Synthesis of a Neoatisiranone, the Enantiomer of a Ketone Obtained by the Acid-catalysed Rearrangement of Isophyllocladene Epoxide

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The constitution and stereochemistry of a compound obtained by the acid-catalysed rearrangement of isophyllocladene epoxide have been confirmed by a synthesis of its enantiomer from (−)-neoatisirene. In addition, it has been shown that the neoatisiranol (XII) on dehydration undergoes skeletal rearrangement to the olefin (XIII).

ISOPHYLLOCLADENE EPOXIDE (I) on treatment with boron trifluoride–ether complex furnishes [1,2] a mixture of two ketones, one of which is the phyllocladanone (II).[2,3] Buchanan and Davis have advanced [2] a structure (III) for the other, mainly on the basis of spectroscopic data. We have also studied the formation of this ketone, m.p. 135—137°, $[\alpha]_D$ −28°, and come to the same conclusion as to its structure by use of nearly identical arguments, which, however, are by no means compelling. Since the most likely pathway for conversion of the epoxide (I) into the ketone (III) involves in formal terms ‡ a fairly complex series of 1,2-alkyl and 1,2- and 1,3- hydride shifts [see (I) → (IV) → (VII) → (III); arrows] it appeared that more convincing evidence for the structure was required.

(−)-Neoatisirene (VIII) was prepared [6] from (−)-kaurene and converted into its endocyclic isomer by heating [7] in acetic acid. Hydroboration [8] of the product gave mainly one alcohol (IX),[9] m.p. 102—104°, which on oxidation furnished the corresponding ketone (X), m.p. 128—130°, with the 17-methyl group in the more congested α-configuration as expected. Epimerisation at C-16 with sodium methoxide in methanol gave a ketone [*enantio*-(III)], m.p. 135—137°, of opposite rotation, $[\alpha]_D$ +25°, to the product from isophyllocladene epoxide but identical in all other respects. This synthesis constitutes an unambiguous proof of the constitution and stereochemistry of the ketone (III).

During the present investigation a further interesting skeletal rearrangement was encountered. In an attempt to convert the ketone (III) into (+)-isoneoatisirene (XI), the derived alcohol (XII), m.p. 156—157°, was heated with phosphoryl chloride in pyridine. However, the sole product was the olefin (XIII), m.p. 103—105°. This ready rearrangement [9] of compound (XII) may be attributed to the *trans*, antiparallel relationship of the bond linking the functional group to C-14 and the C(8)–C(15) σ-bond. The formulation of the product as (XIII) can

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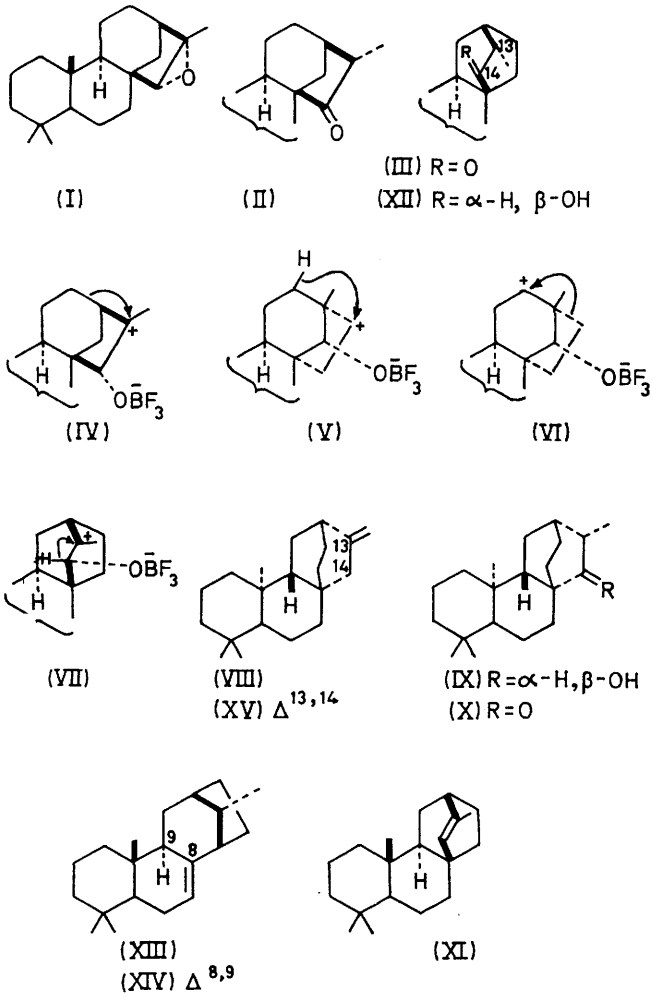
‡ Recent evidence [4–6] from studies of the rearrangements of related compounds indicates that non-classical species may be involved in this transformation.

[1] R. Henderson and R. Hodges, *Tetrahedron*, 1960, **11**, 226.
[2] J. G. St. C. Buchanan and B. R. Davis, *Chem. Comm.*, 1967, 1142.
[3] L. H. Briggs, R. C. Cambie, and P. S. Rutledge, *J. Chem. Soc.*, 1963, 5374.
[4] R. A. Appleton, J. C. Fairlie, R. McCrindle, and W. Parker, *J. Chem. Soc.* (*C*), 1968, 1716.
[5] R. M. Coates and E. F. Bertram, *Chem. Comm.*, 1969, 797.
[6] R. A. Appleton, P. A. Gunn, and R. McCrindle, *J. Chem. Soc.* (*C*), 1970, 1148.
[7] L. H. Zalkow and A. C. Oehlschalager, *J. Org. Chem.*, 1967, **32**, 808.
[8] H. C. Brown and G. Zweifer, *J. Amer. Chem. Soc.*, 1959, **81**, 247.
[9] For an analogous rearrangement see S. W. Pelletier and A. Ichihara, *Chem. and Ind.*, 1967, 2149.

be substantiated as follows. Its n.m.r. spectrum reveals the presence of one vinyl proton (τ 4·83) and, significantly, a secondary methyl group (τ 9·20); its mass spectrum defines the nature and location of the double bond. Thus the base peak at *m/e* 148 is produced by a retro-Diels–Alder fission of ring B, the charge remaining on rings C and D. Confirmatory evidence for our conclusions as



to the constitution of the olefin (XIII) comes from its conversion into its tetrasubstituted isomer (XIV) by exposure to refluxing acetic acid.

It appeared possible that the absence of unrearranged olefin in the product of dehydration with phosphoryl chloride–pyridine could be ascribed to the orientation (*cis*) of the hydroxy-group at C-14 with respect to H-13. Since there is some evidence [10] that phosphorus trichloride–benzene may furnish products of *cis*-dehydration, the alcohol (XII) was subjected to these conditions.

Again only the rearranged olefin (XIII) was formed. A further attempt to effect the desired conversion *via* pyrolysis of a carbonate of (XII) was also unsuccessful. Treatment of the alcohol with ethyl chloroformate in pyridine at −10° and work-up gave as the only isolable products the two rearranged olefins (XIII) and (XIV) in the ratio 7 : 3, although the crude product did contain *ca.* 1% of material which has the same g.l.c. retention time as isoneoatisirene.

EXPERIMENTAL

T.l.c. was carried out on Kieselgel G (Merck). G.l.c. analyses were performed with a Perkin-Elmer F 11 [stainless steel column (1/16 in. × 13 ft.) containing 2·5% SE-30 at 190°; nitrogen gas pressure 17 lb./in.^{2}] or a Varian Aerograph 1200 [stainless steel column (1/8 in. × 5 ft.) containing 3% SE-30 at 180°; nitrogen gas flow rate 25 ml./min.] instrument. For preparative purposes the latter instrument and column were used in conjunction with an effluent splitter (10/1) and microcollector.

M.p.s were determined with a Kofler hot-stage apparatus. Specific rotations refer to solutions in chloroform (*c* 0·5—1) at 20°. Light petroleum refers to the fraction of b.p. 60—80°. I.r. spectra were recorded for solutions in carbon tetrachloride with a Perkin-Elmer 257 grating spectrophotometer, and n.m.r. spectra with Perkin-Elmer R10 and Varian Associates HA-100 spectrometers for dilute solutions in deuteriochloroform with tetramethylsilane as internal standard. Microanalyses were performed by Mr. J. M. L. Cameron, Glasgow, and his staff.

Rearrangement of Isophyllocladene Epoxide.—Isophyllocladene epoxide (I) (500 mg.) was dissolved in anhydrous ether (200 ml.) and boron trifluoride–ether complex (3 ml.) was added. After 10 hr. at 20° the mixture was poured into water (100 ml.). The layers were separated and the aqueous phase was extracted with ether (50 ml.). The combined extracts were washed with brine and dried ($MgSO_4$). Evaporation afforded an oil (410 mg.) which was separated into two components by preparative t.l.c. [ethyl acetate–light petroleum (1 : 49)]. The less polar of these after crystallisation from methanol furnished phyllocladan-15-one (II) (261 mg.) m.p. 128—129° (lit.,[1] 127—129°), $\nu_{max.}$ 1732 cm^{-1}, τ 8·98 (3H, d, *J* 7 Hz) and 9·18, 9·20, and 9·26 (all 3H, s). The more polar component (same mobility on t.l.c. as isophyllocladene epoxide) crystallised from methanol as plates of the neoatisiran-14-one (III) (123 mg.), m.p. 135—137° (lit.,[2] 137°), $[\alpha]_D$ − 28°, $\nu_{max.}$ 1714 cm^{-1}, τ 8·92 (3H, d, *J* 7 Hz), and 9·18, 9·24, and 9·36 (all 3H, s).

(−)-*Isoneoatisirene.*—Neoatisirene (VIII) (256 mg.) was heated [7] in refluxing glacial acetic acid (10 ml.) and the progress of the reaction was followed by g.l.c. analysis. After 3 hr. conversion into the endocyclic isomer was complete and the mixture was poured into water and extracted with ether. This extract was washed with aqueous sodium hydrogen carbonate, dried, and evaporated. Preparative t.l.c. of the oily residue over silica gel–silver nitrate (9 : 1) [ethyl acetate–light petroleum (1 : 49)] afforded isoneoatisirene (XV) (207 mg.), m.p. 73—75° (from methanol) (lit.,[7] 76—77°).

Hydroboration of Isoneoatisirene.—Boron trifluoride-ether complex (3·2 ml.) was added to a stirred solution of isoneoatisirene (XV) (207 mg.) in ether (20 ml.) under nitrogen. Excess of lithium aluminium hydride in ether was then added dropwise and the mixture was stirred at 20° for 2 hr. Work-up with a saturated aqueous solution of sodium sulphate and evaporation of the solvent left a residue which was redissolved in ethanolic sodium hydroxide (3M; 32 ml.).

[10] J. W. B. Fulke, M. S. Henderson, and R. McCrindle, *J. Chem. Soc.* (*C*), 1968, 807.

Hydrogen peroxide (30%; 25 ml.) was added dropwise under nitrogen to this solution with stirring. After 12 hr. at 20° the product was recovered with chloroform and purified by preparative t.l.c. The resulting *alcohol* (IX) (198 mg.) formed needles, m.p. 102—104° (from ethanol–water), τ 6·37 (1H, m), 8·90 (3H, d, *J* 6 Hz), and 9·06, 9·12, and 9·17 (all 3H, s) (Found: C, 82·75; H, 11·7. $C_{20}H_{34}O$ requires C, 82·7; H, 11·8%).

The Ketone (X).—The alcohol (IX) (131 mg.) was oxidised by the Jones [11] technique and the crude product (103 mg.) was purified by preparative t.l.c. [ethyl acetate–light petroleum (1 : 49)] and crystallisation from methanol. The *ketone* (X) had m.p. 128—130°, $\nu_{max.}$ 1709 cm^{-1}, τ 8·83 (3H, d, *J* 7 Hz), and 9·13, 9·20, and 9·37 (all 3H, s) (Found: C, 83·25; H, 11·1. $C_{20}H_{32}O$ requires C, 83·25; H, 11·2%).

The Ketone [enantio-(III)].—The ketone (X) (100 mg.) was heated with potassium hydroxide (300 mg.) in refluxing methanol for 90 min. The product was recovered with chloroform and crystallised from methanol as plates of the *ketone* [enantio-(III)] (84 mg.), m.p. 135—137°, $[\alpha]_D$ +25°, $\nu_{max.}$ 1714 $cm.^{-1}$ (Found: C, 83·15; H, 10·95. $C_{20}H_{32}O$ requires C, 83·25; H, 11·2%), identical (n.m.r. and t.l.c. behaviour) with the ketone (III).

Reduction of the Neoatisiran-14-one (III).—The ketone (III) (107 mg.) was treated with excess of lithium aluminium hydride in refluxing ether for 2 hr. Work-up and crystallisation of the product from aqueous ethanol afforded the alcohol (XII) (104 mg.), m.p. 156—157° (lit.,[2] 156—158°), $[\alpha]_D$ +11°, τ 6·95 (1H, d, *J* 6 Hz), 8·99 (3H, d, *J* 7 Hz), 8·99 (3H, s), and 9·16 (6H, s).

Dehydration of the Alcohol (XII) *with Phosphoryl Chloride–Pyridine.*—The alcohol (XII) (93 mg.) was heated with phosphoryl chloride (2 ml.) in refluxing dry pyridine (10 ml.) for 2 hr. The mixture was cooled, poured into ice–water (40 ml.), and extracted with ether (50 ml.). The organic layer was separated, washed with water, and dried. Evaporation left an oily residue (73 mg.) [essentially one product (g.l.c.)] which after preparative t.l.c. on silica gel–silver nitrate (9 : 1) [ethyl acetate–light petroleum (1 : 24)] and sublimation afforded plates of the *olefin* (XIII), m.p. 103—105°, τ 4·83 (1H, m), 9·20 (3H, d, *J* 7 Hz), and 9·11, 9·14, and 9·23 (all 3H, s) (Found: *M*, 272·2499. $C_{20}H_{32}$ requires *M*, 272·2504).

Dehydration of the Alcohol (XII) *with Phosphorus Trichloride–Benzene.*—Use of an analogous procedure to that described for the dehydration with phosphoryl chloride–pyridine gave the olefin (XIII) as the sole product.

Treatment of the Alcohol (XII) *with Ethyl Chloroformate–Pyridine.*—Redistilled ethyl chloroformate (1 ml.) was added dropwise to a stirred solution of the alcohol (XII) (15 mg.) in pyridine (5 ml.) at −10°. After 1 hr. at −10° and 12 hr. at 0°, the product (11 mg.) was recovered by pouring into water and extraction with ether. G.l.c. and t.l.c. (silica gel–silver nitrate) showed the presence of materials with retention times and mobilities identical to those of the olefin (XIII) (*ca.* 70%), its isomer (XIV) (*ca.* 30%), and isoneoatisirene (XI) (*ca.* 1%).

Acid-catalysed Isomerisation of the Olefin (XIII).—The hydrocarbon (XIII) (32 mg.) was heated in refluxing glacial acetic acid (10 ml.) and the course of the reaction was followed by work-up and g.l.c. analysis of samples taken every 24 hr. After 7 days, when *ca.* 75% conversion into the tetrasubstituted double-bond isomer (XIV) had been effected, the mixture was poured into water and extracted with ether. The extract was washed with aqueous sodium hydrogen carbonate, dried, and evaporated. The oily residue (25 mg.) was fractionated by preparative g.l.c. and the *olefin* (XIV) was obtained as an oil, τ 9·18 (3H, d, *J* 7 Hz), 9·05 (3H, s) ,and 9·11 (6H, s); no olefinic proton(s) (Found: *M*, 272·2504. $C_{20}H_{32}$ requires *M*, 272·2504).

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[11] K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 1946, 39.