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COMPONENTS OF THE ROOT OF *LINDERA STRYCHNIFOLIA* VILL.—X[1]

STRUCTURE OF LINDERENE*

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Abstract—The structure of linderene, a crystalline component of *Lindera strychnifolia* Vill., proposed in 1953 was revised as VIa from the chemical and physical evidence.

IN 1953, Takeda[2] tentatively proposed the structure I for linderene, $C_{15}H_{18}O_2$, m.p. 143–145°, a crystalline component of *Lindera strychnifolia* Vill., from the results of dehydrogenation of linderene itself and of the crude octahydrodehydroxylinderene, $C_{15}H_{26}O$, b.p. 5 mm 135°,[3]† the reduction product of linderene.

Recently, however, the structure of octahydrodehydroxylinderene (II) has been clarified by Hikino *et al.*[4] as a result of the structural elucidation of atractylone (III). Our group also confirmed this result by direct synthesis of II from tetrahydroalantolactone (IV).[1] Further, the structure of linderazulene (V),[5] the dehydrogenation product of linderene, was also established by synthesis from guaiol.[6]

The UV spectra of linderene (VIa) and dihydrolinderene (VIIa) show a maximum at 206·1 mμ (ϵ 10,950) and at 219·8 mμ (ϵ 7,400) respectively and these results indicate the presence of a conjugated chromophore besides the furan ring. This is further confirmed by the NMR spectra of these two compounds VIa and VIIa: in the former the proton signal corresponding to the cyclopropane ring appears at 8·52 τ and in the latter this signal is shifted to 9·47 τ.

Some interesting information was obtained by further studies on the NMR spectra of linderene (VIa) and the natural occurring linderene acetate (VIb),[1] $C_{17}H_{20}O_3$, m.p. 82°. The doublet signal at 5·53 τ (J = 9·7 c/s) corresponding to one proton in the spectrum of linderene shows the presence of a hydrogen atom attached to a carbon bearing hydroxyl group, and this signal is shifted to the lower field (τ = 4·05, J = 10·0 c/s) in the spectrum of linderene acetate. The data mentioned above indicate that the hydroxyl group in linderene is not tertiary but secondary and that a hydrogen atom is present on the adjacent carbon. These NMR studies show that the structure I is untenable for linderene and, together with other chemical evidence, support structure VIa.

* The proceeding communication, *Tetrahedron Letters* No. 6, 277 (1964).

† This compound was isolated as crystallines, m.p. 27°, by careful chromatographic separation.

[1] Part IX: *Tetrahedron*, **20**, 2655 (1964).

[2] K. Takeda, *Chem. Pharm. Bull.* **1**, 244 (1953).

[3] K. Takeda and T. Shimada, *Yakugaku Zasshi* **64**, 154 (1944).

[4] H. Hikino, Y. Hikino and I. Yoshioka, *Chem. Pharm. Bull.* **10**, 641 (1962).

[5] K. Takeda and W. Nagata, *Chem. Pharm. Bull.* **1**, 164 (1953).

[6] K. Takeda, H. Minato and M. Ishikawa, *Tetrahedron Letters* No. 3, 121 (1963); *J. Chem. Soc.* 2591 (1964).

All attempts to isolate the pure linderene acetate or dihydrolinderene acetate by acetylation of VIa or VIIa with acetic anhydride in pyridine under various conditions were unsuccessful. Manganese dioxide oxidation of linderene or dihydrolinderene gives only a resinous substance.

Catalytic hydrogenation of dihydrolinderene (VIIa) with platinic oxide in alcohol gives a fully saturated tetracyclic derivative, hexahydrolinderene (VIIIa), $C_{15}H_{24}O_2$, m.p. 120–121·5°, $[\alpha]_D^{22}$ −30·5°, ν_{max}^{Nujol} 3405 cm^{-1}; NMR 9·52 τ (cyclopropane). The absorption bands at 3076 and 3009 cm^{-1} (in chloroform) in the IR spectrum of this compound show the presence of a —CH_2— group in the cyclopropane ring.[7] Reductive cleavage of the cyclopropane ring in VIIIa is achieved by catalytic hydrogenation

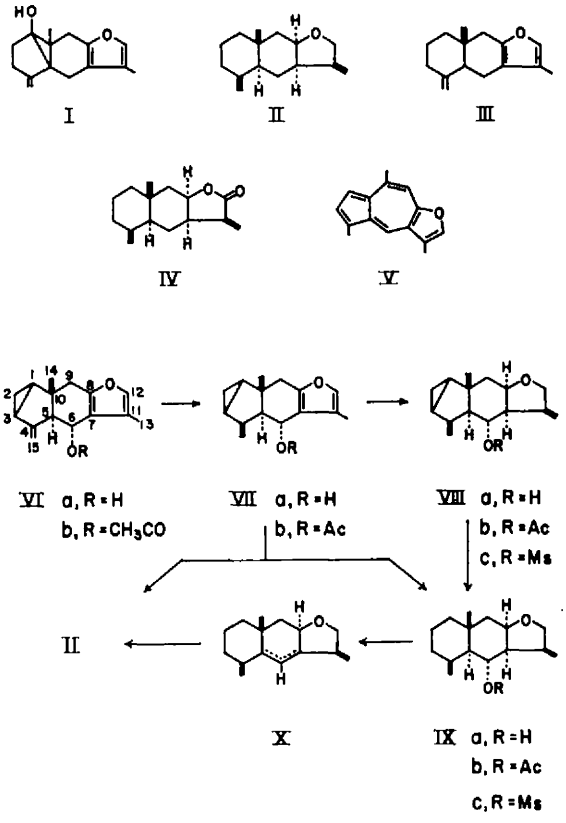

Chart I

with platinic oxide in alcohol containing acetic acid and gives IXa, $C_{15}H_{26}O_2$, m.p. 115°, $[\alpha]_D^{25}$ −44·1°, ν_{max}^{Nujol} 3407 cm^{-1}, in a quantitative yield. This octahydrolinderene (IXa) shows neither the bands at 3076 and 3009 cm^{-1} (cyclopropane ring methylene) in the IR nor a proton signal due to a cyclopropane ring in the NMR spectra. Compound IXa is also obtained directly by catalytic hydrogenation of VIIa with platinic oxide in

[7] A. R. H. Cole, *Chem. & Ind.* 946 (1953); M. Horák, J. Šmejkal and J. Farkaš, *Coll. Czech. Chem. Comm.* **28**, 2280 (1963).

acetic acid with a small amount of II. It is now assumed from these results that the position of the hydroxyl group in linderene is confined to C-6.

Hexahydrolinderene or octahydrolinderene give an acetate (VIIIb), $C_{17}H_{26}O_3$, m.p. 86–88°, or $C_{17}H_{28}O_3$ (IXb), m.p. 100–103°, in the usual manner. Linderene acetate, obtained from the natural source, also gives dihydro (VIIb), m.p. 89–95°, hexahydro VIIIb) and octahydrolinderene acetate (IXb) by catalytic hydrogenation with the method used in the case of linderene. The last two acetates are identical with the corresponding acetate obtained above.

Since the chromium trioxide oxidation of VIIIa under mild conditions gives unchanged starting material and under drastic conditions gives only a resinous substance, dehydration of IXa was attempted, in order to confirm the position of the hydroxyl group more rigorously. When octahydrolinderene mesylate (IXc), m.p. 112°, obtained from IXa by the usual manner, is heated at ca. 100° for 5 hr in dimethylsulfoxide, it gives an oily unsaturated compound (X) which is easily converted to octahydrodehydroxylinderene (II), m.p. 27°, by catalytic hydrogenation. The NMR spectrum of this unsaturated compound (X) shows the following signals: one methyl signal at 8·75 τ as a singlet, two methyl signals at 8·85 τ as a doublet (J = 7·5 c/s) and at 9·02 τ as a doublet (J = 6·3 c/s), and one vinyl proton signal at 4·78 τ as a doublet (J = 2·8 c/s). The only structure of this unsaturated compound which satisfies the NMR data must be represented by X. Therefore, the position of the hydroxyl group in linderene is C-6 and the cyclopropane ring is also located between C-1 and C-3.

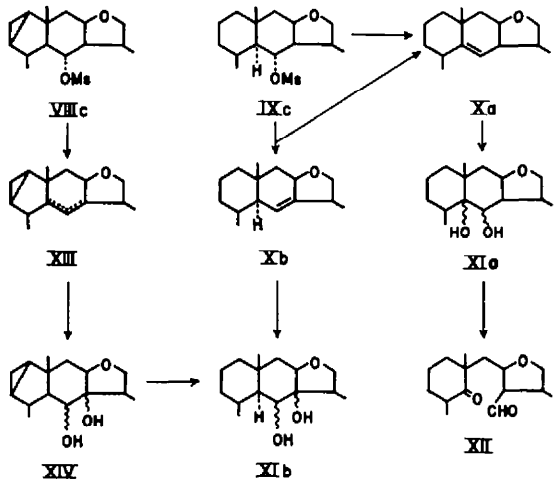

Chart 2

This unsaturated compound gives a glycol (XIa), m.p. 135°, with osmium tetroxide and its periodic oxidation product (XII) shows an aldehyde and the 6-membered ring ketone absorptions in the IR. These results indicate the position of the double bond in Xa is between C-5 and C-6. The signal corresponding to the 14-methyl group in X is shifted to the lower field (τ = 8·75) when compared with that of II (τ = 9·00)[8] and this result also satisfies the structure of Xa. When the mesylate is treated with pyridine it gives a mixture of the unsaturated compounds and this mixture gives

[8] R. F. Zürcher, *Helv. Chim. Acta* **46**, 2054 (1963).

another glycol (XIb), m.p. 156°, together with XIa. On the other hand hexahydrolinderene mesylate gives a mixture of the unsaturated compounds (XIII). From this mixture, only one glycol (XIV), m.p. 125° is obtained in the pure state with osmium tetroxide. Catalytic hydrogenation in acetic acid of this glycol gives a glycol (XIb) derived from octahydrolinderene.

Glycols XIa and XIb are assumed to be the position isomers of the hydroxy group rather than stereoisomers from the results of the NMR spectra and of catalytic hydrogenation of linderene or of the unsaturated compound (X).

The nature of the proton signal (doublet J = 9·7 c/s) of the C-6 hydrogen atom in linderene shows the *trans*-diaxial relationship between C-5 and C-6 hydrogens. This assignment (α-hydroxyl group) is also consistent with the fact that the hydroxyl group in hexahydrolinderene (VIIIa) is resistant to oxidation. The β-configuration of the C-10 methyl group is also confirmed by the conversion of IV to II.

The formation of linderazulene from linderene (VIa) can be rationalized by the following two routes:

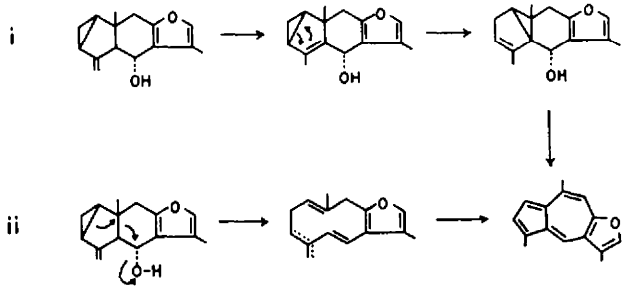

Chart 3

TABLE 1

Position	Linderene	Linderene acetate	Dihydrolinderene
1, 2 or 3	8·52* (t-d?)†	8·52 (t-d?)	9·47 (t-d) (8·6, 5·6)
5	7·32 (d-t-d) (9·7, 2·5, ~1·0)	6·98 (d-t-d) (10·0, 2·4, ~1·0)	7·85 (d-d) (10·0, 8·4)
6	5·53 (d-t) (9·7, 1·8)	4·05 (d-t) (10·0, 1·9)	5·75 (d-t) (10·0, 1·7)
9a|	7·20 (d-d) (~15, 1·8)	7·14 (d-d) (~15, 1·9)	7·35 (d-d) (~15, 1·7)
9b/	7·37 (d-d) (~15, 1·8)	7·31 (d-d) (~15, 1·9)	7·52 (d-d) (~15, 1·7)
12	2·98 (q) (1·2)	2·95 (q) (1·1)	2·98 (q) (1·2)
13	7·93 (d) (1·2)	8·15 (d) (1·1)	7·93 (d) (1·2)
14	9·36 (s)	9·30 (s)	9·20 (s)
15a|	4·79 (m)	4·97 (m)	9·04 (d) (7·5)
15b/	4·92 (m)	5·17 (m)	

* τ value.

† s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; apparent coupling constants (c/s.) are shown in parentheses.

The NMR data of linderene, linderene acetate and dihydrolinderene are shown in Table 1.

The proton spin decoupling experiments of dihydrolinderene (VIIa) at 100 MC. show homoallylic spin-spin coupling (J = ca. 1·8 c/s) between the C-6 proton and C-9 protons.[9]

EXPERIMENTAL

NMR spectra were taken in $CDCl_3$ with a Varian A-60 NMR Spectrometer. All m.ps were measured on a Kofler block (Yanagimoto & Co.) and are uncorrected.

Dihydrolinderene (VIIa) *from linderene* (VIa)

When a mixture of W-2 Raney nickel (300 mg) and VIa (1·158 g) in alcohol (10 ml) was reduced catalytically at room temp, ca. 1·01 moles H_2 were absorbed. The crystalline reduction product (1·1682 g) was chromatographed on neutral alumina containing 1% water and 640 mg VIIa, m.p. 125–127° (from ether–pet. ether = 1:1) was obtained from the third eluate (ether–pet. ether = 1:1). Its isomer, m.p. 109–112°, (270 mg) as colourless fine needles (ether–pet. ether = 1 :1), $[\alpha]_D^{26\cdot5}$ −141·8° (±2°) (*c*, 0·917 alcohol) (Found: C, 77·34; H, 8·68. $C_{15}H_{20}O_2$ requires: C, 77·55; H, 8·68%) was obtained from the first eluate (ether–pet. ether = 1:19) together with the mixture of these two substances (123·6 mg) from the second eluate (ether–pet. ether = 1:9). The structure of this isomer is now under investigation.

Dihydrolinderene acetate (VIIb) *from linderene acetate* (VIb)

Compound VIb (480·4 mg) was reduced catalytically with Raney nickel as described in the case of linderene to give an oily substance. This was dissolved in pet. ether and chromatographed on alumina (Woelm III, neutral). The crystalline substance thus obtained (419 mg) was recrystallized from ether–pet. ether (1:1) giving VIIb, m.p. 89–95°, as fine prisms, $[\alpha]_D^{26\cdot5}$ −6·3° (±2°) (*c*, 1·005 alcohol), ν_{max}^{Nujol} 1735, 1622, 1558 cm^{-1}. (Found: C, 74·23; H, 8·16. $C_{17}H_{22}O_3$ requires: C, 74·42; H, 8·08%).

The mother liquor after recrystallization of VIIb was evaporated leaving an oily residue, which was deacetylated by the action of $LiAlH_4$ in tetrahydrofuran at 0° for 2·5 hr to give an almost equal amount of VIIa and its isomer.

VIIb afforded VIIa by the action of $LiAlH_4$ as described above.

Hexahydrolinderene (VIIIa) *from dihydrolinderene* (VIIa)

Compound VIIa (178 mg) was reduced catalytically with PtO_2 (80 mg) in alcohol (5·5 ml) at room temp yielding 150 mg VIIIa. Recrystallization from ether–pet. ether (1:1) gave pure VIIIa as colourless prisms, m.p. 120–121·5°, $[\alpha]_D^{22}$ −30·5° (±2°) (*c*, 0·913 alcohol), ν_{max}^{Nujol} 3405, $\nu_{max}^{CCl_4}$ 3076, 3009 cm^{-1}. (Found: C, 76·31; H, 10·33. $C_{15}H_{24}O_2$ requires: C, 76·22; H, 10·24%).

Hexahydrolinderene acetate (VIIIb)

(a) *From* VIIIa. Acetyl chloride (0·5 ml) was added to an ice-cooled solution of VIIIa (30·8 mg) in pyridine (1 ml) and left overnight at room temp. Ice water was added, and the ether extract was washed and dried (Na_2SO_4). The residue was chromatographed on alumina (Woelm II, neutral) and the crystalline substance obtained from the first eluate with pet. ether was recrystallized from ether–pet. ether (1:1) to give VIIIb as colourless needles, m.p. 86–88°, $[\alpha]_D^{23}$ −54·6° (±2°) (*c*, 1·0743 alcohol), ν_{max}^{Nujol} 3070, 1727, 1252, 1034 cm^{-1}. (Found: C, 73·61; H, 9·44. $C_{17}H_{26}O_3$ requires: C, 73·34; H, 9·41%). Compound VIIIa and acetic anhydride was heated at 140–160° for 2 hr in the presence of sodium acetate to give the same acetate VIIIb, yield low.

(b) *From* VIIb. A mixture of PtO_2 (16 mg) and VIIb (16·0 mg) in alcohol (1·5 ml) was reduced catalytically at room temp. The product was separated by the preparative thin layer chromatography (20 × 20 cm × 0·5 mm Kieselgel plate; by the ascending method with benzene–ethyl acetate (9:1); detection reagent = 0·01% Morin solution). Compound VIIIb (12·4 mg) was extracted with pet. ether–ethyl acetate (1:1). This is identical with the acetate (VIIIb) obtained from VIIIa by mixed m.p. determination and comparison of IR spectra.

[9] J. T. Pinhey and S. Sternhell, *Tetrahedron Letters* No. 4, 275 (1963).

Octahydrolinderene (IXa) *from hexahydrolinderene* (VIIIa)

Compound VIIIa (46·0 mg) was reduced with PtO_2 (20·9 mg) in alcohol (1·5 ml) containing a small amount of acetic acid (0·3 ml) at room temp and 1·15 moles H_2 were absorbed. Catalyst was removed and the filtrate was concentrated *in vacuo*. Water was added and the precipitate was filtered, washed and dried. The residue was recrystallized from ether–pet. ether (1:1) to give octahydrolinderene (IXa; 38·6 mg) as colourless prisms, m.p. 114–115°, $[\alpha]_D^{25}$ −44·1° (+3°) (*c*, 0·774 alcohol), ν_{max}^{Nujol} 3407 cm^{-1}. (Found: C, 75·60; H, 11·02. $C_{15}H_{26}O_2$ requires: C, 75·58; H, 11·00%).

Catalytic hydrogenation of dihydrolinderene (VIIa) *in acid medium*

When a mixture of VIIa (318·7 mg), PtO_2 (60 mg), alcohol (10 ml) and acetic acid (0·3 ml) was reduced catalytically at room temp, ca. 3·20 moles H_2 (106·1 ml) were absorbed. The reaction mixture was worked up as usual and the residue was chromatographed on alumina (Woelm II, neutral). Compound II, m.p. 25–27° (29 mg) was obtained from the first eluate (pet. ether). The residue obtained from the second eluate (ether–pet. ether = 1:1) was rechromatographed on silica gel to give 166·9 mg IXa together with a small amount of a crystalline substance, m.p. 112–115°. (Found: C, 78·84; H, 11·75%). The latter was not investigated further due to insufficient of the material.

Octahydrolinderene acetate (IXb) *from octahydrolinderene* (IXa)

Compound IXa (10·4 mg) was heated in dry pyridine (0·5 ml) with acetic anhydride (0·2 ml) at 140° for 7 hr. The ether extract was washed with 5% HCl, 5% $NaHCO_3$, and water and dried (Na_2SO_4). The residue was chromatographed on alumina (Woelm III, neutral) followed by recrystallization from pet. ether to give 5·8 mg IXb, m.p. 95–100°. This was identical with the acetate obtained from the following procedure by mixed m.p. determination and comparison of the IR.

Octahydrolinderene acetate (IXb) *from dihydrolinderene acetate* (VIIb)

Compound VIIb (129·5 mg) was reduced catalytically with PtO_2 (30·4 mg) in a mixture of alcohol (5 ml) and acetic acid (0·5 ml) at room temp to give 105·1 mg crude IXb. This was chromatographed on alumina (Woelm III, neutral) followed by recrystallization from pet. ether and gave colourless needles (IXb, 73·3 mg), m.p. 100–103°. (Found: C, 72·56; H, 10·24. $C_{17}H_{28}O_3$ requires: C, 72·82; H, 10·06%). Compound IXb (10·9 mg) was saponified with 5% KOH-methanol (1 ml) in N_2 atm. under reflux to give 7·1 mg of IXa.

Octahydrolinderene mesylate (IXc)

Mesyl chloride (170 mg) was added to an ice-cooled solution of IXa (94·0 mg) in pyridine (1·5 ml) and left for 18·5 hr at 23°. Ice water (10 ml) was added and the separated precipitate (110·6 mg) was filtered, washed, and dried (P_2O_5). Recrystallization from ether–pet. ether (1:1) gave pure IXc as colourless needles, m.p. 110–112°, ν_{max}^{Nujol} 1330 cm^{-1}. (Found: C, 60·66; H, 8·98. $C_{16}H_{28}O_4S$ requires: C, 60·73; H, 8·92%).

Demesylation of IXc *in dimethylsulphoxide*

A solution of IXc (55·0 mg) in dimethylsulphoxide (2 ml) was heated at 100° for 5 hr. Water was added to the reaction mixture, and the ether extract was washed with 5% $NaHCO_3$, water, dried (Na_2SO_4) and evaporated, leaving an oily substance (38·6 mg). This was chromatographed on silica gel and the unsaturated compound (13·1 mg) was obtained from the ether–pet. ether (1:9) eluate. This crude Xa was further purified by chromatography on alumina (Woelm II, neutral), to give a colourless mobile oil (8·8 mg), ν_{max}^{film} 1053, 1017 cm^{-1}, NMR 4·78τ (d. J = 2·8 c/s). Catalytic hydrogenation of this Xa (12·9 mg) with PtO_2 (12·5 mg) in acetic acid (1·5 ml) at room temp afforded II in 75·2% yield.

Osmium tetroxide oxidation of (Xa)

A solution of OsO_4 (149 mg) in dry benzene (0·6 mg) was added to an ice-cooled solution of Xa (58·5 mg) in dry benzene (0·6 ml) and left for 18 days at room temp. Benzene (2·0 ml) was further added and saturated with H_2S. The black precipitate was filtered off and washed with ether. The

filtrate and washings were combined and evaporated *in vacuo* and the residue was recrystallized from ether–pet. ether (1:1) to give 28·5 mg of the glycol (XIa) as colourless plates, m.p. 134–135°, ν_{max}^{Nujol} 3460, 3326 cm^{-1}. (Found: C, 70·81; H, 10·34. $C_{15}H_{26}O_3$, requires: C, 70·83; H, 10·30%).

Oxidation of the glycol (XIa) *with sodium periodate*

A solution of $NaIO_4$ (8·4 mg) in water (0·4 ml) was added to a solution of XIa (5·0 mg) in methanol (0·3 ml) and left at room temp for one week. The mixture was evaporated *in vacuo* and extracted with ether. The ether extract was washed with 5% $NaHCO_3$, dried (Na_2SO_4) and evaporated, leaving an oil (4·1 mg). Purification through alumina chromatograph was unsuccessful. Then the residue was separated by preparative thin layer chromatography to give 0·5 mg of the keto-aldehyde (XII), colourless oil, ν_{max}^{film} 2702, 1721, 1706 cm^{-1}, and 1·9 mg of the starting material.

Demesylation of IXc *in pyridine*

A solution of IXc (100·9 mg) in dry pyridine (3 ml) was heated at 100° for 6·5 hr. Ice water was added and the reaction mixture extracted with ether, washed with 5% HCl, 5% $NaHCO_3$, water, dried (Na_2SO_4) and evaporated to leave a yellow oil (68·1 mg). The demesylated product (44·2mg) was obtained by silica gel column chromatography. As the IR and the thin layer chromatogram of this material showed it to be a mixture, OsO_4 oxidation was then carried out. A solution of OsO_4 (104·0 mg) in dry benzene (0·5 ml) was added to a cooled solution of this demesylation product (41·0 mg) in dry benzene (0·5 ml) and left for 6 days at room temp, and worked up as usual. The violet coloured residue (44·2 mg) was purified by the combination of crystallization (pet. ether) and alumina chromatography and 13·6 mg XIb, m.p. 154–156° was obtained as colourless plates, ν_{max}^{Nujol} 3430, 3353 cm^{-1}, (Found: C, 70·68; H, 10·59. $C_{15}H_{26}O_3$ requires: C, 70·83; H, 10·30%), together with 3·2 mg XIa, m.p. 128–134·5°.

Conversion of the demesylation product of VIIIc *into the glycol* XIb

Mesyl chloride (215·9 mg) was added to an ice-cooled solution of VIIIa (111·2 mg) in pyridine (1·8 ml) and left for 19 hr at 25°. The mesylate (VIIIc; 75 mg), m.p. 84–87° (from ether–pet. ether = 1:1), colourless prisms, ν_{max}^{Nujol} 1338, 1168 cm^{-1}, was obtained by the usual manner. This (74·6 mg was demesylated as in the case of IXc and 16·2 mg of unsaturated compound XIII was obtained, ν_{max}^{film} 1039, 1013 cm^{-1}. Compound XIII was assumed to be a mixture from the result of the thin layer chromatogram and was then oxidized with OsO_4 without purification and gave only one glycol XIV (2·5 mg), m.p. 120–125·5°, colourless prisms, ν_{max}^{Nujol} 3460 (shoulder), 3362, 3072, 1034 cm^{-1}, after alumina chromatography followed by crystallization from pet. ether, in a pure state.

This glycol (2·0 mg) was reduced catalytically with PtO_2 in acetic acid at room temp to give 1·1 mg of the reduction product, m.p. 140–154° (as colourless prism). This compound was identical with the glycol (XIb) obtained from IXa by mixed m.p. determination and comparison of IR spectra.

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