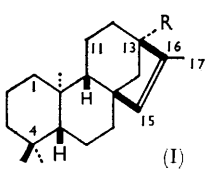
1158. *Diterpenes. Part IX.*[1] *Bromo-derivatives in the (+)-Phyllocladene and (−)-Isokaurene Series*

By LINDSAY H. BRIGGS, R. C. CAMBIE, P. S. RUTLEDGE, and D. W. STANTON

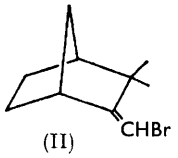
Allylic bromination of isokaurene with *N*-bromosuccinimide gives a mixture of 17-bromokaur-15-ene (V; R = Br) and 13-bromokaur-15-ene (I; R = Br). The formation of the latter bromide is the first example of successful bromination at a bridgehead with *N*-bromosuccinimide. Only 17-bromophylloclad-15-ene (XI; R = Br) is formed in the corresponding reaction with isophyllocladene while with 17-norphylloclad-15-ene (XIII), in which the only allylic position is at a bridgehead, the dibromide (XIV) is the only reaction product.

Bromination of phyllocladene with bromine in carbon tetrachloride forms 16,17-dibromophyllocladane (XX) which undergoes facile dehydrobromination to the allylic bromide, 17-bromophylloclad-15-ene (XI; R = Br). Bromination of isophyllocladene with one molecular equivalent of bromine does not result in addition but in allylic substitution to form the same bromide (XI; R = Br). With two molecular equivalents of reagent, however, bromination proceeds by substitution and addition to form 15α,16epi,17-tribromophyllocladane (XXI), a product which undergoes ready dehydrobromination to the unsaturated dibromide, 15α,17-dibromophylloclad-16-ene (XXII).

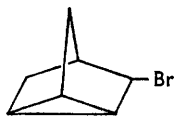
IN Part VIII [1] we reported, without discussion, the allylic bromination of (−)-isokaurene (I; R = H) with *N*-bromosuccinimide to give, in low yield, 13-bromokaur-15-ene (I; R = Br)* whose structure is now supported by its nuclear magnetic resonance (n.m.r.) spectrum. In addition to saturated methyl peaks at δ 0·80, 0·85, and 1·01, the spectrum exhibits a further three-proton peak at δ 1·26 assigned to a C-17 allylic methyl group,



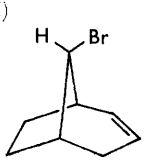
(I)



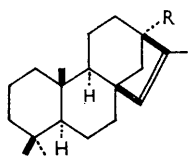
(II)



(III)



(IV)



(VI)

while a characteristic multiplet in the region δ 2·4—2·6 due to a C-13 proton in isokaurene derivatives [2] is absent. This is the first successful bromination at a bridgehead position

* The stereochemistry of (−)-kaurane has been defined in ref. 14.

[1] Part VIII, L. H. Briggs, R. C. Cambie, and P. S. Rutledge, *J.*, 1963, 5374.

[2] L. H. Briggs and R. C. Cambie, unpublished results.

with this reagent, all other attempts having failed to yield allylic bromination products. Thus, in the presence of a radical promoter, camphene gave a mixture of monobromides whose chief component was 8-bromocamphene (II)[3] while norbornene (bicyclo[2,2,1]-hept-2-ene) afforded 3-bromonortricylene (III).[4] Bicyclo[2,2,2]oct-2-ene also gave a mixture of products, the major one being *endo*-8-bromobicyclo[3,2,1]oct-2-ene (IV).[5]

The generally accepted mechanism of allylic bromination with *N*-bromosuccinimide involves an intermediate radical produced by removal of an allylic hydrogen atom.[6] In all the above examples the only allylic hydrogen atoms lie at bridgehead sites precluding resonance stabilisation of intermediate allylic radicals by contributions of forms involving a bridgehead double bond. Since the preferred configuration of radicals is planar, rigid bridgehead radicals would only be expected to form with difficulty and an ionic process has been suggested by Le Bel *et al.*[5] as a possible mechanism for the formation of the rearrangement products from norbornene and bicyclo[2,2,2]oct-2-ene.[5] They have also stated that the *N*-bromosuccinimide bromination of olefins having bridgehead allylic hydrogen atoms results in the generation of appreciable amounts of bromine in the reaction mixture. It is probably bromine generated in this way which accounts for the formation of 13-bromokaur-15-ene when isokaurene is treated with *N*-bromosuccinimide.

In addition to the C-13 bridgehead hydrogen atom, isokaurene possesses three further allylic hydrogen atoms of the C-16 methyl group, and the major product from the treatment[1] of (−)-isokaurene with *N*-bromosuccinimide has now been identified as the expected 17-bromokaur-15-ene (V; R = Br). Its n.m.r. spectrum showed the presence of only three quaternary methyl peaks at δ 0·80, 0·85, and 1·04, corresponding to the C-4 *gem* dimethyl and C-10 methyl groups, and a split two-proton peak at δ 4·20 ascribed to the C-17 protons. Hydrolysis with aqueous potassium carbonate gave the known allylic alcohol kaur-15-en-17-ol (V; R = OH),* which in turn yielded 17-methoxykaur-15-ene (V; R = OMe) on methylation by Purdie's method.

Inspection of Drieding models of (−)-isokaurene and isophyllocladene (VI; R = H) shows no difference in the relative environments of their C-13 bridgehead sites and C-16 methyl groups. It thus appeared possible that treatment of isophyllocladene with *N*-bromosuccinimide might lead to the formation of some 13-bromophylloclad-15-ene (VI; R = Br),† a potential intermediate for the synthesis of (−)-hibaene (VII).[7] Some support for this possibility arises from the fact that during our investigation of the structure and stereochemistry of isophyllocladene[8] it had been demonstrated that oxidation of isophyllocladene with ozone or potassium permanganate in dry acetone proceeded to a significant extent by allylic attack. In the latter case the direct isolation from the oxidation mixture of the lactonol (VIII) and of the hydroxy-aldehyde (IX; R = OH)‡, as its 2,4-dinitrophenylhydrazone, supported the view that allylic hydroxylation had taken place before fission of the bridge ring had occurred. Such a pathway provides a laboratory analogy

* Alone, the formation of the alcohol cannot be taken as unequivocal evidence of structure (V; R = Br) for the bromide since the αβ-unsaturated alcohol could be produced by hydrolysis of a C-15 allylic bromide *via* a mesomeric cation.

† The stereochemistry of phyllocladane has been defined in ref. 8.

‡ We have recently shown[9] that the structure (X) previously assigned to this product is incorrect. This followed from a comparison of the n.m.r. spectrum of its 2,4-dinitrophenylhydrazone with that of the corresponding derivative of phylloclad-15-en-17-al (IX; R = H).

[3] J. D. Roberts and E. R. Trumbull, *J. Amer. Chem. Soc.*, 1949, **71**, 1630.

[4] J. D. Roberts, E. R. Trumbull, W. Bennett, and R. Armstrong, *J. Amer. Chem. Soc.*, 1950, **72**, 3116.

[5] N. A. Le Bel, J. E. Huber, and L. H. Zalkow, *J. Amer. Chem. Soc.*, 1962, **84**, 2226.

[6] C. Djerassi, *Chem. Rev.*, 1948, **43**, 271; J. M. Tedder, *Quart. Rev.*, 1960, **14**, 336.

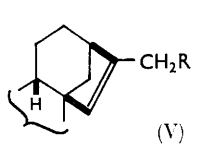
[7] (*a*) Y. Kitahara and A. Yoshikoshi, *Tetrahedron Letters*, 1964, 1771; (*b*) R. D. H. Murray and R. McCrindle, *Chem. and Ind.*, 1964, 500; (*c*) A. H. Kapadi and S. Dev, *Tetrahedron Letters*, 1964, 275; (*d*) L. H. Briggs, R. C. Cambie, P. S. Rutledge, and D. W. Stanton, *Tetrahedron Letters*, 1964, 2223; (*e*) E. Wenkert, P. W. Jeffs, and J. R. Mahajan, *J. Amer. Chem. Soc.*, 1964, **86**, 2218.

[8] L. H. Briggs, B. F. Cain, R. C. Cambie, and B. R. Davis, *J.*, 1962, 1840.

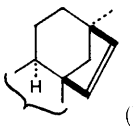
[9] L. H. Briggs, R. C. Cambie, and D. W. Stanton, *Chem. and Ind.*, 1965, 515.

for the position and stereochemistry of hydroxylation in the naturally occurring diterpenoids, gibberellic acid, gibberellins A_1, A_5, A_6, and A_8,[10] and steviol.[11]

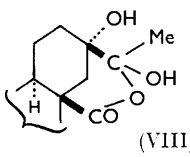
However, treatment of isophyllocladene with *N*-bromosuccinimide, with or without the presence of a radical promoter and for long periods of reflux, gave, as the sole product, 17-bromophylloclad-15-ene (XI; R = Br)* whose structure was adduced from the following evidence. The infrared spectrum exhibited strong bands at 837 and 847 cm.$^{-1}$, indicating that the product still possessed a trisubstituted double bond as in isophyllocladene.



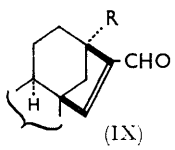
(V)



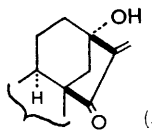
(VII)



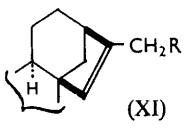
(VIII)



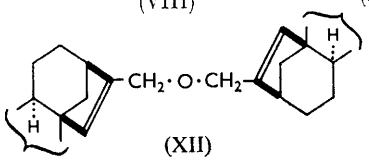
(IX)



(X)



(XI)



(XII)

In these and succeeding diagrams the bracket denotes a derivative of phyllocladane where H-9 has the α-configuration and a kaurane derivative where it has the β-configuration.

Its n.m.r. spectrum showed the presence of only three methyl peaks at δ 0·74, 0·82, and 0·85, corresponding to the C-10 methyl and C-4 *gem*-dimethyl groups,[12] respectively, and a one-proton olefinic peak at δ 5·84 split by long-range coupling with one or more allylic protons. A split peak at δ 4·06 corresponded to two protons and could be ascribed to the grouping HC:C(C)·CH_2Br (cf. δ 3·93 for allyl bromide[13]). Further support for structure (XI; R = Br) was obtained by hydrolysis with aqueous potassium carbonate to the known allylic alcohol phylloclad-15-en-17-ol (XI; R = OH).[14] Finally, hydrogenolysis of the bromide occurred during hydrogenation over a palladium catalyst since isophyllocladene was isolated as one of the products. This result would be unlikely for a C-13 halide since reduction of a bridgehead halogen atom would be expected to be more difficult than the hydrogenation of a double bond.[11,15]

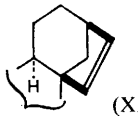
Reactivity of the allylic bromide was shown by the formation of the methyl ether (XI; R = OMe) when it was treated with methanolic potassium hydroxide. A quantitative yield of this ether was formed on methylation of the allylic alcohol (XI; R = OH) by Purdie's method. Besides phylloclad-15-en-17-ol (XI; R = OH), hydrolysis of the allylic bromide gave a minor product whose polarity was less than that of the alcohol. Its n.m.r. spectrum was virtually identical with that of phylloclad-15-en-17-ol except for the absence of a hydroxyl resonance and for the fact that its integrated proton count was 31. From its molecular formula, $C_{42}H_{62}O$, determined from elemental analysis, the absence of hydroxyl absorption but the presence of an ether band (at 1067 cm.$^{-1}$) in the infrared spectrum, and the integrated n.m.r. spectrum, the compound was formulated as the ether (XII). Its

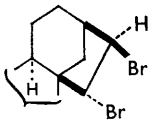
* Treatment of phyllocladene with *N*-bromosuccinimide also gave the same bromide but in lower yield. For the *N*-bromosuccinimide bromination of a similar compound with a 9β-hydrogen which also afforded a rearranged allylic bromide see W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Amer. Chem. Soc.*, 1963, **85**, 2342.

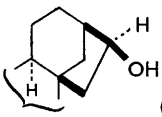
[10] J. F. Grove, *Quart. Rev.*, 1961, **15**, 56.
[11] E. Mosettig, U. Beglingler, F. Dolder, H. Lichti, P. Quitt, and J. A. Waters, *J. Amer. Chem. Soc.*, 1963, **85**, 2305.
[12] P. R. Jefferies, R. S. Rosich, and D. E. White, *Tetrahedron Letters*, 1963, 1793; see also ref. 7*d*.
[13] N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, Varian High Resolution N.M.R. Spectra Catalogue, 1962, spectrum No. 24.
[14] L. H. Briggs, B. F. Cain, R. C. Cambie, B. R. Davis, and P. S. Rutledge, *J.*, 1962, 1850.
[15] However, cf. the ready reduction of 1-bromobicyclo[2,2,2]octane, C. A. Grob, M. Ohta, E. Renk, and A. Weiss, *Helv. Chim. Acta*, 1958, **41**, 1191; U. Schöllkopf, *Angew. Chem.*, 1960, **72**, 147.

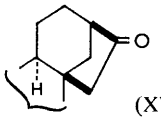
derivation by nucleophilic attack of the alkoxide anion on unreacted allylic bromide is clear, and its structure was confirmed by a Williamson synthesis which afforded the ether in 46% yield.

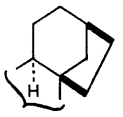
In view of the failure to introduce a bromine atom into the C-13 bridgehead position of isophyllocladene, an attempt was made to accomplish a similar objective by *N*-bromosuccinimide bromination of 17-norphylloclad-15-ene (XIII) in which the sole allylic position

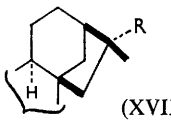

(XIII)


(XIV)


(XV)


(XVI)


(XVII)


(XVIII)

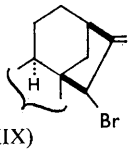
is at a bridgehead. However, the only product isolated from the reaction mixture other than starting material was a low yield of a dibromo-compound whose tentative configuration (XIV) is discussed later. This derivative was identical with the product obtained on bromination of 17-norphylloclad-15-ene with bromine in carbon tetrachloride. The formation of the dibromo-derivative (XIV) is not unexpected since it probably arises from the bromine generated from the *N*-bromosuccinimide.[5]

The 17-norphylloclad-15-ene required for the above experiment was obtained by heating the toluene-*p*-sulphonate of 17-norphyllocladan-16β-ol (XV) in refluxing quinoline according to Henderson and Hodges' method.[16] In addition, a new method [17] of preparing alkenes from ketones, involving the treatment of the derived thioketal in ketonic solvents with moderately active W-2 Raney nickel catalyst, which has been used with success with steroidal ketones, was applied to 17-norphyllocladan-16-one (XVI). Conversion of the norketone into the ethylene dithioketal proceeded in good yield in the presence of boron trifluoride etherate, but desulphuration of the product over W-2 Raney nickel afforded a mixture of 17-norphyllocladane (XVII) (78%) and 17-norphylloclad-15-ene (22%) as determined by gas–liquid chromatography. The mechanism of normal desulphuration to form an alkane involves chemisorption of the sulphur atoms on the surface of the catalyst followed by homolytic fission of the carbon–sulphur bond,[18] further reactions then proceeding either by hydrogenation or by recombination of the radicals. Djerassi and Williams [19] also reported the presence of alkenes among the desulphuration products of steroidal ethylene dithioketals, and demonstrated that alkene formation is favoured by a high catalyst-to-substrate ratio and the use of deactivated W-7 Raney nickel. They suggest that the formation of an alkane proceeds as above with the formation of a di-radical which gains two hydrogen radicals from the catalyst to give a thioether which then undergoes subsequent desulphuration. However, if the concentration of hydrogen radicals is low the di-radical could yield a thioenol ether by intramolecular hydrogen-radical abstraction from an adjacent position. Subsequent desulphuration would then lead to the alkene. Application of such a mechanism would account for the observed products in the present case.

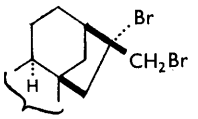
Prior to our successful preparation of the naturally occurring phyllocladan-16-ol (XVIII; R = OH),[20] 16-bromophyllocladane (XVIII; R = Br), the known hydrobromide

[16] R. Henderson and R. Hodges, *Tetrahedron*, 1960, **11**, 226.
[17] J. Fishman, M. Torigoe, and H. Guzik, *J. Org. Chem.*, 1963, **28**, 1443.
[18] G. R. Pettit and E. E. van Tamelen, *Org. Reactions*, 1963, **12**, 356.
[19] C. Djerassi and D. H. Williams, *J.*, 1963, 4046.
[20] T. Kondo, H. Imamura, and M. Suda, *J. Pharm. Soc. Japan*, 1959, **79**, 1298; *Bull. Agric. Chem. Soc. Japan*, 1960, **24**, 65.

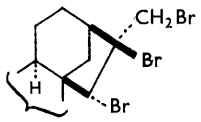
derived from both phyllocladene and isophyllocladene,[21] was treated with aqueous potassium carbonate and was also chromatographed on deactivated alumina. Both experiments led to the formation of isophyllocladene in almost quantitative yields,* the dehydrobromination being in marked contrast to the hydrolysis observed on similar treatment of 16-bromokaurane.[1] In view of this facile dehydrobromination it was proposed to treat in a similar manner the previously reported discrete dibromides [21] of phyllocladene and isophyllocladene in the hope of forming the allylic bromides (XI; R = Br) and (XIX). In the



(XIX)



(XX)



(XXI)

case of 16,17-dibromophyllocladane (XX), which probably possesses the stereochemistry shown, the allylic bromide (XI; R = Br) was readily formed by chromatography on alumina. The dibromo-compound (XX), prepared in quantitative yield by the action of bromine in acetic acid on phyllocladene, melted at 146°, considerably higher than recorded (122—125°) in the literature.[21] Its structure was consistent with its n.m.r. spectrum which exhibits a two-proton singlet at δ 3·90 corresponding to equivalent C-17 protons. Two protons at C-15 give rise to a doublet, centred at δ 2·41 and with a geminal coupling constant J = 6 c./sec., which overlies a one-proton multiplet centred at δ 2·52 due to the C-13 bridgehead proton.

Repeated attempts were made to form a dibromide of isophyllocladene by Uota's method,[21] using one molecular equivalent of bromine. In all cases the initial product was an oil and the reaction was characterised by the immediate liberation of hydrogen bromide on the addition of the bromine. When two molecular equivalents or more of bromine were added a solid, m. p. 134—136°, was readily prepared whose analysis and n.m.r. spectrum indicated that it was a tribromide. Chromatography of the latter on alumina afforded a further solid, m. p. 154°, corresponding to an unsaturated dibromide.

Closer investigation showed that when isophyllocladene was treated with bromine in acetic acid, chloroform, or carbon tetrachloride, allylic substitution occurred prior to addition. The oily product formed on the addition of one molecular equivalent of reagent consisted of a mixture of unreacted isophyllocladene and the major constituent, 17-bromophylloclad-15-ene (XI; R = Br), which was isolated with difficulty from the oil by chromatography on alumina followed by fractional crystallisation.

The solid product, m. p. 134—136°, obtained with two molecular equivalents or an excess of bromine, is tentatively formulated as 15α,16epi,17-tribromophyllocladane (XXI) in which the double bond of the initially formed allylic bromide had now been brominated. That 17-bromophylloclad-15-ene was indeed the precursor of the tribromo-derivative was shown by bromination of isophyllocladene with amounts of bromine intermediate between one and two molecular equivalents, and examination of the n.m.r. spectra of the products. As the amount of bromine was increased the olefinic peak in the spectrum of the product at δ5·84 gradually decreased in intensity and was replaced by a peak at δ 4·36 due to a C-15 proton adjacent to a bromine atom. The C-17 protons also showed a diamagnetic shift to δ 3·86 in the pure tribromide.

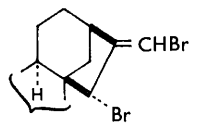
The tribromide was readily converted into an unsaturated dibromide, by chromatography on alumina and even to some extent by continued recrystallisation from acetone. On analogy with the stereochemistry of the tribromide (XXI), the dibromide is formulated as 15α,17-dibromophylloclad-16-ene (XXII). Its infrared spectrum showed strong double-bond absorption at 1645 cm.$^{-1}$ while its n.m.r. spectrum showed one-proton peaks at δ

* Dehydrochlorination of 16-chlorophyllocladane (XVIII; R = Cl) on alumina gave a mixture of isophyllocladene (60%) and phyllocladene (40%), as estimated from the infrared spectrum.

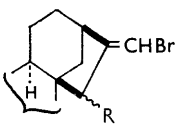
[21] H. Uota, *J. Dept. Agric. Kyushu Imp. Univ.*, 1937, **5**, 117 (*Chem. Abs.*, 1937, **31**, 7416).

6·53 and 5·26 corresponding to protons at C-17 and C-15, respectively, both of which were weakly split by allylic coupling. Hydrolysis of the unsaturated bromide with aqueous potassium carbonate replaced only the C-15 bromo-atom to give 17-bromophylloclad-16-en-15ξ-ol (XXIII; R = OH). Reaction with methanolic potassium hydroxide led to a mixture of 17-bromophylloclad-16-en-15ξ-ol and 17-bromo-15ξ-methoxyphylloclad-16-ene (XXIII; R = OMe) which was separated by chromatography on alumina.

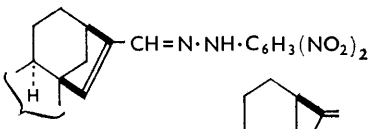
Confirmation that the position of the double bond in the unsaturated dibromide (XXII) is as shown follows from the position (δ 0·91) of the C-10 methyl group in its n.m.r. spectrum. The position corresponds to that of an unshielded methyl group as in phyllocladene (δ 0·92) and is quite distinct from that in all isophyllocladene derivatives (*ca.* δ 0·75) which show a marked upfield shift as a result of the shielding effect of the C-15 double bond.[2] The corresponding peak in the spectra of isokaurene derivatives occurs at δ 1·01—1·06, and indeed the n.m.r. spectra are diagnostic for distinguishing between the two systems.[2,22]



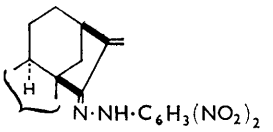
(XXII)



(XXIII)



(XXIV)



(XXV)

It is not possible to define with certainty the stereochemistry of the bromo-compounds (XIV), (XXI), and (XXII). Comment on the steric compression of the C-10 methyl group on a β-substituent at C-15 in the (+)-phyllocladane series but not in the (−)-kaurane series has already been made.[1,7d,22] For this reason structure (XIV), in which the C-15 bromine atom is in the more favourable α-configuration, is preferred for the product formed by the bromination of 17-norphylloclad-15-ene (XIII). If bromination occurs by a normal *trans* process then the bromine atom at C-16 will be in the β-position. In the case of the tribromide (XXI), attack at the C-15 atom of 17-bromophylloclad-15-ene (IX; R = Br) from the less hindered α-face would lead to the stereochemistry as shown. A further but less likely possibility of *cis*-addition exists on analogy with the anomalous *cis*-hydroxylation of isophyllocladene with peracetic acid.[2,8]

It is of interest to note that the anomalous bromination of isophyllocladene to yield the allylic bromide (XI; R = Br) parallels both the action of Prévost's reagent (silver benzoate–iodine) to give the corresponding allylic benzoate (XI; R = OBz),[14] and the reaction with 2,4-dinitrobenzenediazonium chloride to give the allylic derivatives (XXIV) and (XXV).[9]

Experimental

Infrared spectra, unless otherwise stated, were measured for potassium bromide discs with a Beckman IR2 or Perkin-Elmer Infracord spectrophotometer. N.m.r. spectra were measured for deuterochloroform solutions with a Varian A60 spectrometer with tetramethylsilane as internal reference. Light petroleum was of b. p. 40—60°, and alumina for chromatography was Spence Grade H. Optical rotations are for chloroform solutions. Derivatives of kaurene were prepared from the lævorotatory form.

16,17-*Dibromophylloclad*ane (XX).—A solution of phyllocladene (2·0 g.) in dry ether (30 c.c.) and glacial acetic acid (30 c.c.) was treated at 0° with bromine (1·2 g.) and the mixture kept at 20° for 12 hr. The dibromide (3·2 g.) crystallised from light petroleum as needles, m. p. 146°, $[\alpha]_D^{20}$ +10° (*c* 2·0) (lit.,[21] m. p. 122—123°, $[\alpha]_D^{18}$ +9·34°) (Found: C, 56·0; H, 7·6; Br, 37·1. Calc. for $C_{20}H_{32}Br_2$: C, 55·7; H, 7·5; Br, 36·8%); n.m.r. 0·80 and 0·85 (C-4 *gem*-dimethyl), 0·85 (C-10 methyl), 2·41 (doublet, J = 6 c./sec., C-15 protons), 2·52 (multiplet, C-13 proton), and 3·90 δ (singlet, C-17 protons); total protons, 32.

[22] C. A. Henrick and P. R. Jefferies, *Austral. J. Chem.*, 1964, **17**, 915; see also refs. 7*d* and 7*e*.

17-*Bromophylloclad*-15-*ene* (XI; R = Br).—A solution of 16,17-dibromophyllocladane (420 mg.) in light petroleum was percolated through alumina (50 g.; grade I—II). Removal of the solvent gave an oil (340 mg.) which crystallised from acetone to yield 17-*bromophylloclad*-15-*ene* as needles, m. p. 68—69°, $[\alpha]_D^{25}$ −28° (*c* 1·0) (Found: C, 68·4; H, 8·9; Br, 23·3. $C_{20}H_{31}Br$ requires C, 68·4; H, 8·9; Br, 22·8%), $\nu_{max.}$ 3049, 1616, 848, and 837 cm.$^{-1}$ (trisubstituted double bond); n.m.r. 0·74 (C-10 methyl), 0·82 and 0·85 (C-4 *gem*-dimethyl), 2·49 (broad multiplet, C-13 proton), 4·06 (doublet, C-17 protons split by allylic coupling with C-15 proton, $J < 1$ c./sec.), and 5·84 δ (doublet, C-15 proton split by allylic coupling); total protons 31.

Hydrogenolysis of 17-*Bromophylloclad*-15-*ene*.—Treatment of the above unsaturated bromide (3·5 g.) in methanol with hydrogen at 49 p.s.i. and 20°, over 10% palladium–charcoal for 25 hr. gave an oil (1·21 g.) and needles of isophyllocladene (910 mg.), m. p. and mixed m. p. 109—110° (identical infrared spectra).

Phylloclad-15-*en*-17-*ol* (XI; R = OH).—17-Bromophylloclad-15-ene (380 mg.), potassium carbonate (390 mg.), and water (40 c.c.) were heated under reflux for 6 hr., and the cooled mixture was extracted with light petroleum. Solvent was removed and diphylloclad-15-en-17-yl ether (7·5 mg.) separated from the resulting oil by trituration with light petroleum. Crystallisation of the remaining oil from light petroleum or chromatography on alumina gave phylloclad-15-en-17-ol (286 mg.) as needles, m. p. and mixed m. p. 126°, $[\alpha]_D^{20}$ +15° (*c* 1·0) (identical infrared spectra); n.m.r. 0·75 (C-10 methyl), 0·84 and 0·85 (C-4 *gem*-dimethyl), 1·69 (OH, exchanged with D_2O), 2·43 (broad multiplet, C-13 proton), 4·20 (doublet, C-17 proton split by allylic coupling, J = 1·2 c./sec.), and 5·69 δ (broadened doublet, C-15 proton split by allylic coupling with C-17 and C-13 protons); total protons 32.

Hydrogenation of the unsaturated alcohol (250 mg.) in ethanol (5 c.c.) over palladium–charcoal at 21 p.s.i. and 20° for 70 hr. followed by chromatography of the product from light petroleum on alumina gave phyllocladane (172 mg.), m. p. and mixed m. p. 74—75°, $[\alpha]_D^{25}$ +18° (*c* 2·2) (identical infrared spectra); n.m.r. 0·81 and 0·85 (C-4 *gem*-dimethyl), 0·89 (C-10 methyl), 0·98 (doublet, J = 7 c./sec., C-17 methyl), and 2·08 δ (multiplet, C-13 proton); total protons 34.

17-*Methoxyphylloclad*-15-*ene* (XI; R = OMe).—17-Bromophylloclad-15-ene (240 mg.), water (20 c.c.), methanol (14 c.c.), and potassium hydroxide (920 mg.) were heated under reflux for 6 hr. Most of the methanol was removed and the remaining mixture was extracted with light petroleum. Removal of solvent from the dried extracts gave 17-*methoxyphylloclad*-15-*ene* (181 mg.) which formed plates, m. p. 66—66·5° (from methanol), $[\alpha]_D^{25}$ −8° (*c* 4·2) (Found: C, 83·0; H, 11·3. $C_{21}H_{34}O$ requires C, 83·4; H, 11·3%), $\nu_{max.}$ 3030, 1639, and 839 (trisubstituted double bond) and 1100 cm.$^{-1}$ (aliphatic ether); n.m.r. 0·77 (C-10 methyl), 0·84 and 0·85 (C-4 *gem*-dimethyl), 2·40 (broad multiplet, C-13 proton), 3·35 (OMe), 3·97 (broad singlet, C-17 protons), and 5·70 δ (broad singlet, C-15 proton); total protons 34.

Methylation of phylloclad-15-en-17-ol (100 mg.) with methyl iodide (5 c.c.) and silver oxide (500 mg.) under reflux for 8 hr. also gave 17-methoxyphylloclad-15-ene (104 mg.), m. p. and mixed m. p. 66—66·5° (identical infrared spectra).

Diphylloclad-15-*en*-17-*yl Ether* (XII).—(*a*) The crude product from treatment of 17-bromophylloclad-15-ene (610 mg.) with potassium carbonate (470 mg.) and water (50 c.c.) as above, was chromatographed on alumina (grade II). Fractions eluted with light petroleum–benzene (1 : 1) crystallised from ethyl acetate to yield *diphylloclad*-15-*en*-17-*yl ether* (35 mg.) as needles, m. p. 142—144°, $[\alpha]_D^{25}$ −10° (*c* 3·0) (Found: C, 86·0; H, 11·0. $C_{40}H_{62}O$ requires C, 85·95; H, 11·2%), $\nu_{max.}$ 3003, 1634, 848 and 832 (trisubstituted double bond), and 1067 cm.$^{-1}$ (aliphatic ether); n.m.r. 0·76 (C-10 methyl), 0·83 and 0·85 (C-4 *gem*-dimethyl), 2·42 (broad multiplet, C-13 proton), 4·02 (broad singlet, C-17 protons), and 5·66 δ (broad singlet, C-15 protons); total protons 62.

Further fractions, eluted from the column with benzene and benzene–ether, gave phylloclad-15-en-17-ol (78%), m. p. and mixed m. p. 126—127°.

(*b*) A solution of phylloclad-15-en-17-ol (42 mg.) in dry benzene (2 c.c.) was added to a suspension of potassium (*ca.* 10 mg.) in dry benzene (2 c.c.) and the mixture was heated under reflux for 1 hr. 17-Bromophylloclad-15-ene (51 mg.) in dry benzene (2 c.c.) was added and the refluxing continued for 3 hr. The cooled mixture was then chromatographed on alumina, to yield diphylloclad-15-en-17-yl ether (37 mg.), m. p. and mixed m. p. 141—143° (identical infrared spectra), in initial eluates followed by phylloclad-15-en-17-ol (40 mg.), m. p. and mixed m. p. 125—126°.

Reaction of N-Bromosuccinimide with Isophyllocladene.—A solution of isophyllocladene (7·61 g.) and freshly crystallised *N*-bromosuccinimide (5·25 g.) in dry carbon tetrachloride was heated under reflux in the presence of benzoyl peroxide (10 mg.) and ultraviolet light for 5½ hr. The succinimide was removed, washed with carbon tetrachloride, and the combined filtrate and washings were concentrated *in vacuo* to yield 17-bromophylloclad-15-ene (7·46 g., 76%), m. p. and mixed m. p. 68—69° (identical infrared spectra). In a further experiment for a period of 2 hr. and without the use of benzoyl peroxide the yield was 57%. Similar bromination of phyllocladene for 4 hr. gave the same product, m. p. and mixed m. p. 68—69° (20%).

Dehydrobromination of 16-Bromophyllocladane.—A cooled solution of isophyllocladene (1·03 g.) in dry ether (10 c.c.) and glacial acetic acid (25 c.c.) was treated with a stream of dry hydrogen bromide for 90 min. Removal of the ether and filtration of the solid (1·2 g.) afforded 16-bromophyllocladane, plates (from light petroleum), m. p. 139°, $[\alpha]_D^{20}$ +7° (*c* 2·0) (lit.,[21] m. p. 141—142°, $[\alpha]_D^{17}$ +8·06°).

A mixture of the hydrobromide (1·0 g.), potassium carbonate (1·5 g.), and water (10 c.c.) was heated at 90° for 2 hr. during which needles separated from the reaction mixture. These were removed from the cooled mixture and recrystallised from methanol to give isophyllocladene (821 mg.), m. p. and mixed m. p. 109—110° (identical infrared spectra).

The hydrobromide (1·3 g.) was chromatographed on alumina (grade III) from light petroleum. Initial fractions eluted with the same solvent gave isophyllocladene (998 mg.), m. p. and mixed m. p. 109—111°.

Dehydrochlorination of 16-Chlorophyllocladane.—16-Chlorophyllocladane (phyllocladene hydrochloride [21]), m. p. 106—108°, $[\alpha]_D^{20}$ +8° (*c* 2·5) (lit.,[21] m. p. 106°, $[\alpha]_D$ +7·77°), was chromatographed on alumina. Initial fractions, eluted with light petroleum, contained a mixture of phyllocladene (40%) and isophyllocladene (60%) which was separated by fractional crystallisation from ethyl acetate and methanol.

Ethylene Dithioketal of 17-Norphyllocladan-16-one.—Boron trifluoride etherate (6 c.c.) was added to a solution of 17-norphyllocladan-16-one [8] (3·0 g.) in ethanedithiol (6 c.c.). The precipitate was homogenised with glacial acetic acid (10 c.c.), the mixture kept at 20° for 10 hr., and the product collected. Crystallisation from ethanol gave the *ethylene dithioketal* (3·4 g.) as plates, m. p. 145·5—146°, $[\alpha]_D^{20}$ +7° (*c* 3·7) (Found: C, 71·5; H, 9·9; S, 18·2. $C_{21}H_{34}S_2$ requires C, 71·9; H, 9·8; S, 18·3%).

Desulphuration of the Dithioketal.—A solution of the above dithioketal (2·1 g.) in acetone (200 c.c.) was heated with W-2 Raney nickel (10 g.) under reflux for 6 hr. The catalyst was removed and the solution was concentrated, to yield a solid (1·36 g.) which, after repeated crystallisation from ethanol or chromatography on alumina, had m. p. 84—85°. Gas–liquid chromatography with 10% silicone oil on a Celite column (Pye Argon chromatograph) at 250° showed that the product consisted of 17-norphylloclad-15-ene (22%) and 17-norphyllocladane (78%).

Hydrogenation of the product in ethyl acetate over platinum oxide gave 17-norphyllocladane, m. p. 85—86° (lit.,[16] 85—86°); n.m.r. 0·93 (C-10 methyl), 0·81 and 0·84 (C-4 *gem*-dimethyl), and 2·04 δ (broad multiplet, C-13 proton); total protons 32.

Reaction of N-Bromosuccinimide with 17-Norphylloclad-15-ene.—A solution of 17-norphylloclad-15-ene [16] (400 mg.), *N*-bromosuccinimide (858 mg.), and dry carbon tetrachloride (100 c.c.) was heated under reflux with benzoyl peroxide (5 mg.) in the presence of ultraviolet light for 18 hr. A small amount of succinimide was removed and the filtrate was washed with water, dried, and the solvent removed. Chromatography of the product on alumina gave, from light petroleum eluates, 17-norphylloclad-15-ene and an oil, slow crystallisation of which from carbon tetrachloride and then acetone gave 15α,16β-*dibromo*-17-*norphyllocladane* (51 mg.) as shining rods, m. p. 166—167°, $[\alpha]_D^{20}$ −38° (*c* 3·5) (Found: C, 55·0; H, 7·3; Br, 37·7. $C_{19}H_{30}Br_2$ requires C, 54·55; H, 7·2; Br, 38·2%); n.m.r. 0·82 and 0·85 (C-4 *gem*-dimethyl), 0·90 (C-10 methyl), 2·20 (multiplet, C-13 proton), 5·84 (C-15 proton), and 4·62 δ (doublet, J = 2·5 c./sec., C-16 proton coupled with C-13 proton); total protons 30.

15α,16β-Dibromo-17-norphyllocladane (83%), m. p. and mixed m. p. 165—167° (identical infrared spectra), was also obtained from the reaction of bromine (0·2 g.) in carbon tetrachloride with 17-norphylloclad-15-ene (276 mg.), when a solution of the product, dissolved in light petroleum, was percolated through alumina.

Bromination of Isophyllocladene.—(a) *With equimolar proportions.* A solution of isophyllocladene (1·72 g.) in carbon tetrachloride (10 c.c.) was treated in portions at 20° with a solution

of bromine (1·0 g., 1 mole/mole) in carbon tetrachloride (5 c.c.). The reaction was characterised by the immediate evolution of hydrogen bromide fumes. After the final addition the mixture was kept at 20° for 1 hr. and the solvent evaporated. Fractional crystallisation of the resultant oil from acetone gave isophyllocladene (682 mg.) and a gum which was chromatographed on alumina. Repeated crystallisation of the product from light petroleum eluates gave 17-bromophylloclad-15-ene (920 mg.), m. p. and mixed m. p. 67—68° (identical infrared spectra).

In further experiments, after the separation of as much isophyllocladene as possible, the remaining oils were hydrolysed with aqueous potassium carbonate as for 17-bromophylloclad-15-ene. Chromatography of the products on alumina gave isophyllocladene (5—10%) and phylloclad-15-en-17-ol (95—90%).

In a series of bromination experiments with amounts of bromine intermediate between 1 and 2 moles/mole of isophyllocladene, oils were obtained whose n.m.r. spectra indicated the increasing formation of 15α,16epi,17-tribromophyllocladane and decreasing formation of 17-bromophylloclad-15-ene.

(b) *With excess of bromine.* In a typical experiment, a solution of isophyllocladene (1·83 g.) in carbon tetrachloride (10 c.c.) was treated in portions at 20° with a solution of bromine (2·69 g.) in carbon tetrachloride (5 c.c.). After the final addition (30 min.) the mixture was kept at 20° for 1 hr. and the excess of bromine and solvent was removed *in vacuo*. Repeated crystallisation of the resultant oil from acetone gave 15α,16epi,17-*tribromophyllocladane* (3·12 g.), which crystallised from acetone as needles, m. p. 134—136°, $[\alpha]_D^{20}$ −29° (*c* 7·7) (Found: C, 47·1; H, 6·0; Br, 46·8. $C_{20}H_{31}Br_3$ requires C, 47·0; H, 6·1; Br, 46·9%); n.m.r. 0·82 and 0·85 (C-4 *gem*-dimethyl), 0·91 (C-10 methyl), 2·69 (multiplet, C-13 proton), 3·86 (singlet, C-17 protons), and 4·36 δ (singlet, C-15 proton); total protons 31. The same product was also isolated when isophyllocladene, dissolved in a mixture of ether and acetic acid (1 : 1) or in chloroform, was treated with an excess of bromine.

15α,17-*Dibromophylloclad*-16-*ene* (XXII).—(*a*) A solution of 15α,16epi,17-tribromophyllocladane (942 mg.) in light petroleum was percolated through a column of alumina (grade I—II). Removal of the solvent from the eluant gave an oil which crystallised from acetone to yield 15α,17-*dibromophylloclad*-16-*ene* (624 mg.) as shining rods, m. p. 154°, $[\alpha]_D^{20}$ −165° (*c* 3·8) (Found: C, 56·0; H, 6·9; Br, 37·1. $C_{20}H_{30}Br_2$ requires C, 55·8; H, 7·0; Br, 37·4%), $\nu_{max.}$ (CCl_4) 1642 and 846 cm.$^{-1}$ (trisubstituted double bond); n.m.r. 0·82 and 0·87 (C-4 *gem*-dimethyl), 0·91 (C-10 methyl), 2·98 (broad multiplet, C-13 proton), 5·26 (broad singlet, half-height width 3 c./sec. C-15 proton) and 6·53 δ (broad singlet, C-17 proton split by allylic coupling); total protons 30.

(*b*) A solution of 17-bromophylloclad-15-ene (701 mg.) in carbon tetrachloride was treated dropwise with bromine (323 mg.) at 20°. The solution was left overnight to evaporate and the crystalline mass remaining was washed with a little acetone. Recrystallisation from acetone gave 15α,17-dibromophylloclad-16-ene (825 mg., 96%), m. p. and mixed m. p. 153—154° (Found: C, 55·7; H, 7·3; Br, 37·5%) (identical infrared spectra).

17-*Bromophylloclad*-16-*en*-15ξ-*ol* (XXIII; R = OH).—15α,17-Dibromophylloclad-16-ene (83 mg.) was heated under reflux with potassium carbonate (80 mg.) and water (10 c.c.) for 6 hr. and the cooled mixture extracted with ether. The resulting oil was chromatographed on alumina and the product, eluted with benzene, was crystallised from aqueous methanol to give 17-*bromophylloclad*-16-*en*-15ξ-*ol* (24 mg.) as needles, m. p. 92° (Found: C, 65·4; H, 8·6; Br, 21·0. $C_{20}H_{31}BrO$ requires C, 65·4; H, 8·5; Br, 21·75%), $\nu_{max.}$ (CCl_4) 3571 (OH), 1642 (C:C), and 1116 cm.$^{-1}$ (sec. OH); n.m.r. 0·83 and 0·89 (C-4 *gem*-dimethyl), 0·95 (C-10 methyl), 2·18 (sharp singlet, OH exchanged with D_2O), 2·98 (multiplet, C-13 proton), 4·53 (broad singlet, C-15 proton, half-height width 3·5 c./sec.) and 6·44 δ (broad singlet, C-17 proton split by allylic coupling); total protons 31.

17-*Bromo*-15ξ-*methoxyphylloclad*-16-*ene* (XXIII; R = OMe).—15α,17-Dibromophylloclad-16-ene (85 mg.) was heated under reflux with 2N-methanolic potassium hydroxide (20 c.c.) for 10 hr. Most of the methanol was removed, water was added, and the mixture extracted with ether. Chromatography of the resulting oil on alumina gave 17-*bromo*-15ξ-*methoxyphylloclad*-16-*ene* (45 mg.) in light petroleum eluates and 17-bromophylloclad-16-en-15ξ-ol (28 mg.) in benzene eluates. 17-Bromo-15ξ-methoxyphylloclad-16-ene crystallised from acetone–methanol as plates, m. p. 108—109°, $[\alpha]_D^{20}$ −62° (*c* 2·4) (Found: 66·1; H, 8·9; Br, 21·3. $C_{21}H_{33}BrO$ requires C, 66·1; H, 8·7; Br, 20·95%), $\nu_{max.}$ (CCl_4) 1639, and 840 (trisubstituted

double bond) and 1096 cm.$^{-1}$ (aliphatic ether); n.m.r. 0·82 and 0·86 (C-4 *gem*-dimethyl), 0·91 (C-10 methyl), 2·90 (multiplet, C-13 proton), 3·39 (OMe), 4·00 (broad singlet, C-15 proton), and 6·35 δ (singlet, C-17 proton); total protons 33.

17-*Bromokaur*-15-*ene* (V; R = Br).—Treatment of isokaurene with *N*-bromosuccinimide as previously described [1] gave, after fractional crystallisation, 13-bromokaur-15-ene (5%), m. p. and mixed m. p. 237—238°; n.m.r. 0·80, 0·85 (C-4 *gem*-dimethyl), 1·01 (C-10 methyl), 1·26 (C-17 methyl), and 5·80 δ (singlet, C-15 proton), and **17-*bromokaur*-15-*ene*** (67%), which formed irregular plates, m. p. 36—37° (from acetone) (Found: C, 68·0; H, 8·6; Br, 23·4. $C_{20}H_{31}Br$ requires C, 68·4; H, 8·9; Br, 22·8%). The infrared spectrum indicated that the product was not homogeneous. N.m.r. 0·80 and 0·85 (C-4 *gem*-dimethyl), 1·03 (C-10 methyl), 2·53 (multiplet, C-13 proton), 4·20 (doublet, C-17 proton split by allylic coupling with C-15 proton, $J < 1$ c./sec.), and 5·50 δ (doublet, C-15 proton); total protons 31.

Kaur*-15-*en*-17-*ol (V; R = OH).—17-Bromokaur-15-ene (86 mg.) was heated under reflux with potassium carbonate (100 mg.) and water (20 c.c.) for 6 hr. The cooled mixture was extracted with ether and the extract crystallised from methanol to afford needles (65 mg.) of kaur-15-en-17-ol, m. p. and mixed m. p. 133—134°, $[\alpha]_D^{25}$ −25° (*c* 4·9) (identical infrared spectra); n.m.r. 0·80 and 0·86 (C-4 *gem*-dimethyl), 1·04 (C-10 methyl), 1·73 (OH, exchanged by D_2O), 2·55 (multiplet, C-13 proton), 4·19 (doublet, C-17 protons split by allylic coupling, $J < 1$ c./sec.), and 5·39 δ (doublet, C-15 proton); total protons 32.

17-*Methoxykaur*-15-*ene* (V; R = OMe).—Kaur-15-en-17-ol (30 mg.) was heated under reflux with methyl iodide (2 c.c.) and silver oxide (100 mg.) for 6 hr. Removal of the solvent from the filtered solution followed by chromatography of the product on alumina gave an oil from benzene eluates. Crystallisation from methanol afforded **17-*methoxykaur*-15-*ene*** (20 mg.) as plates, m. p. 36—38°, $[\alpha]_D^{25}$ −29° (*c* 4·8) [Found: (on a sample dried at room temperature) C, 81·2; H, 11·1. $C_{21}H_{34}O,\frac{1}{2}CH_3OH$ requires C, 81·1; H, 11·4%], $\nu_{max.}$ (on a further dried sample) (CCl_4) 1102 (aliphatic ether) and 837 cm.$^{-1}$ (trisubstituted double bond); n.m.r. 0·82 and 0·87 (C-4 *gem*-dimethyl), 1·06 (C-10 methyl), 2·55 (multiplet, C-13 proton), 3·35 (OMe), 3·98 (broad singlet, C-17 protons), and 5·39 δ (broad singlet, C-15 proton); total protons 34.

The authors thank Mr. C. R. Southward for some preliminary experiments, and one of us (L. H. B.) gratefully acknowledges assistance from the Chemical Society, the Rockefeller Foundation of New York, the Australia and New Zealand Association for the Advancement of Science, and the Research Grants Committee of the University of New Zealand.

Department of Chemistry, University of Auckland,
New Zealand.

[*Received, April 26th,* 1965.]