XII), b.p. 140° (bath)/0·8 mm, $(\alpha)_D^{27}$ +12·23° (*c*, 3·93), $n_D^{27.5}$ 1·4913; ν_{max} 3448, 1036 cm^{-1} (—OH); 1389, 1370 cm^{-1} (isopropyl group). GLC analysis on a polyazelate column showed the presence of two epimers in the ratio 30:70. (Found: C, 80·91; H, 12·70. $C_{15}H_{28}O$ requires: C, 80·37; H, 12·59%).

The ketone (XIII)

(a) To XII (170 mg) in glacial acetic acid (3 ml), CrO_3 (120 mg) was added in glacial acetic acid (4 ml) containing distilled water (3 drops) and the mixture left at room temp for 1 hr. It was diluted with water and extracted with ether. The combined ether extracts were washed with dil Na_2CO_3 aq

and water dried over Na_2SO_4 and the solvent removed to furnish the crude ketone which was chromatographed over alumina (gr. II, 10 g) and eluted with pet. ether–benzene (8:2, 50 ml) to furnish pure XIII (130 mg). Ether (40 ml) eluted unreacted alcohol (25 mg). The ketone was distilled to furnish an analytical specimen, b.p. 118°(bath)/0·35 mm, $(\alpha)_D^{27}$ +16·92° (*c*, 2·24), n_D^{27} 1·4833. It was a mixture of 2 epimers in the ratio 31:69 by GLC; ν_{max} 1712, 1424 cm^{-1} (six membered ring $CH_2.CO$); NMR signals: 9·37 (sharp S, <3H; J > 11 c/s, probably due to part of C_2 methyl), 7·83 (d, 3H, 5; C_2 and C_4 protons). (Found: C, 81·49; H, 11·79. $C_{15}H_{26}O$ requires: C, 81·08; H, 11·71%).

(b) The above mixture of epimers (XIII, 60 mg) was heated for 6 hr with a solution of K (100 mg) in absolute t-butanol (10 ml) on a water bath. The product was diluted with water and extracted with ether. The combined ether extracts were washed with water, dried over Na_2SO_4 and the solvent removed to furnish the ketone (48 mg) which was found to be a mixture of epimers in the ratio (13:87) by GLC and was totally converted to the 2,4-dinitrophenylhydrazone which was initially obtained as a liquid and was chromatographed over alumina (10 g, gr. II). Elution with pet. ether–benzene (9:1, 30 ml) gave 10 mg of material. Further elution with pet. ether–benzene (1:1, 20 ml) gave 26 mg derivative, m.p. 179–180° (shining orange needles from ethanol). Benzene (30 ml) eluted impure material (5 mg). (Found: C, 83·11; H, 9·69; N, 21·00. $C_{21}H_{30}N_4O_4$ requires: C, 83·45; H, 9·93; N, 21·19%).

The trans-*diol* (XIb)

The epoxide (X, 1·0 g) was heated for 2 hr on a water bath with glacial acetic acid (10 ml). The acetic acid was removed under red. press. and the product chromatographed over alumina (gr. II, 30 g). Elution with pet. ether–benzene (8:2, 100 ml) gave the impure enol-acetate (220 mg) as a by-product, ν_{max} 1733, 1235 (ester), 1631, 878 (>C=CH_2), 843 (825) cm^{-1} (trisubstituted double bond). This was saponified with alcoholic alkali and the 2,4-dinitrophenylhydrazone prepared and purified by chromatography, m.p. 177–179° identified as the derivative of XIII by mixed m.p.

Further elution of the original column with ether (100 ml) gave XIa (620 mg) which was saponified by refluxing with alcoholic potash (10 ml, 20%) and purified by chromatography over alumina (gr. III, 25 g) and distilled to furnish an analytical specimen of the *trans*-diol (XIb), b.p. 133°(bath)/0·13 mm, $(\alpha)_D^{28}$ +9·8° (*c*, 6·5), n_D^{28} 1·5028; ν_{max} 3521 (strong, —OH). NMR signals: 8·88 (S, 3H; C_2 methyl); 9·35, 9·23, 9·18, 9·07, 9·02 (other methyls); 6·56 (S, one H; C_3 proton). (Found: C, 76·28; H, 11·86. $C_{15}H_{28}O_2$ requires: C, 76·02; H, 11·67%). It did not react with sodium metaperiodate under varied conditions.

The cis-*diol* (XIb)

The monoene (V, 800 mg) was mixed with a solution of OsO_4 (1·0 g) in dry ether (25 ml) containing dry pyridine (4 ml) and left for 6 days. The chocolate coloured precipitate was filtered off and refluxed for 4 hr with a mixture of benzene (50 ml), methanol (50 ml), water (50 ml), KOH (5·0 g) and mannitol (5·0 g). The mixture was diluted with water (100 ml), the benzene layer separated and the aqueous layer extracted with benzene (3 × 50 ml). The combined benzene extracts were washed with water and the solvent removed to furnish the *cis*-diol (690 mg) which was chromatographed over alumina (gr. III, 15 g). Pet. ether (70 ml) eluted unreacted hydrocarbon (280 mg). Benzene–ether (9:1, 50 ml) eluted the *cis*-diol (XIb, 380 mg), b.p. 140°(bath)/0·15 mm, n_D^{28} 1·5060, ν_{max} 3584 cm^{-1} (strong, —OH). (Found: C, 75·71; H, 11·56. $C_{15}H_{28}O$ requires: C, 75·02; H, 11·67%).

Hydroxy aldehyde (XXI)

The *cis*-diol (XIb, 150 mg) in dioxane (6 ml) was stirred with a solution of sodium metaperiodate (150 mg) in water (13 ml) for 3 hr, diluted with water, extracted with ether, the ether extracts washed with water and the solvent removed at 40°. The last traces of moisture and dioxane were removed by adding benzene and removing the solvent under red. press. at 40°. The product (XXI, 135 mg) showed ν_{max} 3603 (broad, —OH), 2770, 1730 cm^{-1} (broad, aldehyde); positive Fehling's test, negative iodoform test; ε 240–247 mμ, 140–170; NMR signal: 0·2 (broad, about one H, aldehyde proton). Distillation *in vacuo* did not lead to any appreciable dehydration as checked by UV measurements.

Ozonization of the monoene

The monoene (V, 750 mg) in dry ethyl acetate (25 ml) was cooled to −20° and a stream of ozonized O_2 was bubbled in until absorption ceased (3·5 hr). Pd-C (150 mg, 10%) was added and the product

hydrogenated. Absorption of H_2 (110 ml) was over in 2 hr at atm. press. The catalyst was filtered off and the solvent removed under red. press. (below 40°) to afford a viscous oil (700 mg); ν_{max} ~3330 (broad, hydroxyl), 2762, 1745–1724 cm^{-1} (broad, aldehyde), 1637 cm^{-1} (sh); NMR signals: 0·2 (about one H, aldehyde proton, 3·0 (unreacted monoene, double bond proton), no signal attributable to a methyl ketone, positive Fehling's test, negative iodoform test. These results are comparable to those of XXI obtained by cleavage of the *cis*-diol.

The ester (XXII)

The above ozonization product (600 mg) in methanol (20 ml) containing Ag_2O (1·0 g) was stirred in the dark for 24 hr, after which KOH (300 mg) in methanol (5 ml) and water (3 ml) was added and stirred for another 24 hr. The product was diluted with water and extracted with ether. The aqueous layer was carefully acidified with dil. HCl aq in the cold, saturated with NH_4Cl and extracted with ether. The combined ether extracts (about 100 ml) were washed with water till free from mineral acid, dried and the solvent removed leaving the crude material (300 mg) which in ether (20 ml), was treated with the calculated amount of anethereal solution of diazomethane at 0°. Immediately, acetic acid was added to decompose excess diazomethane. The solvent was removed and the product distilled to furnish XXII (105 mg), b.p. 127°(bath)/0·2 mm, n_D^{28} 1·4720, ν_{max} 1722, 1178 (methyl ester), 1663 cm^{-1} (tetrasubstituted double bond in conjunction with ester carbonyl), λ_{max} 229 mμ (ε 7,800). NMR signals: 8·35 (broad S, about 3H; methyl on double bond), 6·39 (S, 3H; carbomethoxy protons). The compound was about 85% pure by GLC. No further purification was attempted. (Found: C, 75·36; H, 10·20. $C_{16}H_{26}O_2$ requires: C, 76·81; H, 10·40%).

1-Carbomethoxy-2-methyl-cyclopent-1-(2)-ene is reported[11] to absorb at λ_{max} 232 mμ (ε 11,100) and 1-carbomethoxy-cyclopent-1-ene at 222 mμ[11] (ε 11,500). Isolauranolic acid prepared according to Shive *et al.*[12] and esterified quickly with diazomethane gave an analytical specimen (GLC) of methyl isolauranolate (XXIII) λ_{max} 229 mμ (ε 9,850). (Found: C, 78·82; H, 10·42. Calc. for $C_{10}H_{16}O_2$: C, 78·96; H, 10·51%).

Dehydrogenation

Agarospirol (1·63 g) was heated with Se (1·6 g) in a N_2 atm. at 285–290° for 18 hr. The reaction product was totally eluted through a column of alumina (gr. I, 50 g) using pet. ether (300 ml). Traces of azulenes (20 mg, unidentified) were removed by washing with phosphoric acid and the non-azulenic portion (1·43 g) treated with an equal amount of picric acid in ethanol (20 ml) to furnish the crude picrate, the weight corresponding to approximately 31% conversion to the naphthalene compound which agrees well with the conversion calculated from UV (about 34%). Crystallization from ethanol gave eudalene picrate, m.p. 93–94·5°, undepressed on admixture with an authentic specimen. The picrate was decomposed by passing over a column of alumina (gr. I) to furnish a GLC pure sample of eudalene identical in UV and IR with an authentic sample. The TNB adduct was obtained as yellow needles, m.p. 110–111° (alcohol), undepressed on admixture with an authentic specimen.

The monoene (V), the diene (IV), the monoene (VIII) and the alcohol (IIIa) under comparable conditions gave respectively eudalene in 24–28, 32–34, 7–10 and 6·5–7·8% yields as estimated from the UV spectrum. Only traces of azulenic compounds were detected in each case.

The carbinol (XXIX)

Methyl-lithium[23] was prepared by adding methyl iodide (4·7 ml) to Li metal (1·4 g) in 5 pieces suspended in dry ether (40 ml) and stirring mechanically under reflux for 4 hr after which the excess Li was carefully removed.

To the clear solution, a solution of the ketone (XIII, 350 mg) in dry ether (10 ml) was added and the mixture refluxed with stirring for 48 hr. Excess of the reagent was decomposed with $NaSO_4$ aq containing some $Na_2S_2O_3$. The ether layer was washed with water, dried over Na_2SO_4 and the solvent removed to furnish the crude product which was separated from the unreacted ketone by chromatography over alumina (gr. II, 10 g) to furnish the pure carbinol (XXIX, 240 mg), ν_{max} 3490 cm^{-1} (—OH). (Found: C, 80·32; H, 12·34. $C_{16}H_{30}O$ requires: C, 80·67; H, 12·61%).

1,4-*Dimethyl-6-isopropylnaphthalene* (XXVII)

The carbinol (XXIX, 200 mg) was mixed with Se (200 mg) and dehydrogenated under the conditions used for agarospirol. The product was eluted through a column of alumina (gr. I, 10 g) with

[23] G. Stork and F. H. Clarke (Jr), *J. Amer. Chem. Soc.* **83**, 3114 (1961).

pet. ether and converted into the picrate, m.p. 101–102° after crystallizations from alcohol, sym-TNB adduct, m.p. 135–136° after 4 crystallizations from alcohol. (Found: C, 60·82; H, 3·2; N, 10·22. $C_{21}H_{21}N_3O_6$ requires: C, 61·32; H, 3·42; N, 10·22%). Lit. reports: m.p. 102–103° for the picrate and 144–145° for the sym-TNB adduct.[24a] (The picrate of 1,2-dimethyl-7-isopropylnaphthalene melts at 113–114·5° and sym-TNB adduct at 141–142°).[24b] The NMR spectrum of the TNB adduct (taken in dil. CS_2 solution) showed the isopropyl protons at 75 and 82 c/s and the methyl protons at 156 and 158 c/s. The aromatic protons appear at 559 c/s. The observed positions are in agreement with the calculated values[25] (158 c/s).

2,6-Dimethylcyclohexanone

6-Hydroxy-methylene-2-methylcyclohexanone was prepared from o-methylcyclohexanone (B.D.H. b.p. 161–162°/718 mm; pure by GLC; 2,4-dinitrophenylhydrazone, m.p. 141–143°; semicarbazone, m.p. 191–192°, Lit:[34] 143 and 191° respectively) by the method of Johnson and Posvic[35] in 80% yield and methylated by the method suggested by King and King[36] to get a mixture of o-methylcyclohexanone and 2,6-dimethylcyclohexanone (4:6, GLC) which was subjected once again to Johnson and Posvic hydroxy methylation[37a] to furnish in 62% yield 2,6-dimethylcyclohexanone, b.p. 173–174°/718 mm, 2,4-dinitrophenylhydrazone, m.p. 149–151° (shining orange red flakes from ethanol), semicarbazone m.p. 195–196°. Lit.[36,37b] reports 149–150° and 194–196° respectively.

The alkylidene ester (XXXI)

The method is essentially that of Cope[28] but for the large excess of catalyst and longer reaction time employed*. A mixture of 2,6-dimethylcyclohexanone (0·2 mole, 25·2 g) and ethyl cyanacetate (0·2 mole, 22·6 g) in dry benzene (30 ml) was mixed with glacial acetic acid (7·2 ml) and ammonium acetate (2·3 g) and refluxed in an oil bath at 165–170° with an azeotropic distillation head for 6 hr while 4·5 ml of the aqueous layer was collected. After the second and fourth hr more catalyst mixture (acetic acid and ammonium acetate) was added. The reaction mixture was washed with water, dried, solvent removed and fractionated. The material distilling upto 180°(bath)/13 mm was collected and again reacted 3 times. The higher boiling fractions were combined and distilled to get the pure alkylidene ester (15·4 g; 40% on the basis of ketone), b.p. 126–128°/0·5 mm, n_D^{28} 1·4855, ν_{max} 2212 (—C≡N); 1718 (broad), 1225 cm^{-1} (conjugated ester); 1570 cm^{-1} (=C—C≡N). (Found: C, 70·87; H, 9·10. $CH_{19}NO_{132}$ requires: C, 70·60; H, 8·60%).

β-2,6-Dimethylcyclohexylidene-α,α'-dicyanoglutarimide (XXXII)

According to the method of McElvain and Clemens,[27] to a cold solution of Na (2·08 g) in absolute methanol (75 ml), cyanacetamide (7·602 g) was added with stirring. To the clear solution, a solution of the alkylidene ester (XXXI, 10·0 g) in methanol (25 ml) was added in 3 installments. The mixture was left at room temp for 24 hr, diluted with water (200 ml) and extracted with ether (2 × 50 ml). The aqueous layer was acidified in the cold with dil. HCl. The separated oil solidified on freezing. Filtration and crystallization from a small volume of ethanol furnished XXXII (4·2 g, yield 38·3%). An analytical specimen was obtained as tiny white crystals, m.p. 254–55° (dec). (Found: C, 67·02; H, 5·95; N, 14·6. $C_{14}H_{17}N_3O_2$: requires C, 67·39; H, 6·092; N, 15·05%).

The diacid (XXXIIIa) *and the diester* (XXXIIIb)

(a) The above glutarimide (XXXII, 2·4 g) was mixed with conc. H_2SO_4 (6 ml) and water (1·6 ml) and heated for 1 hr at 170° in an oil bath with occasional shaking. To the black reaction mixture, water (10 ml) was added and refluxed for 1 hr during which time frothing was observed. The black precipitate was filtered off, dissolved in ethanol and decolourized with animal charcoal. Concentration of the alcoholic solution followed by addition of benzene precipitated the acid (1·83 g, yield 93%) which was once again purified in a similar manner to furnish an analytical specimen of XXXIIIa,

* According to a recent report in the literature (C. H. Grogan *et al. J. Med. Chem.* **6**, 388 (1963), 3,3,5-trimethylcyclohexanone does not undergo this condensation under the Cope conditions.

[34] R. B. Carlin and H. P. Landerl, *J. Amer. Chem. Soc.* **75**, 3919 (1953).

[35] W. S. Johnson and H. Posvic, *J. Amer. Chem. Soc.* **69**, 1361 (1947).

[36] F. E. King and T. J. King, *J. Chem. Soc.* 1373 (1954).

[37a] W. J. Bailey and M. Madloff, *J. Amer. Chem. Soc.* **76**, 2707 (1954);

[b] R. E. Ireland and J. A. Marshall, *J. Org. Chem.* **27**, 1619 (1962).

m.p. 189° (dec., no colour change), mol. wt. 234·8 (via acid equivalent; cal: 228·28). (Found: C, 63·28; H, 8·76. $C_{12}H_{20}O_4$ requires: C, 63·2; H, 8·77%).

(b) The diacid (XXXIIIa, 6·0 g) in absolute ethanol (20 ml) and benzene (40 ml) containing conc H_2SO_4 (0·2 ml) was azeotropically refluxed for 24 hr using silica gel in the flow-back tube during the later stages to absorb any moisture. The cooled reaction mixture was washed with dil. Na_2CO_3 aq and water, dried, and the solvent removed and the residue distilled to furnish the pure diester (XXXIIIb, 5·63 g, yield 83%), b.p. 110°/0·35 mm, ν_{max} 1726, 1176 (fork) cm^{-1} (ester). (Found: C, 67·87; H, 9·64. $C_{16}H_{28}O$ requires: C, 67·60; H, 9·98%). The purity was ascertained by GLC.

The dimethyl ester prepared by treatment with diazomethane showed NMR signals: 9·17, 9·06 (d, 6H, 6, two methyls), 8·75, 8·59 (ring protons), 7·79, 7·31 (S, 2H each, $—CH_2$ COOMe), 6·40, 6·42 (6H, methoxy protons).

The acyloin (XXXIVa)

A suspension of pulverized Na-K alloy (1:1) was prepared by stirring Na (2·0 g) and K (2·0 g) in dry refluxing xylene (400 ml) by vigorously stirring in an atmosphere of dry, oxygen free nitrogen for ½ hr during which time some xylene (50 ml) was distilled off. A solution of the diester (4·5 g, XXXIIIb) in dry xylene (50 ml) was added during 1 hr and the refluxing continued for another 1·5 hr with efficient stirring. The flask was surrounded by ice and the excess alloy decomposed with ethanol followed by stirring with dil. HCl aq (50 ml; 18%). The xylene layer was separated and repeatedly washed with water and the solvent removed under red. press. in a stream of N_2 to furnish the crude acyloin (2·54 g) which was chromatographed over acetic acid–deactivated alumina (gr. III, 40 g). Elution with pet. ether–benzene (85:15, 100 ml) gave material (1·2 g) which was a mixture of a saturated hydrocarbon, b.p. 183°(bath)/1·0 mm, $n_D^{28.5}$ 1·4688 (presumably a dimeric product which is under investigation), the keto ester (XXXVI) and ketone (XXXVII) separated by further chromatography to pure XXXVI (210 mg), ν_{max} 1786, 1745, 1445, 1408, 1383, 1342 and 1176 cm [1]. (Found: C, 71·84; H, 8·73; $C_{15}H_{22}O_3$ requires: C, 72·01; H, 8·80%) and pure XXXVII (620 mg), b.p. 135°(bath)/4·0 mm, ν_{max} 1780 cm [1]. (Found: C, 79·43; H, 10·65. $C_{11}H_{16}O$ requires: C, 79·52; H, 10·85%). 2,4-Dinitrophenyl hydrazone m.p. 121–123° crystallized from alcohol. (Found: N, 15·51; $C_{18}H_{22}N_4O_4$ requires: N, 15·64%). Elution with ether (150 ml) furnished the pure enolic acyloin (XXXIVa, 810 mg), b.p. 128°(bath)/0·1 mm, ν_{max} 3509 (S, —OH), 1751, 1706, (split carbonyl bands due to CO—CH(OH) 1639 cm^{-1} (C=C), 1439 (CH_2—CO), 1402 (m), 1376 (s), 1346 (m) cm^{-1} (spiro-system) which was subjected to short-path distillation under high vacuum. (Found: C, 73·23; H, 9·98. $C_{12}H_{20}O_2$ requires: C, 73·47; H, 10·11%).

The synthetic ketone (XV)

(a) The acyloin (XXXIVa, 800 mg) in dry pyridine (10 ml) was mixed with a solution of *p*-toluene sulfonyl chloride (1·5 g) in dry pyridine (10 ml) and left at room temp for 48 hr. The product was diluted with water (60 ml) and extracted with ether (3 × 30 ml). The combined ether extracts were washed with dil. HCl aq and water and the solvent removed to furnish the keto-tosylate (XXXIVb, 1·32 g). Its IR spectrum showed complete absence of hydroxyl absorption.

(b) The crude tosylate in dry ether (20 ml) was added to a suspension of $LiAlH_4$ (700 mg) in dry ether (30 ml) and stirred under reflux for 10 hr. Excess reagent was decomposed with aqueous alcohol followed by dil. HCl aq. The aqueous layer was washed once with ether and the combined ether extracts washed with dil. Na_2CO_3 aq and water, dried and the solvent removed to furnish the monol (XXXV, 513 mg) which was directly oxidized in acetic acid (15 ml) containing CrO_3 (500 mg) for 1 hr. The product was chromatographed over neutral alumina (gr. II, 20 g). Pet. ether (70 ml) eluted an hydrocarbon (140 mg) presumably XXXVIII. Pet. ether–benzene (50 ml) eluted the synthetic ketone (XV, 200 mg), b.p. 117°(bath)/1·5 mm, ν_{max} 1735, 1708, 1433, 1370, 1340, 881 cm^{-1}. The IR spectrum was nearly superimposable on that of the derived ketone (XVa). (Found: C, 79·77; H, 11·27. $C_{12}H_{20}O$ requires: C, 80·00; H, 11·11%). NMR signals (Fig. 5); 9·17, 9·07 (d, 6H, 6·5, superimposed methyls), 8·60 (broad, six-membered ring protons), 8·06, 7·86 (6H, 13·5, five-membered ring protons).

GLC analysis on a polysuccinate column (6 ft) at 202° and H_2 flow rate (conditions under which the two epimers of the derived ketone (XVa) were resolved well enough for comparison) showed it to be identical with the second component, present in larger amount (55%) in the derived ketone. The 2,4-dinitrophenylhydrazone was obtained as orange plates m.p. 179–182°. (Found: N, 15·26.

[38] G. A. R. Kon and J. F. Thorpe, *J. Chem. Soc.* 686 (1919).

$C_{18}H_{34}N_4O_4$ requires: N, 15·55%), which showed a mixed m.p. of 178–184° on admixture with an equal amount of the derivative, m.p. 194–196° of the derived ketone. This difference is evidently due to the racemic nature of the synthetic product. The IR spectrum (in nujol) of the derivative of the synthetic ketone (m.p. 179–182°) was superimposable but for the relative intensities at certain points on that of the derivative of the derived ketone (m.p. 194–196°).

Acknowledgements—The authors take this opportunity to thank Dr. R. B. Bates, University of Arizona, whose conclusion from the NMR spectrum first led to the suspicion of a spiro-system in agarospirol and Dr. P. M. Nair for some helpful discussions on the NMR spectra at certain points. Our thanks are also due to Mr. V. S. Pansare and his colleagues for the micro-analyses, to Messrs. H. Gopinath, K. G. Deshpande and (Mrs.) H. V. Kamath for the IR and UV spectra and to Mr. B. V. Bapat and Dr. V. G. Naik for GLC analyses and to Mr. I. Mullah for the NMR measurements.