349. *Diterpenes. Part VI.*[1] *A Novel Prévost Reaction.**

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Treatment of isophyllocladene and isokaurene with Prévost's reagent (silver benzoate–iodine) causes allylic benzoyloxylation at $C_{(17)}$. Investigations of the reaction and the variant using silver acetate–iodine with the above compounds, phyllocladene, and kaurene are also described. Iodine isomerises phyllocladene and kaurene to isophyllocladene and isokaurene, respectively. Allylic oxidation with selenium dioxide followed by Wolff–Kishner reduction of the resulting αβ-unsaturated aldehydes converts isophyllocladene into phyllocladene and isokaurene into kaurene.

During attempted stepwise degradations of isophyllocladene (I), Prévost's[2] method for the preparation of the diol dibenzoate of an alkene was applied.

Isophyllocladene, however, on treatment with silver benzoate and iodine in refluxing

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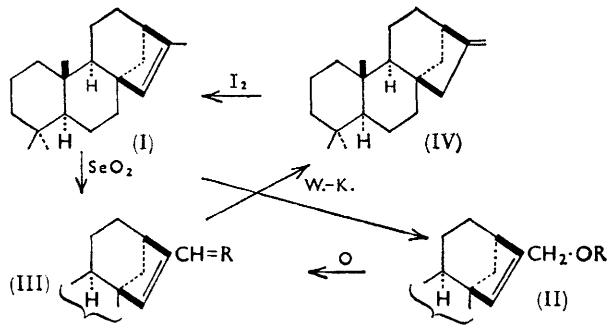
* A preliminary account of a portion of this work has been published; Briggs, Cain, and Davis, *Tetrahedron Letters*, 1960, No. 17, 9.

[1] Part V, preceding paper.

[2] Prévost, *Compt. rend.*, 1933, **196**, 1129; **197**, 1661; Wilson, *Org. Reactions*, 1957, **9**, 350.

dry benzene gave, in high yield, an unsaturated benzoate (II; R = Bz) which on alkaline hydrolysis gave the corresponding allylic alcohol (II; R = H). Oxidation of the alcohol with chromium trioxide-pyridine formed the αβ-unsaturated aldehyde (III; R = O). Confirmation of the structures of these products was provided in the following manner.



The aldehyde (III; R = O) was identical with the product formed by oxidation of isophyllocladene or of phyllocladene (IV) with selenium dioxide,* phyllocladene isomerising during the reaction. The allylic benzoate (II; R = Bz) was identical with the product previously obtained [1] by dehydration and benzoylation of phyllocladane-16,17-diol under vigorous conditions. Finally Wolff–Kishner reduction of the semicarbazone (III; R = N·NH·CO·NH_2) produced phyllocladene (IV), following the expected double-bond shift.[4] The infrared spectra of the allylic alcohol, its acetate (II; R = Ac), and benzoate all showed the presence of a trisubstituted double bond (bands at 837, 841, and 853 $cm.^{-1}$, respectively) while the C–O stretching band at 1015 $cm.^{-1}$ in the spectrum of the alcohol was consistent with that of an α-branched, αβ-unsaturated primary alcohol.[5] The bands of the ultraviolet spectrum of (III; R = O) at 253 and 258 mμ are at longer wavelength than would be expected for a disubstituted αβ-unsaturated aldehyde [6] and this shift is probably an indication of strain in the bicyclo[3,2,1]octane system.[7]

In view of the novel reaction undergone by isophyllocladene, Prévost reactions with phyllocladene, (—)-kaurene (VI), and isokaurene (V) † were investigated. Treatment of phyllocladene with silver benzoate–iodine again led to the allylic benzoate (II; R = Bz). This unexpected result was subsequently explained when it was found that heating

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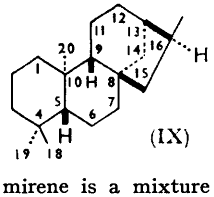
* Since this work was completed Henderson and Hodges [3] have reported the preparation of (III; R = O) by the same method. Reduction of (III; R = O) with lithium aluminium hydride yielded (II; R = H) from which (III; R = O) was re-formed by oxidation with manganese dioxide.

† *Note added in proof.* In a forthcoming publication it will be shown that (—)-kaurene has the structure enantiomorphic with that previously given to mirene (Briggs, Cain, Cambie, and Davis, *Tetrahedron Letters*, 1960, No. 24, 18). This has been reported in a preliminary communication (Djerassi, Quitt, Mosettig, Cambie, Rutledge, and Briggs, *J. Amer. Chem. Soc.*, 1961, **83**, 3720). On analogy with the stereochemistry assigned to phyllocladene,[1, 8] the name (—)-kaurane is assigned the structure (IX).

In Part III (*J.*, 1950, 955) the isolation of mirene was recorded, isomeric with both phyllocladene and kaurene. We have since briefly reported (Briggs, *J. New Zealand Inst. Chem.*, 1959, **23**, 92; Briggs, Cain, Davis, and Wilmshurst, *Tetrahedron Letters*, 1959, No. 8, 8, 13, 17; Briggs, Cain, Cambie, and Davis, *Tetrahedron Letters*, 1960, No. 24, 18) on the derived nor-ketone. A careful examination of the hydrocarbon, and derivatives, however, has shown that mirene is a mixture of (+)-phyllocladene and (+)-kaurene and its name therefore should be discontinued. We are grateful to Dr. J. N. Shoolery of Varian Associates for nuclear magnetic resonance spectra which assisted in this matter.



(IX)

[3] Henderson and Hodges, *Tetrahedron*, 1960, **11**, 226.

[4] Fischer, Lardelli, and Jeger, *Helv. Chim. Acta*, 1951, **34**, 1577.

[5] Zeiss and Tsutsui, *J. Amer. Chem. Soc.*, 1953, **75**, 897.

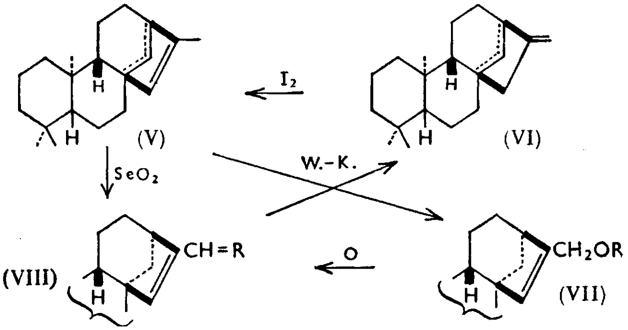
[6] Cf. cyclopent-1-enealdehyde ($\lambda_{max.}$ 237—238 mμ); Brown, Henbest, and Jones, *J.*, 1950, 3634.

[7] Moore and Fisher, *J. Amer. Chem. Soc.*, 1956, **78**, 4362; Bottomley, Cole, and White, *J.*, 1955, 2624; Wiesner, Bickelhaupt, Babin, and Götz, *Tetrahedron*, 1960, **9**, 254.

[8] Grant and Hodges, *Tetrahedron*, 1960, **8**, 261.

phyllocladene under reflux with a trace of iodine in dry benzene gave isophyllocladene. When Woodward and Brutcher's [9] variant of the Prévost reaction was employed the allylic alcohol (II; $R = H$) was again obtained. Kaurene (VI) and isokaurene (V) reacted analogously to phyllocladene and isophyllocladene.

Reduction (Wolff-Kishner) of the semicarbazone (VIII; $R = N{\cdot}NH{\cdot}CO{\cdot}NH_2$) of kaur-15-en-17-al to (—)-kaurene and selenium dioxide oxidation gives a general method for the conversion of the acid-stable into the acid-unstable isomer in this series and constitutes the first conversion of isophyllocladene into phyllocladene and of isokaurene into kaurene.



Available evidence suggests that the normal Prévost reaction is heterolytic, initiated by attack of an I^+ cation. Thus Wiberg and Saegebarth [10] showed that norbornylene yielded characteristic products of ionic rearrangement in the " wet " reaction. Again, Woodward and Brutcher [9] postulated an identical initial step to account for the stereochemistry of the final product. There is evidence, however, to suggest the presence of free radicals in solutions of silver benzoate–iodine. Bryce-Smith and Clarke have shown [11] that in an aromatic substrate biphenyls are formed, and Prévost himself showed [12] that anthracene gave the 9,10-dihydro-9,10-dibenzoate (cf. the similar oxidation with lead tetra-acetate, probably a free-radical process [13]).

There is as yet insufficient evidence to explain the mechanism in the present case but the natures of the reactants, solvents, and products suggest free-radical attack, although the isomerisations of phyllocladene into isophyllocladene and kaurene into isokaurene undoubtedly occur through an ionic process.

EXPERIMENTAL

Analyses were by Dr. A. D. Campbell and associates, University of Otago, New Zealand. Infrared spectra were measured for potassium bromide discs with a Beckman IR2 instrument, and ultraviolet spectra for ethanol solutions with a Beckman DU instrument. Alumina (Spence and Co., Grade H) was used for chromatography and " AnalaR " benzene was used throughout. Light petroleum was of b. p. 50—60°.

Phylloclad-15-*en*-17-*yl Benzoate* (II; $R = Bz$).—Isophyllocladene (1·1 g.) and silver benzoate (2·25 g.; dried at 100°) in benzene were dried by azeotropic distillation, resublimed iodine (1·23 g.) in dry benzene was added, and the mixture was heated under reflux for 3 hr. with stirring. The silver salts were removed and washed with hot benzene. The combined benzene solutions were concentrated *in vacuo*, ethanol was added, and the product was crystallised from benzene–ethanol, yielding phylloclad-15-en-17-yl benzoate (790 mg.) as needles, m. p. 161—163° (Found: C, 82·3,82·3; H, 9·4, 9·0. Calc. for $C_{27}H_{36}O_2$: C, 82·6; H, 9·2%), $\nu_{max.}$ 1709 (OBz), 853 cm.$^{-1}$ (C:CH).

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[9] Woodward and Brutcher, *J. Amer. Chem. Soc.*, 1958, **80**, 209.
[10] Wiberg and Saegebarth, *J. Amer. Chem. Soc.*, 1957, **79**, 6256.
[11] Bryce-Smith and Clarke, *J.*, 1956, 2264.
[12] Prévost, *Compt. rend.*, 1935, **200**, 408.
[13] Fieser and Putnam, *J. Amer. Chem. Soc.*, 1947, **69**, 1038.

The same product was prepared by similar treatment of phyllocladene.

Phylloclad-15-*en*-17-*ol* (II; R = H).—(*a*) Sodium (200 mg.) was added to the benzoate (II; R = Bz) (400 mg.) in dry benzene–ethanol, and the solution heated under reflux for 4 hr. Solvent was removed and the product precipitated by water. Crystallisation from 80% aqueous ethanol gave phylloclad-15-en-17-ol (240 mg.) as needles, m. p. 126—127° (Found: C, 82·3; H, 11·0. Calc. for $C_{20}H_{32}O$: C, 83·3; H, 11·2%), $\lambda_{max.}$ 215 mμ (log ε 3·54), $\nu_{max.}$ 3279 (OH), 1015 (C–O), 837 cm.$^{-1}$ (C:CH). The recorded [5] m. p. was 125·5—126·5°.

The acetate (II; R = Ac), prepared by heating with acetic anhydride under reflux for 4 hr., formed long plates and needles, m. p. 37—38°, from 85% aqueous ethanol (Found: C, 79·9; H, 10·4. Calc. for $C_{22}H_{34}O_2$: C, 79·95; H, 10·4%), $\nu_{max.}$ 1745 (OAc), 841 cm.$^{-1}$ (C:CH). The recorded [5] m. p. was 38—39°. Treatment of (II; R = H) with benzoyl chloride and pyridine at 100° re-formed (II; R = Bz), m. p. and mixed m. p. 161—163°.

(*b*) Silver acetate (2·54 g.) was added to a warm solution of isophyllocladene (1·8 g.) in glacial acetic acid (150 c.c.) and water (3 c.c.). Finely powdered iodine (1·6 g.) was added during ½ hr. with vigorous stirring, and the suspension was kept at room temperature for 16 hr. Silver salts were removed, the filtrate was concentrated *in vacuo*, and the residue, in methanol, was treated with potassium hydroxide (0·9 g.). Precipitated silver oxide was removed and the solution heated under reflux for 4 hr. Isophyllocladene (130 mg.), m. p. and mixed m. p. 108°, was separated from the cooled solution and the residue, after removal of solvent, triturated with light petroleum. Crystallisation of the insoluble fraction (0·40 g.) from aqueous ethanol gave the alcohol (II; R = H), m. p. and mixed m. p. 122—124°.

Phylloclad-15-*en*-17-*al* (III; R = O).—(*a*) The alcohol (II; R = H) (305 mg.) in pyridine (3 c.c.) was added to the complex formed from chromium trioxide (300 mg.) and pyridine (3 c.c.), and the mixture kept at room temperature for 3 hr. Treatment with saturated aqueous oxalic acid gave phylloclad-15-en-17-al (quantitative yield) as stout rods and plates, m. p. 125—127°, from 80% aqueous ethanol (Found: C, 84·2; H, 10·2. Calc. for $C_{20}H_{30}O$: C, 83·9; H, 10·6%), $\lambda_{max.}$ 253 (log ε 3·87), 258 (log ε 3·88), and 322 (sh) mμ (log ε 3·09), $\nu_{max.}$ 1681 (C:C·CH:O), 856 cm.$^{-1}$ (C:CH). The recorded [5] m. p. was 129—130°.

The *semicarbazone* (III; R = N·NH·CO·NH_2), obtained in quantitative yield, crystallised from benzene–ethanol as rectangular plates, m. p. 262—264° (Found: C, 73·6; H, 9·6. $C_{21}H_{33}N_3O$ requires C, 73·4; H, 9·7%), $\lambda_{max.}$ 275·5 mμ (log ε 4·54). The 2,4-*dinitrophenylhydrazone*, obtained in quantitative yield, formed red needles, m. p. 234°, from chloroform–methanol (Found: C, 67·5; H, 7·2; N, 12·0. $C_{26}H_{34}N_4O_4$ requires C, 66·9; H, 7·4; N, 12·0%), $\lambda_{max.}$ 234 (log ε 4·32), 255 (log ε 4·32), 291 (log ε 4·18), and 384 mμ (log ε 4·51).

(*b*) Isophyllocladene (480 mg.) and selenium dioxide (750 mg.) were heated under reflux in acetic acid–dioxan (1 : 1, 50 c.c.) for 1½ hr. Selenium was removed and the product isolated from the concentrated solution by pouring on ice and sodium hydroxide solution. Crystallisation from aqueous ethanol gave the aldehyde (III; R = O) as needles, m. p. and mixed m. p. 126—127°; semicarbazone, m. p. and mixed m. p. 262—264°.

Similar treatment of phyllocladene (500 mg.) gave the aldehyde (quantitative yield); semicarbazone, m. p. and mixed m. p. 262—264°; 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 232—234°.

Wolff–Kishner Reduction of the Semicarbazone (III; R = N·NH·CO·NH_2).—The semicarbazone (140 mg.), potassium hydroxide (100 mg.), and hydrazine hydrate (80%; 3 c.c.) in trimethylene glycol (6 c.c.) were heated at 180° (oil-bath) for 7 hr. The cooled solution was poured into water, and the product repeatedly crystallised from 80% aqueous ethanol to yield phyllocladene (80 mg.), m. p. and mixed m. p. 95—96° (identical infrared spectrum).

Kaur-15-*en*-17-*ol* (VII; R = H).—(*a*) Isokaurene (1·30 g.), silver benzoate (2·3 g.), and iodine (1·3 g.) in dry benzene were treated as for isophyllocladene for 6 hr. Chromatography of the product in light petroleum gave kaur-15-en-17-yl benzoate (VII; R = Bz) as a clear gum which did not crystallise. It was hydrolysed with sodium in dry benzene–ethanol and the product adsorbed on alumina. Fractions eluted with light petroleum and benzene crystallised from light petroleum and then methanol to yield *kaur*-15-*en*-17-*ol* (360 mg.) as needles, m. p. 134° (Found: C, 83·5; H, 10·8. $C_{20}H_{32}O$ requires C, 83·3; H, 11·2%), $\nu_{max.}$ 3333 (OH), 1018 (C–O), 831 cm.$^{-1}$ (C:CH). The same product (330 mg.) was prepared by similar treatment of kaurene (1·24 g.).

The *acetate* (VII; R = Ac), prepared by the use of acetic anhydride–pyridine (100°; 9 hr.), crystallised from ether–ethanol as plates, m. p. 70° (Found: C, 79·6; H, 10·0. $C_{22}H_{34}O_2$

requires C, 79·95; H, 10·4%), $\nu_{max.}$ 1730 (OAc), 833 cm.$^{-1}$ (C:CH). Attempts to crystallise the benzoate (VII; R = Bz) prepared from (VII; R = H) were unsuccessful.

(*b*) Treatment of isokaurene (200 mg.) in moist acetic acid (10 c.c.) with silver acetate (280 mg.) and iodine (200 mg.) as previously described, followed by hydrolysis and chromatography, gave the alcohol (VII; R = H), m. p. and mixed m. p. 134° (identical infrared spectrum).

Kaur-15-*en*-17-*al* (VIII; R = O).—Oxidation of the alcohol (VII; R = H) (300 mg.) with chromium trioxide (300 mg.) and pyridine (3 c.c.) followed by chromatography of the product in light petroleum gave kaur-15-en-17-al (200 mg.) as an oil which did not crystallise.

The same product (270 mg.) was formed after oxidation of isokaurene (456 mg.) with selenium dioxide for 10 hr.

The 2,4-*dinitrophenylhydrazone*, after chromatography in benzene, formed orange-red needles, m. p. 236—237°, from chloroform–methanol (Found: C, 67·2; H, 7·3; N, 12·2. $C_{26}H_{34}N_4O_4$ requires C, 66·9; H, 7·35; N, 12·0%), $\lambda_{max.}$ 225 (log ε 4·18), 258 (log ε 4·16), 263 (log ε 4·14), 290 (log, ε 4·01) and 384 mμ (log ε 4·46).

The *semicarbazone* (VIII; R = N·NH·CO·NH$_2$) crystallised from aqueous methanol and then from benzene–ethanol as needles, m. p. 258—260° (Found: C, 73·0; H, 9·2. $C_{21}H_{33}N_3O$ requires C, 73·4; H, 9·7%).

Wolff–Kishner Reduction of the Semicarbazone (VIII; R = N·NH·CO·NH$_2$).—The semicarbazone (150 mg.), potassium hydroxide (100 mg.), and hydrazine hydrate (80%, 3 c.c.) in trimethylene glycol (6 c.c.) were heated under reflux at 180° for 6 hr. The product was adsorbed on alumina from light petroleum and fractions eluted with the same solvent crystallised from ethanol to yield irregular plates of kaurene (90 mg.), m. p. and mixed m. p. 49—50° (identical infrared spectrum).

Isomerisation with Iodine.—Phyllocladene (120 mg.) in dry benzene was heated under reflux with a few crystals of iodine for 4½ hr. Removal of solvent and crystallisation of the residue from ethanol (charcoal) gave isophyllocladene (100 mg.), m. p. and mixed m. p. 111—111·5° (identical infrared spectrum). Similarly, kaurene (170 mg.; m. p. 50—51°) after 6 hr. gave isokaurene (160 mg.), m. p. and mixed m. p. 62—63° (identical infrared spectrum).

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