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SESQUITERPENES OF *NEOLITSEA ZEYLANICA* MERR.—II*

STRUCTURE OF NEOLINDERANE

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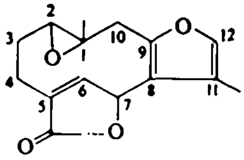
Abstract—Neolinderane, a new sesquiterpene constituent of *Neolitsea Zeylanica* Merr. is assigned structure I on the basis of spectral and degradation evidence.

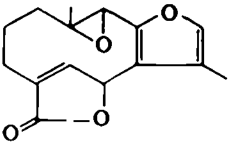
THE isolation of neolinderane, a new sesquiterpene from *Neolitsea Zeylanica* Merr. was described in an earlier paper.[1] Neolinderane $C_{15}H_{16}O_4$, m.p. 170°, $[\alpha]_D^{28°}$ +31·5° showed a UV max at 210 mμ (log ε 4·09) and IR bands at 1750 (α,β-unsaturated γ-lactone) and 3120, 3040, 1605 and 1540 cm^{-1} (furan ring). The compound gave a crimson colour with Ehrlich reagent. The NMR spectrum (Fig. 1): 1·0 (s, 3H, Me on carbon bearing epoxy oxygen), 2·1 (d, J = 1 c/s, 3H, Me on double bond), 7·0 (1H, α-proton of furan ring) and 7·1 δ (d, J = 1 c/s, 1H, β-proton on α,β-unsaturated γ-lactone system).

Catalytic reduction of neolinderane in ethanol (Pd–C) gave dihydroneolinderane, m.p. 225°, which had a UV max at 220 mμ (log ε 3·85) and the lactone carbonyl band at 1762 cm^{-1} (saturated γ-lactone). Its NMR spectrum showed the disappearance of the olefinic proton of neolinderane at 7·1 and the appearance of a triplet centred at 5·35 δ (J = 8 c/s).

Hydrogenation of neolinderane in presence of PtO_2 in acetic acid occurred with absorption of two moles of hydrogen and gave an epoxyfurano carboxylic acid, neolinderanic acid $C_{15}H_{20}O_4$, by reduction of one double bond and hydrogenolysis of the lactone ring. This showed that the lactonic oxygen must be attached to an allylic position. Since the acid gives a positive Ehrlich test and has the signal at 7·0 δ (furan, α-proton) in the NMR spectrum, the furan ring in neolinderane is unaffected under the hydrogenation conditions.



I



II

Neolinderane on treatment with perchloric acid gave an amorphous diol, yielding a crystalline monoacetate. Dihydroneolinderane gave similarly a crystalline diol, m.p. 265°, yielding a monoacetate, m.p. 253°. A study of the NMR spectra

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* Contribution No. 56 from CIBA Research Centre.

[1] B. S. Joshi, V. N. Kamat and T. R. Govindachari, *Tetrahedron* 23, 261 (1967).

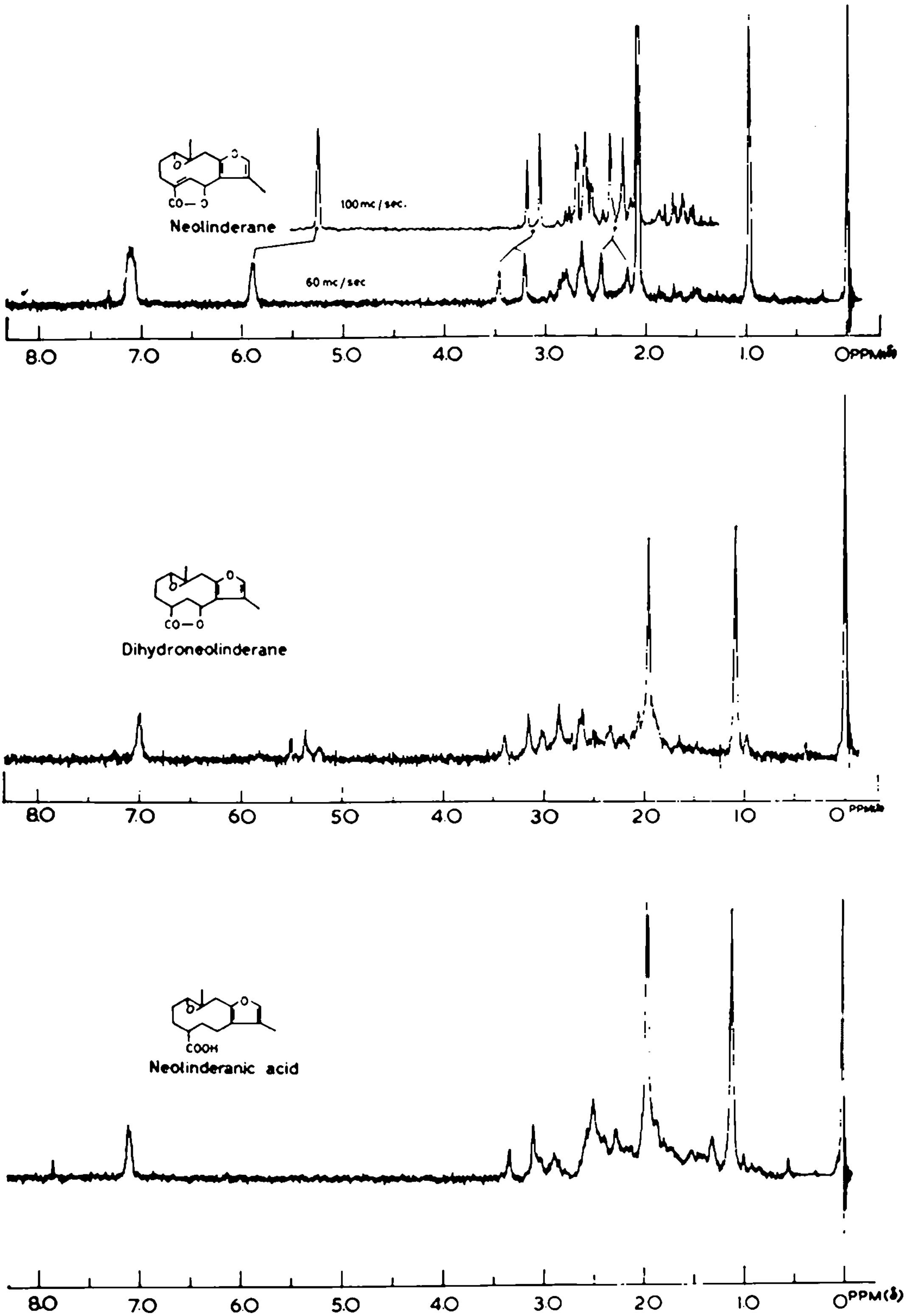
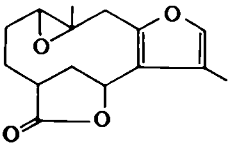

CO—O
Neolinderane
100 mc/sec.
60 mc/sec
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0 PPM(δ)
CO—O
Dihydroneolinderane
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0 PPM(δ)
COOH
Neolinderanic acid
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0 PPM(δ)

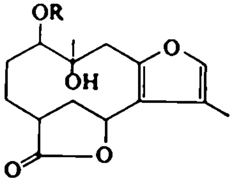
FIG. 1

of neolinderane, dihydroneolinderane and neolinderanic acid reveals that one of the methyl groups must be located on the furan ring and the other methyl group on a carbon bearing an epoxy oxygen. Further, neolinderane, for which only structures I or II can be written, should be a ten-membered sesquiterpene, closely related to linderalactone and linderane.

A decision between the two structures could be reached by a study of the 100 Mc NMR spectra of neolinderane (Fig. 1) and dihydroneolinderane. The C-10 proton in II would be expected to be a sharp singlet. However, two doublets are seen at 2·3 and 3·25 δ ($J = 15$ c/s)[2] constituting an AB spectrum ascribable to geminal coupling between the two protons at C-10 as in structure I. In dihydroneolinderane, the doublets at 2·48 and 3·21 δ ($J = 15$ c/s) could be assigned to the C-10 protons and this was further confirmed by double resonance experiments. Dihydroneolinderane could therefore be formulated as III and the diol obtained from it as IVa. The NMR spectrum of the monoacetate IVb is consistent with this formulation. This shows a broad multiplet at 4·9 δ due to the C-2 proton split by two adjacent hydrogens at C-3. Neolinderanic acid could therefore be formulated as V.

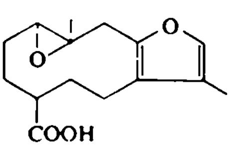


III

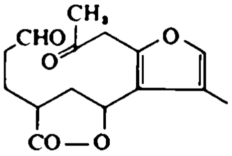


IV a: R = H
b: R = $COCH_3$

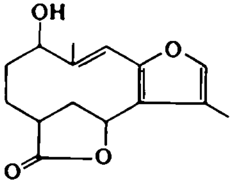
Cleavage of the diol IVa with sodium metaperiodate yielded an amorphous keto aldehyde whose IR spectrum showed bands at 2740 (aldehyde), 1760 (γ-lactone) and 1710 cm^{-1} (saturated ketone). The presence of a —$COCH_3$ was confirmed by the iodoform reaction. The NMR spectrum showed signals at 9·8 (aldehyde proton) and 2·2 δ (—$COCH_3$), consistent with the formulation of the cleavage product as VI. Further, a bis-2,4-dinitrophenylhydrazone was formed (pure by TLC) showing a UV max at 360 $m\mu$, whereas the furfuraldehyde 2,4-dinitrophenylhydrazone derived from structure II would be expected to absorb about 380 $m\mu$.



V



VI



VII

Dehydration of the diol IVa with thionyl chloride yielded an amorphous product

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[2] L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy* p. 85. Pergamon Press (1959).

(pure by TLC) which showed a UV max at 250 mμ, (log ε 3·78) which would be consistent with its formulation as VII.[3,4]

EXPERIMENTAL

Dihydroneolinderane (III). Neolinderane (1·3 g) was dissolved in EtOH (75 ml) and hydrogenated at 26° using 10% Pd–C (0·4 g). The reaction was stopped when 112 ml H (1 mole) was absorbed. After filtration, the solvent was removed and the residue crystallized from CH_2Cl_2–EtOH (650 mg), m.p. 225°. TLC on si-gel (R_f 0·41, chf–EtOAc 19:1), $[\alpha]_D^{26°}$ $-98·3°$, (*c*, 2·3; dioxan); UV (EtOH): 220 mμ (log ε, 3·85). IR (nujol): 1760, 1269, 1259, 1222, 1180, 1160, 1145, 1125,1103, 1020, 1010, 972, 945, 910, 835, 780, 748 cm^{-1}. (Found: C, 68·9; H, 6·8; mol. wt. by mass spectrum 262. $C_{15}H_{18}O_4$ requires: C, 68·7; H, 6·9%; mol. wt. 262.)

Reaction of perchloric acid on dihydroneolinderane to give the diol (IVa). To a soln of III (1·2 g) in CH_2Cl_2 (24 ml) and MeOH (48 ml) was added 70% perchloric acid (6 ml) and water (24 ml). The mixture was stirred at 26° for 24 hr. The reaction mixture turned slight pink. It was diluted with water and extracted with CH_2Cl_2. The extract was washed with $NaHCO_3$aq, dried (Na_2SO_4) and then evaporated leaving a semicrystalline residue. Recrystallization from CH_2Cl_2–ether gave IVa, 380 mg, m.p. 265°. TLC on si-gel (R_f 0·40, $CHCl_3$–EtOAc 1:1), UV (EtOH): 218 mμ (log ε, 3·85). IR (nujol): 3450, 3290, 1760, 1275, 1262, 1188, 1151, 1102, 1060, 1040, 1012, 900, 798, 755 cm^{-1}. The NMR ($CDCl_3$ + CD_3SOCD_3): 7·2 (1H; α-proton of furan), 5·7 (1H; multiplet due to C-7 proton); 1·92 (3H; Me on C-11); 1·1 (3H; Me on C-1); and a broad band at 3·75 δ due to OH group. (Found: C, 64·3; H, 7·0. $C_{15}H_{20}O_5$ requires: C, 64·3; H, 7·2%.)

Acetylation of IVa. To a soln of IVa (300 mg) in pyridine (3 ml) was added Ac_2O (4·5 ml) and the mixture left overnight at room temp. The reaction mixture was diluted with ice and extracted with CH_2Cl_2. The extract is washed with $NaHCO_3$aq, dried (Na_2SO_4), and evaporated leaving a glassy residue. Crystallization from CH_2Cl_2–EtOH gave IVb (250 mg), m.p. 253°. TLC on si-gel (R_f 0·47, $CHCl_3$–EtOAc 3:1) UV (EtOH): 218 mμ (log ε, 3·94). IR (nujol): 3488, 1760, 1722, 1325, 1288, 1250, 1225, 1182, 1158, 1140, 1130, 1070, 1040, 999, 802, 770, 732 cm^{-1}. The NMR ($CDCl_3$ + CD_3SOCD_3): 7·2 (1H; furan α-proton), 5·7 (1H, broad multiplet due to C-7 proton); 4·9 (1H; broad multiplet; C-2 proton carrying the acetate group); 2·0 (3H; Ac); 1·9 (3H; Me on C-11); 1·09 δ (3H; Me on C-1). (Found: C, 63·7; H, 6·9. $C_{17}H_{22}O_6$ requires: C, 63·3; H, 6·9%.)

Neolinderanic acid (V). A soln of neolinderane (1·5 g) in glacial AcOH (100 ml) was hydrogenated using PtO_2 (1 g) catalyst. The reduction was stopped after 4 hr (H uptake 2 moles). The soln was filtered and the AcOH removed *in vacuo*. The gummy residue was dissolved in CH_2Cl_2 and extracted with $NaHCO_3$aq. The bicarbonate extract was acidified with HCl and the ppt extracted with CH_2Cl_2. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated to give a glassy residue, which on crystallization from CH_2Cl_2–ether gave V (360 mg), m.p. 195°. TLC on si-gel (R_f 0·43, toluene:ethyl formate: formic acid 5:4:1). IR (nujol): 1722, 1292, 1275, 1240, 1212, 1182, 1135, 1100, 930, 912, 890, 808, 755 cm^{-1}. (Found: C, 68·0; H, 7·4. $C_{15}H_{20}O_4$ requires: C, 68·1; H, 7·6%.)

Methyl ester of V. In an attempt to open the epoxide to form the diol using $HClO_4$ in MeOH, only the methyl ester was obtained. To a soln of V (300 mg) in CH_2Cl_2 (6 ml) and MeOH (24 ml) was added 70% $HClO_4$ (1·5 ml) and water (6 ml). The mixture was stirred at 26° for 24 hr. It was diluted with water and extracted with CH_2Cl_2. The extract was washed with H_2O, $NaHCO_3$aq, dried (Na_2SO_4) and then evaporated when a gummy residue (240 mg) was obtained. On sublimation at 90°/5 × 10^{-3} mm, the crystalline methyl ester was obtained (120 mg), m.p. 95–100°. TLC on si-gel (R_f 0·55, toluene: ethyl formate: formic acid 5:4:1), UV (EtOH) 216 mμ (log ε, 3·86). IR (nujol): 1737, 1212, 1200, 1172, 1100, 997, 927, 885, 842, 759, 732 cm^{-1}. (Found: C, 68·4; H, 7·8. $C_{16}H_{22}O_4$ requires: C, 69·0; H, 8·0%.) NMR ($CDCl_3$): 7·02 (1H; furan α-proton), 3·7 (3H; OMe), 2·0 (3H; $J = 1·2$ c/s; Me on furan), 1·18 δ (3H; Me on carbon bearing epoxide).

Action of perchloric acid on neolinderane. To a soln of I (2·5 g) in CH_2Cl_2 (25 ml) and MeOH (100 ml) was added 70% $HClO_4$ (12·5 ml) and H_2O (50 ml). The mixture was stirred overnight at 26°,

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[3] K. Takeda, H. Minato and I. Hirobe, *Tetrahedron* **19**, 2308 (1963).

[4] A. I. Scott, *Interpretation of Ultraviolet Spectra of Natural Products*. p. 45. Pergamon Press (1964).

diluted with water and extracted with CH_2Cl_2. The extract was washed with $NaHCO_3$aq, dried (Na_2SO_4) and then evaporated to obtain a glassy residue (2·15 g). A number of attempts to obtain it in a crystalline form were unsuccessful. The compd gave a positive periodate test for a vicinal diol.

TLC on si-gel showed it to be a mixture of two closely moving substances (R_f 0·17 and 0·23; chf-EtOAc 9:1). IR (nujol): 3443, 1748, 1723, 1303, 1263, 1195, 1138, 1088, 1050, 1018, 943, 928, 893, 863, 815, 768, 753, 723 cm^{-1}.

Acetylation of the above diol. To a soln of the diol (2·1 g) in pyridine (10 ml) was added Ac_2O (21 ml) and the mixture left overnight at room temp. The reaction mixture was diluted with ice and extracted with CH_2Cl_2. The extract was washed with dil. HCl, $NaHCO_3$aq, dried (Na_2SO_4), and then evaporated, leaving a crude crystalline mass. This was dissolved in CH_2Cl_2, excess ether added and the soln filtered. The clear filtrate on concentration gave a colourless crystalline product (800 mg), m.p. 115°. TLC on si-gel showed this to be a mixture of two closely moving substances (R_f 0·6 and 0·66; chf:EtOAc 9:1). Attempts to separate these, either by fractional crystallization or by chromatography on a column were not successful. These were eventually separated by using a thin layer preparative plate. The faster moving major compd (R_f 0·66) crystallized from CH_2Cl_2–ether as heavy prismatic rods, m.p. 127°, UV (EtOH):206 mμ (log ε, 3·98). IR (nujol): 3575, 3520, 3115, 3095, 1745, 1723, 1647, 1545, 1310, 1267, 1218, 1215, 1174, 1143, 1055, 955, 910, 880, 825, 778 cm^{-1}. The NMR spectrum: 7·15 (1H; furan α-proton); 6·82 (1H, C-6 proton); 5·75 (1H; C-7 proton); 5·4 (1H; C-2 proton carrying the acetate group); 2·2 (3H; Ac); 2·15 (3H; furan Me); 1·58 δ (3H; Me on C-1). (Found: C, 64·1; H, 6·0. $C_{17}H_{20}O_6$ requires: C, 63·7; H, 6·3%.)

Reaction of $NaIO_4$ *on* (IVa). The crystalline IVa (100 mg) was dissolved in MeOH (10 ml) and a soln of $NaIO_4$ (250 mg in 2 ml H_2O) was added and the mixture stirred at room temp for 20 hr. The MeOH was removed under red. press. and the residue extracted with CH_2Cl_2 leaving a gummy product. The crude compd showed UV (EtOH): 212, 284 mμ (ε, 6000 and 1100); IR (nujol): 2740 (aldehyde), 1760 (saturated γ-lactone), 1710 (ketone) cm^{-1}. The cleavage product gave CHI_3 with NaIO (mixed m.p., m.p. 118°. NMR spectrum: 9·8 (—CHO), 7·15 δ (J = 1·1 c/s, furan α-proton), 5·25 (broad, H-7), 2·2 (3H; Ac), 2·0 δ (d, 3H; furan Me J = 1·1 c/s).

The crude ketoaldehyde gave an amorphous 2,4-dinitrophenylhydrazone, UV (EtOH): 360 mμ.

Reaction of $SOCl_2$ *on* IVa. The diol IVa (200 mg) in pyridine (5 ml) was stirred with $SOCl_2$ (0·2 ml) at 5°. It was stirred for 2 hr longer and worked up as usual. The residue obtained (190 mg) was chromatographed on si-gel and eluted with benzene (100 ml), $CHCl_3$ (100 ml) and $CHCl_3$–AcOEt (90:10; 50 ml). The last fraction (50 mg) showed a single spot on TLC and showed UV (EtOH): 250 mμ (log ε, 3·78).

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