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THE STRUCTURE OF VERMEERIN

A SESQUITERPENOID DILACTONE FROM *GEIGERIA AFRICANA* GRIES

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Abstract The structure of vermeerin, a sesquiterpenoid dilactone from *Geigeria africana* Gries, was shown to be I. Vermeerin is the dilactone of the physiologically active vermeeric acid which causes "vomiting disease" among sheep in South Africa

THREE CRYSTALLINE sesquiterpenoid lactones, vermeerin, geigerin and geigerinin have been isolated from *Geigeria aspera* Harv.[1,2] and the structures of geigerin[3] and geigerinin[4] have been determined.

The sesquiterpenoid acetoxy lactone, gafrinin,[5,6] and sesquiterpenoid dilactone, vermeerin, have been isolated from *Geigeria africana* Gries, the "vermeerbos" responsible for "vermeersiekte" (vomiting disease) among sheep in South Africa. Geigerinin was also isolated for the first time from this particular species.

Vermeerin was isolated from *G. aspera* by Rimington[1] who showed in a preliminary study that it was the dilactone of vermeeric acid. He also showed that vermeeric acid was, in fact, the active principle of the plant. We were able to isolate vermeerin only from *G. africana* and all our attempts to isolate vermeeric acid from this species failed.

Rimington suggested an empirical formula, $C_{18}H_{24}O_5$ for vermeerin, based on lactone titrations and elemental analyses. This formula is now revised to $C_{15}H_{20}O_4$, since a mass spectrum showed the molecular ion peak at *m/e* 264 and no other peaks beyond this value. The C_{15}-formula is more favourable biogenetically than the C_{18}-formula, since it would be difficult to account for the three additional carbon atoms unless it was assumed that vermeerin possesses an open chain fatty ester of three carbon atoms (propionate). No fatty acid was, however, obtained when vermeerin

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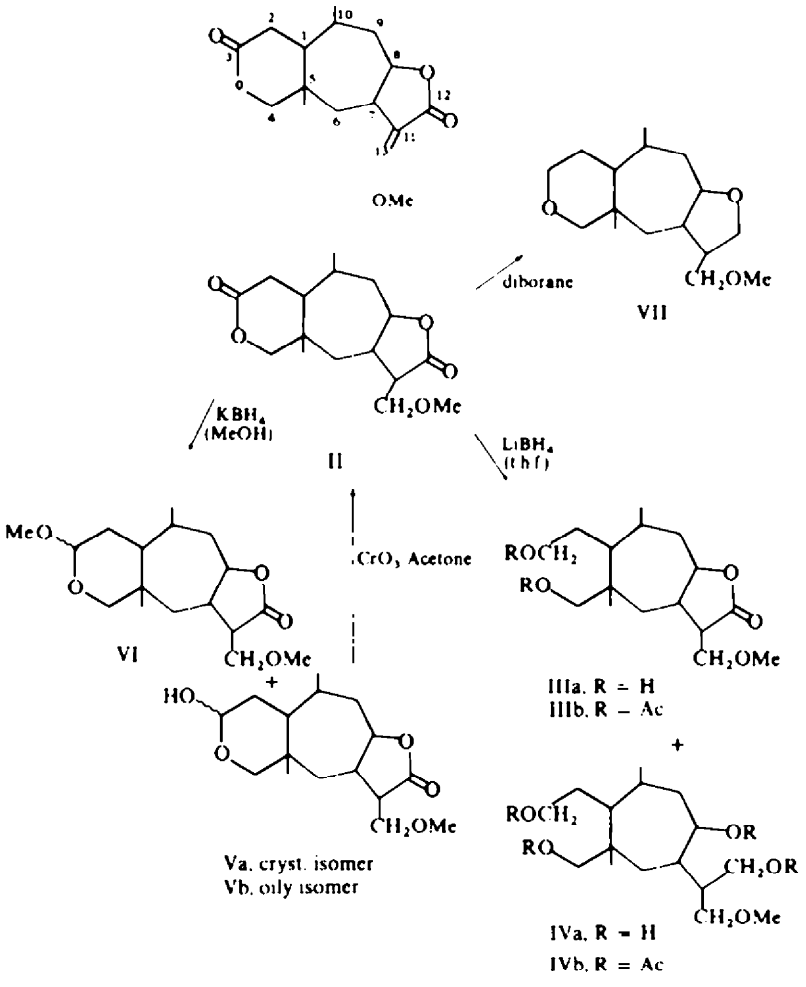
[1] C. Rimington and G. C. S. Roets, *Onderstepoort J. Vet. Sci.* 7, 485 (1936).
[2] J. de Villiers, *J. Chem. Soc.* 2412 (1959).
[3] D. H. R. Barton and J. E. D. Levisalles, *J. Chem. Soc.* 4518 (1958).
[4] J. de Villiers and K. G. R. Pachler, *J. Chem. Soc.* 4989 (1963).
[5] J. de Villiers, *J. Chem. Soc.* 2049 (1961).
[6] I. A. P. Anderson, W. T. de Kock, W. Nel, K. G. R. Pachler and G. van Tonder, in press.

was saponified with 0·5N NaOH and subsequently worked up for a fatty acid according to Garbers and Karrer[7] and followed by paper chromatography according to Lindquist and Storgårds.[8]

Two of the oxygen functions of vermeerin are accounted for by the presence of an α-β-unsaturated γ-lactone with an exocyclic methylene group. This was established by the strong carbonyl band at 1745 cm^{-1} in the IR, and the maximum absorption at 209 mμ (ε 12,340) in the UV spectrum.

The NMR spectrum showed two doublets at τ = 3·87 (J = 3·5 c/s) and τ = 4·60 (J = 3·0 c/s). These are characteristic for an exocyclic methylene group in conjunction with γ-lactonic carbonyl.[2, 9, 10] The splitting of these resonances arises from allylic



[7] C. F. Garbers, H. Schmid and P. Karrer, *Helv. Chim. Acta* **37**, 1336 (1954).

[8] B. Lindquist and T. Storgårds, *Acta Chem. Scand.* **7**, 87 (1953).

[9] H. B. Kagan, H. E. Miller, W. Renold, M. V. Lakshmikantham, L. R. Tether, W. Herz and T. J. Mabry, *J. Org. Chem.* **31**, 1629 (1966).

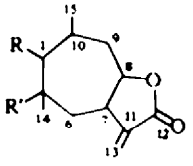
[10] W. Herz, S. Rajappa, S. K. Roy, J. J. Schmid and R. N. Mirrington, *Tetrahedron* **22**, 1907 (1966).

couplings to the proton on C-7[10]* while the coupling between the two methylene protons is not resolved.

Vermeerin gave a crystalline pyrazoline[11] derivative with diazomethane, and ozonolysis of vermeerin gave rise to formaldehyde.

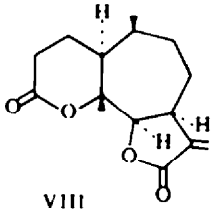
Treatment of vermeerin (I) with sodium methoxide in dry methanol resulted in a Michael addition of methanol to the α,β-unsaturated γ-lactone to give the methyl ether II. The Michael reaction on the α,β-unsaturated γ-lactone of sesquiterpenoids is well known.[12] The vinyl proton signals (doublets at $\tau = 3{\cdot}87$ and $\tau = 4{\cdot}60$) in the NMR spectrum of vermeerin (I) had disappeared in the spectrum of II, but a new methoxyl signal (singlet, $\tau = 6{\cdot}66$) and signals for the methylene protons adjacent to the methoxyl group had now appeared at $\tau = 6{\cdot}39$.

The NMR spectrum of vermeerin displayed signals characteristic for one tertiary (singlet, $\tau = 8{\cdot}93$) and one secondary Me group (doublet, $\tau = 9{\cdot}00$, $J = 6{\cdot}5$ c/s). The resonance of the proton on the carbon bearing the lactone oxygen appeared as a multiplet at $\tau = 6{\cdot}05$ overlapped by the AB-pattern of the C-4-protons. The splittings involved are close to those observed for geigerinin.[2] This suggested the partial structure A for vermeerin, similar to that of geigerinin.



A

If the lactonized OH function had been attached to C-6 the proton on this carbon atom would have given rise to a clear doublet in the NMR spectrum as observed for psilostachyin C (VIII).[9]



VIII

The remaining two oxygen functions of vermeerin were shown to belong to a δ-lactone group on the following evidence: the absence of a ketone group was established by the fact that vermeerin gave no 2,4-dinitrophenylhydrazone, nor ketonic UV absorption or Cotton effects characteristic of ketonic chromophores. All attempts to acetylate vermeerin failed and an active hydrogen determination was also negative. A lactone titration, however, required two equivalents of alkali suggesting the presence

* We have independently confirmed the findings of Herz *et al.*[10] by a detailed double-resonance study of gafrinin,[6] another sesquiterpenoid lactone isolated from *Geigeria africana* Gries containing the same γ-lactone grouping.

[11] P. G. Deuel and T. Geissman, *J. Am. Chem. Soc.* **79**, 3778 (1957).
[12] W. Herz, K. Ueda and S. Inayama, *Tetrahedron* **19**, 483 (1963).

of a second lactone. The IR spectrum showed no OH absorption in the 3400 cm^{-1} region, but a strong carbonyl band at 1730 cm^{-1} characteristic of a δ-lactone.

The following reactions supplied further evidence for the presence of a δ-lactone in vermeerin: Treatment of the Michael adduct II with lithium borohydride in boiling tetrahydrofuran gave the two oily alcohols IIIa and IVa. Only the δ-lactone ring was reduced in IIIa while both δ- and γ-lactones were opened in IVa. The IR spectrum of IIIa only showed carbonyl absorption at 1775 cm^{-1} (saturated γ-lactone) and an OH band at 3550 cm^{-1}, while the IR spectrum of IVa showed no carbonyl absorption and strong OH absorption at 3450 cm^{-1}. Acetylation of IIIa gave an oily diacetate IIIb and acetylation of the tetrol IVa gave a crystalline tetra-acetate IVb. The presence of two acetyl groups in the diacetate IIIb was supported by the IR bands at 1750 and 1240 cm^{-1} and by two acetyl signals at τ = 7·94 and 7·97 in the NMR spectrum.

Treatment of the Michael adduct II with potassium borohydride in methanol gave a mixture of lactol isomers in which only the carbonyl function of the δ-lactone had been reduced. The mixture of lactols was separated into a crystalline isomer Va and an oily isomer Vb. Both these isomers could be converted to II by oxidation with chromic acid in acetone.[13] A similar reduction of a δ-lactone to a lactol was recently reported by Baran[14] in the steroid field. A crystalline dimethoxyl compound VI was also isolated from the potassium borohydride reduction mixture of II.

The NMR spectra of compounds Va and VI (Table) exhibit the usual resonances of the secondary and tertiary Me groups on C-10 and C-5, respectively, the complex pattern of the C-8-proton and the AB-system assigned to the C-4 protons. The C-13 methylene group, as in VI (τ = 6·39, S = 3·7 c/s), usually a deceptively simple[15] doublet with a splitting of 3·6 4·0 c/s, appeared in Va as the AB-part of an ABX-pattern centred around τ = 6·42. The proton on C-3 gave a triplet (J = 2·3 c/s) at τ = 4·96 for compound Va which, as expected,[16] was shifted to higher field on methylation of the OH group [τ = 5·35 for VI]. The alcohol Va showed one OMe singlet at τ = 6·71 while the corresponding dimethoxyl compound VI gave rise to two OMe resonances at τ = 6·66 and 6·67.

The lactone carbonyl functions of vermeerin were finally reduced with diborane to give the dicyclic ether VII. This compound showed no carbonyl or OH absorption in the IR and only strong ether bands at 1135, 1110 and 1035 cm^{-1}.

The δ-lactone can be attached to the partial structure A in six different ways as indicated on p. 4158.

NMR evidence supports structure *c* as there are proton signals at τ = 5·95 and 6·18 in vermeerin constituting an AB-system with a coupling constant J_{AB} = 10·9 c/s. The τ-value agrees well with the value found for δ-valerolactone (τ_{CH_2O} = 5·91[17,18]), the coupling constant is close to those found for geminal protons on a sp^3-hybridized carbon atom,[19] and the absence of further splittings indicates the neighbourhood of a quaternary carbon atom.

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[19] N. Sheppard and H. J. Bernstein, *J. Chem. Phys.* **37**, 3012 (1962).

TABLE 1. NMR DATA[a] ON VERMEERIN AND DERIVATIVES

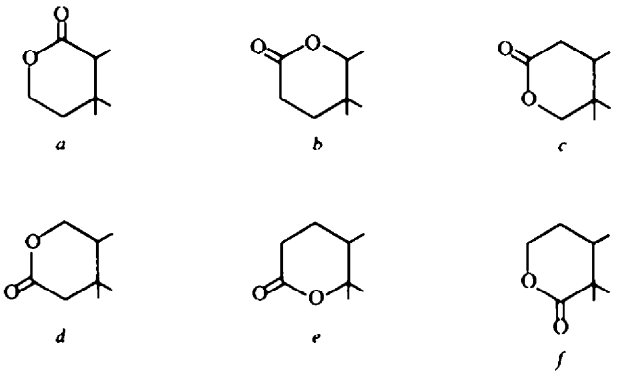
Proton in position[b]	Compound I	II	IIIb	Va	VI	VII
1	7·98 (X)	7·95 (X)	—			
2	7·37 (A); 7·65 (B) ABX	7·35 (A); 7·62 (B) ABX				
	J_{AB} = 17·3; J_{AX} = 5·3; J_{BX} = 8·1	J_{AB} = 17·0; J_{AX} = 5·7; J_{BX} = 8·5				
3		—	~6·0	4·96 (t) J = 2·3	5·35 (t) J = 2·4	~6·7
4	5·95; 6·18: AB	5·93; 6·19: AB	5·90; 6·11: AB	6·56; 7·10: AB	6·48; 7·06: AB	
	J = 10·9	J = 11·2	J = 11·3	J = 10·7	J = 10·8	
7						7·93 (c)
8	6·05 (o)	6·03 (o)	~6·0	6·09 (o)	6·09 (o)	6·01 (d, b)
	S: 4·5; 9·6; 11·2	S: 4·5; 9·8; 10·8		S: 4·3; 9·8; 11·0	S: 4·5; 9·3; 11·3	S: ~11·5
12				—	—	6·06 (A); 6·34 (B): ABX
						J_{AB} = 8·7; J_{AX} = 8·8; J_{BX} = 6·8
13	3·87 (d) J = 3·5	6·39 (d) S = 4·0	6·39 (d) S = 3·6	6·38 (A); 6·45 (B): ABX	6·39 (d) S = 3·7	~6·7
	4·60 (d) J = 3·0			J_{AB} = 10·0; J_{AX} = 4·2; J_{BX} = 3·0		
14	8·93 (s)	8·96 (s)	9·10 (s)	9·10 (s)	8·98 (s)	8·99 (s)
15	9·00 (d) J = 6·5	9·02 (d) J = 6·5	8·90 (d) J = 7·0	9·08 (d) J = 6·3	9·09 (d) J = 6·4	9·10 (d) J = 6·4
3-OMe					6·66 (s)	
12-OMe		6·66 (s)	6·68 (s)	6·71 (s)	6·67 (s)	
3-OAc, 4-OAc			7·94 (s); 7·97 (s)			

[a] Chemicals shifts are given in ppm on the τ-scale, coupling constants in c.s. AB and ABX spectra are analysed following the usual procedures. Splittings (S) are given if no exact analysis has been performed.

Abbreviations: s = singlet; d = doublet; t = triplet; o = octet; b = broad; S = splitting.

[b] The numbering corresponds to structure I.

Further support for the suggested δ-lactone structure is obtained from the analysis of the NMR signals of the C-2-protons of compounds I and II. They constitute an ABX-pattern with τ_A and τ_B ranging from 7·35 to 7·65 in good agreement with the



corresponding protons in δ-valerolactone (τ_{CH_2CO} = 7·73[17,18]). The AB-coupling of 17 c/s corresponds to a geminal coupling with a hyperconjugative enhancement[20] caused by the π-electrons of the carbonyl group. The two vicinal couplings J_{AX} and J_{BX} confirm the neighbourhood of a tertiary carbon atom (C-1). None of the other δ-lactone isomers would agree with these assignments.

Psilostachyin C (VIII), recently isolated from *Ambrosia psilostachya* DC by Kagan *et al.*,[9] was the first sesquiterpenoid lactone possessing both a δ- and γ-lactone. Vermeerin is isomeric with psilostachyin C and differs from it in the position of attachment of the unsaturated γ-lactone and the position of the oxygen functions in the δ-lactone.

EXPERIMENTAL

M.ps are uncorrected. Unless otherwise stated, $[\alpha]_D$ and UV spectra refer to EtOH, IR spectra to $CHCl_3$ and NMR spectra to $CDCl_3$ solns. IR spectra were recorded on a Unicam Model S.P. 200 spectrometer, UV spectra on a Unicam Model S.P. 800 spectrometer and NMR spectra on a Varian HA-100 spectrometer. Chemical shifts were measured on the τ-scale relative to TMS as internal standard (τ = 10·0); τ-values are estimated to be accurate to ±0·01 ppm, coupling constants to ±0·2 c s. Mass spectra were recorded on a MS-9 spectrometer.

TLC was carried out on silica gel plates using $CHCl_3$–MeOH (19:1) as solvent system. The spots were developed with the vanillin–phosphoric acid reagent or with 0·5% potassium permanganate in saturated copper acetate.

Geigeria africana was obtained from the Rietondale Experimental Farm, Pretoria, through the courtesy of Dr. T. Terblanche of Onderstepoort.

Extraction and isolation of vermeerin. Ground, air-dried *G. africana* (31·7 kg) was extracted 3 times with hot, 96% EtOH. The extract was concentrated to 5 l. and water (2 l.) added. Chlorophyll and fats were extracted with hexane and the aqueous residue then treated with a hot soln of basic lead acetate (1·5 kg in 1·5 l. water). The lead acetate ppt was filtered off, the filtrate concentrated and then thoroughly extracted with $CHCl_3$. The latter was removed *in vacuo* and the tarry residue (250 g) taken up in $CHCl_3$ containing 0·5% EtOH and chromatographed on neutral alumina (3 kg). The fractions eluted with $CHCl_3$ containing 2·5% EtOH contained most of the sesquiterpenoids. These fractions were combined (113 g tar) and taken up in formamide. A small quantity of less polar sesquiterpenoids was first extracted with benzene and the formamide residue then diluted with two parts of water and thoroughly extracted with $CHCl_3$. The $CHCl_3$ was washed with water and removed *in vacuo*. The oily residue (63·5 g) was chromatographed on

[20] M. Barfield and D. M. Grant, *J. Am. Chem. Soc* **85**, 1899 (1963)

cellulose (1·5 kg) impregnated with a 40% soln of formamide in acetone. The chromatogram was controlled by TLC of the individual fractions.

Benzene–hexane (3:1) eluted fractions which gave green spots (R_f 0·45) with the permanganate reagent on TLC. The combined fractions were evaporated to dryness and the residue (9·25 g) crystallized from $CHCl_3$–ether to give *vermeerin* (6·65 g) as colourless needles, m.p. 147°, $[\alpha]_D$ −58° (*c*, 1·5), λ_{max} 209 mμ (ε 12,340), ν_{max} 1745 and 1410 (α,β-unsat. γ-lactone), 1730 (δ-lactone), 1275, 1010, 995, 944 and 813 cm^{-1}. [Found: C, 68·1; H, 7·6; *M* (mass spect.) 264. $C_{15}H_{20}O_4$ requires: C, 68·2; H, 7·6%; *M*, 264.]

Pyrazoline derivative[11] *of vermeerin.* A suspension of I (100 mg) in abs ether (100 ml) was treated with diazomethane prepared from nitrosomethyl urea (350 mg). Another portion of diazomethane was added after one day. After 3 days in the refrigerator, the solvent was removed and the residue crystallized from MeOH to give colourless *crystals* (46 mg), m.p. 126–127·5°, $[\alpha]_D$ −393° (*c*, 0·36). [Found: C, 62·3; H, 7·3; N, 9·2; *M* (mass spect.) 306. $C_{16}H_{22}O_4N_2$ requires: C, 62·7; H, 7·2; N, 9·2%; *M*, 306.]

Ozonolysis of vermeerin. Vermeerin (100 mg) in AcOH (25 ml) was treated with a stream of O_2 containing 3 mg of O_3 min for 90 min. The mixture was steam-distilled into aqueous dimedone. Upon concentration, a ppt (20 mg) was formed which had m.p. 191° alone or mixed with the formaldehyde derivative of dimedone.

Treatment of vermeerin with sodium methoxide in methanol. A soln of Na (1·3 g) in dry MeOH (150 ml) was added to a soln of vermeerin (3·2 g) in dry MeOH (150 ml) and left at 3° for 4 days. The soln was acidified to pH 4 with HCl and then extracted with $CHCl_3$ (6 × 50 ml). The latter was washed with water, dried over Na_2SO_4 and evaporated to dryness. The oily residue was crystallized from $CHCl_3$–ether to give colourless needles of the *Michael adduct* (II), m.p. 155–156°, $[\alpha]_D$ −36·4° (*c*, 0·65), ν_{max} 1780 (sat. γ-lactone) and 1740 cm^{-1} (δ-lactone). (Found: C, 64·8; H, 8·3. $C_{16}H_{24}O_5$ requires: C, 64·8; H, 8·2%.)

Reduction of II *with* $LiBH_4$ *in tetrahydrofuran.* The adduct II (1·5 g) was dissolved in dry THF (20 ml) and KBH_4 (1 g), followed by hot, vacuum-dried LiCl (1·5 g) added. The mixture was refluxed for 4 hr on a water-bath, cooled, acidified to pH 4 with HCl and then extracted, first with $CHCl_3$ and subsequently with AcOEt. The organic phases were separately washed with water, dried over Na_2SO_4 and evaporated to dryness *in vacuo*.

The $CHCl_3$ extract yielded a crude, oily product (840 mg) which was chromatographed on silica gel (100 g). $CHCl_3$–EtOH (9:1) eluted IIIa as an oil (426 mg), ν_{max} 3450 (OH) and 1775 cm^{-1} (sat. γ-lactone). Acetylation of this compound (362 mg) with Ac_2O–perchloric acid at 0° for 1 hr gave a crude diacetate which gave, after chromatography on silica gel (30 g) in hexane–benzene (4:1), a purified, oily *diacetate* IIIb (100 mg), $[\alpha]_D$ −13·4° (*c*, 0·7), $\nu_{max}^{CS_2}$ 1790 (sat. γ-lactone), 1750 and 1240 cm^{-1} (diacetate). (Found: C, 62·0; H, 8·1. $C_{20}H_{32}O_7$ requires: C, 62·5; H, 8·4%.)

The AcOEt extract also gave a crude, oily product (380 mg) which was purified by chromatography on silica gel (20 g). $CHCl_3$–EtOH (7:3) eluted an *oil* (IVa; 170 mg), ν_{max} 3450 (OH). Acetylation of this product with Ac_2O–perchloric acid at 0° and crystallization of the acetate from ether–hexane gave colourless *needles* of IVb, m.p. 74–76°, $[\alpha]$ +49° (*c*, 1·0), $\nu_{max}^{CS_2}$ 1725 and 1230 cm^{-1} (acetate). [Found: C, 61·1; H, 8·4; *M* (mass spect.) 472. $C_{24}H_{40}O_9$ requires: C, 61·0; H, 8·5%; *M*, 472.]

Reduction of II *with* KBH_4 *in methanol.* A suspension of KBH_4 (0·5 g) in MeOH (50 ml) was added to a suspension of II (1 g) in MeOH (25 ml) and the reaction mixture left at room temp for 30 min. It was then diluted with water (150 ml), acidified to pH 4 with dil acid and extracted with $CHCl_3$ (5 × 50 ml). The $CHCl_3$ extract was washed with water, dried over Na_2SO_4 and removed *in vacuo*. The residual oil (980 mg) was chromatographed on formamide-impregnated cellulose powder.

Hexane–benzene (95:5) eluted an oily dimethoxyl-*compound* (VI; 200 mg) which crystallized from hexane–ether as colourless plates, m.p. 90–91°, $[\alpha]_D$ +108·3° (*c*, 1·1), ν_{max}^{KBr} 1760 (γ-lactone), 1460, 1180, 1130, 1050 and 865 cm^{-1}. (Found: C, 65·2; H, 8·9. $C_{17}H_{28}O_5$ requires: C, 65·4; H, 9·0%.)

Hexane–benzene (3:1) eluted the *lactol* (Va; 119 mg) which crystallized from $CHCl_3$–ether as colourless needles, m.p. 162–164°, $[\alpha]_D$ +37° (*c*, 1·0), $\nu_{max}^{CS_2}$ 3420 (OH), 1770 (γ-lactone), 1380, 1140, 960 and 930 cm^{-1}. [Found: *M* (mass spect.) 298. $C_{16}H_{26}O_5$ requires: *M*, 298.]

Chloroform finally eluted the isomeric oily *lactol* (Vb; 187 mg), ν_{max} 3400 (OH), 1760 (γ-lactone), 1460, 1180, 1130 and 1010 cm^{-1}.

Oxidation of lactols Va *and* Vb *with* CrO_3 *in acetone*[13]. Ten drops of 8N CrO_3 soln (2·67 g CrO_3 dissolved in 10 ml water and 2·3 ml conc H_2SO_4) was added to a soln of Vb (187 mg) in acetone (10 ml) at 5° and left at this temp for 40 min. The excess chromic acid was decomposed by the addition of MeOH (3 ml) and the reaction mixture then diluted with water (100 ml) and extracted with $CHCl_3$ (5 × 20 ml). The $CHCl_3$ extract was washed with water, dried over Na_2SO_4 and distilled off to give an oily residue (120 mg) which

crystallized from $CHCl_3$–ether as colourless needles. This product was shown to be identical with II of vermeerin (m.p., mixed m.p. and IR spectrum).

The crystalline lactol isomer Va was similarly oxidized to II.

Reduction of the Michael adduct II *with diborane*. The methyl ether (II; 1 g) in dry THF (50 ml) and BF_3-etherate (20 ml) was added, with stirring, to a soln of LAH (1 g) in dry THF (100 ml) at 0° over a period of 25 min. The reaction mixture was left at 0° for a further 25 min and then refluxed on a water-bath for 3 hr. The excess of LAH was decomposed with wet AcOEt, followed by water and 10% H_2SO_4. Most of the THF was removed by distillation *in vacuo* and the aqueous layer then extracted with $CHCl_3$ (5 × 50 ml). The $CHCl_3$ extract was washed with water, dried over Na_2SO_4 and evaporated to dryness to give an oily residue (1·78 g). This residue was chromatographed on silica gel. $CHCl_3$ eluted an oil which was subsequently distilled (70° 0·005 mm) to give a colourless *oil* (VII, 272 mg), $[\alpha]_D$ +57·7° (*c*, 0·88); $\nu_{max}^{CS_2}$ 1380, 1230, 1135, 1110, 1035 and 980 cm^{-1}. [Found: C, 71·4; H, 10·4; *M* (mass spect.) 268. $C_{16}H_{28}O_3$ requires: C, 71·6; H, 10·5; *M*, 268.]

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