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SESQUITERPENES OF *NEOLITSEA ZEYLANICA* MERR.—III*

STRUCTURE OF ZEYLANINE, ZEYLANICINE AND ZEYLANIDINE

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Abstract—Zeylanine, Zeylanicine and Zeylanidine, three new sesquiterpenes isolated from *Neolitsea zeylanica* Merr. are assigned structures III, V and VI respectively on the basis of spectral and degradation evidence.

The isolation of three new sesquiterpenes, zeylanine, zeylanicine and zeylanidine from the roots of *Neolitsea zeylanica* Merr. was reported earlier.[1] Evidence is now presented on the basis of which structures can be assigned to these compounds.

Structure of zeylanine. Zeylanine $C_{17}H_{18}O_5$, m.p. 175° $[\alpha]_D$ +271° showed UV max at 204 and 252 mμ (log ε, 4·06, 3·76) and IR bands at 1755 (α,β-unsaturated γ-lactone), 1745, 1244 (acetate) and 3130, 1640, 1530 and 880 cm^{-1} (furan). The NMR spectrum† showed signals at 1·88 δ (d, J = 1·1 c/s, 3H, Me on double bond), 2·12 δ (d, J = 1·1 c/s, 3H, Me on double bond), 1·9 δ (s, 3H, Me of acetate group), 7·1 δ (broad m, 1H, olefinic proton), 6·22 δ (broad m, 1H, olefinic proton) and 7·2 δ (d, 1H, α-proton of furan ring). A positive Ehrlich colour test confirmed the presence of a furan ring.

Hydrolysis of zeylanine with methanolic HCl gave desacetylzeylanine, $C_{15}H_{16}O_4$, m.p. 219–220°, which could be reacetylated to zeylanine. The NMR spectrum of desacetylzeylanine shows the disappearance of the broad multiplet centered at 4·9 δ and the appearance of a quartet at 3·8 δ (J = 5 c/s). The OH proton seen at 4·65 δ disappears on deuteration. Reduction of zeylanine (PtO_2) proceeded with absorption of 5 moles of hydrogen yielding octahydrozeylanic acid $C_{17}H_{28}O_5$. The NMR spectrum of the product showed that the furan ring and the two double bonds had been reduced and the lactone ring opened by hydrogenolysis. The two methyl doublets (J = 7 c/s) at 0·95 δ and 1·1 δ show that the furan ring is not cleaved. The acetyl group is present as shown by the singlet at 2·05 δ and by the IR spectrum showing bands at 1734 and 1231 cm^{-1}. The hydrogenolysis of the lactone ring showed that the lactonic oxygen is allylic to the furan double bond or another olefinic bond.[2]

From the foregoing observations, it can be concluded that zeylanine contains a ten-membered ring apart from the furan ring and the γ-lactone system. One of the double bonds is conjugated with the γ-lactone carbonyl. From the UV spectrum, (252 mμ) it is evident that the other double bond should be in conjugation with the

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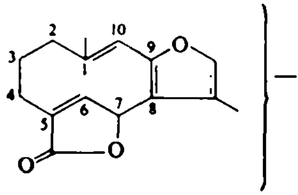
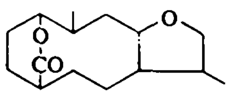
† Available on application to the authors.

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

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



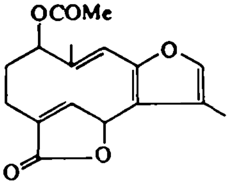
I



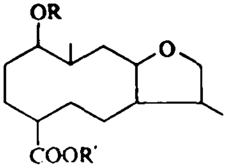
II

furan ring.[2,3] These facts lead to the partial structure I for zeylanine. That there was a proton at C-7 was apparent from the NMR signal at 5·75 δ as in linderalactone and neolinderane. If there had been a double bond at the 4,5 instead of the 5,6-position, the C-7 proton would have appeared as a broad triplet centered at about 5·2 δ, as in the case of dihydrolinderalactone and dihydroneolinderane.[1,4] Further, the signal at 7·1 δ is consistent with an olefinic double bond at the 5,6 instead of the 4,5-position. The acetoxy group should therefore be located at C-2, C-3 or C-4.

Octahydrozeylanic acid $C_{17}H_{28}O_5$ described earlier was converted to a methyl ester with methanolic HCl but alkaline hydrolysis yielded a hydroxy carboxylic acid $C_{15}H_{28}O_4$, m.p. 127°. This could be converted to a lactone, $C_{15}H_{22}O_5$, m.p. 208° showing IR bands at 1729 and 1709 cm^{-1}, proving that the newly formed lactone can only be a 6-membered lactone. Consequently, the acetoxy group in zeylanine has to be placed uniquely at C-2. Zeylanine could therefore be constituted as III and the hydrogenolysis product $C_{17}H_{28}O_5$ as IVa and the lactone as II.



III



IV

a: R = —COMe,
R' = H
b: R = H
R' = —Me
c: R = —COMe
R' = Me
d: R = R' = H.

Structures of zeylanicine and zeylanidine. Zeylanicine, $C_{17}H_{18}O_6$, m.p. 235°, $[\alpha]_D$ −153°, exhibited a UV max at 210 mμ and IR bands at 1758 (α,β-unsaturated γ-lactone), 1743 and 1230 (acetate) and 3130, 1640, 1580 and 886 cm^{-1} (furan). It gave a positive Ehrlich test. The NMR spectrum* showed the following signals; 2·07 (3H, acetate Me group), 2·03 (3H, Me on furan ring), 1·0 (s,3 H, Me on C bearing

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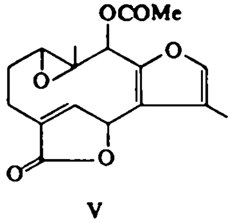
* Available on application to the authors.

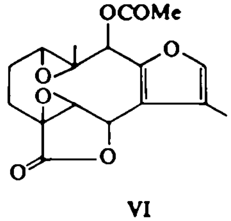
[3] A. I. Scott, *Interpretation of the UV spectra of natural products* p. 45. Pergamon Press, Oxford (1964).

[4] Part II; B. S. Joshi, V. N. Kamat and T. R. Govindachari, *Tetrahedron* 23, 267 (1967).

epoxy O), 7·17 (α-proton on furan ring) and 7·03 δ (broad, 1H, β-proton of the α,β-unsaturated lactone system). Reduction of zeylanicine in presence of Pd/C gave dihydrozeylanicine, in whose NMR spectrum the signal at 7·03 δ disappeared. The proton on the carbon carrying the acetoxy groups showed a sharp singlet peak at 5·95 δ in both zeylanicine and dihydrozeylanicine and the C-7 proton of zeylanicine at 5·83 δ appeared as a triplet centered at 5·4 δ (J = 17 c/s) in the dihydro compound. Zeylanicine can therefore be constituted as V. Zeylanidine, $C_{17}H_{18}O_7$, m.p. 226°, [α]$_D$ −174°, showed UV max at 214 and 224 mμ (log ε, 3·75 and 3·74) and IR bands at 1779 (γ-lactone), 1744, 1224 (acetate) and 3130, 3060, 1650, 890 cm^{-1} (furan). It gave a positive Ehrlich test. The NMR spectrum* showed the following signals: 2·0 (3H, Me of acetate), 2·05 (d, J = 1·4 c/s, 3H Me group on furan ring), 1·18 (s, 3H, Me on C bearing epoxy O), and 7·2 δ (1H, α-proton of furan ring). Since zeylanidine does not contain hydroxyl groups and four of the oxygens are accounted for in the lactone, furan and acetate functions of the molecule, the remaining two oxygens must be present at ethers, probably as epoxides and structure VI can be proposed for zeylanidine. This was borne out by the conversion of zeylanidine to zeylanicine (V) in 75% yield on treatment with chromous chloride. One of the epoxy rings must therefore be situated on C-5 and C-6. The singlet at 3·95 δ can be attributed to the C-6 proton and the singlet at 5·32 δ to the C-7 proton in the NMR spectrum of zeylanidine (cf. the NMR spectrum of linderane[1]). The sharp singlet at 5·95 δ must then be attributed to the protons on the carbon carrying the acetoxy group at C-2. In the NMR spectrum of desacetylzeylanidine obtained by hydrolysis of zeylanidine with methanolic KOH, the C-2 proton appears at 4·9 δ, the broad signal (influence of OH proton) becoming sharp on addition of D_2O. These observations are all consistent with structure VI proposed for zeylanidine.



V



VI

EXPERIMENTAL

Octahydrozeylanic acid (IVa). A soln of zeylanine (1·5 g) in glacial AcOH (50 ml) was hydrogenated using PtO_2 (1 g). The reaction was stopped after 7 hr. The soln was filtered from the catalyst, and the AcOH removed *in vacuo*. The semicrystalline residue was recrystallized from CH_2Cl_2–ether (300 mg), m.p. 180°. TLC on Si-gel (R_f 0·55; toluene:ethyl formate:formic acid 5:4:1). IR spectrum (nujol): 3240, 1734, 1691, 1288, 1273, 1231, 1159, 1130, 1089, 1059, 1030, 994, 898, 810, 764, 728 cm^{-1}. (Found: C, 65·5; H, 9·0. $C_{17}H_{28}O_5$ requires: C, 65·4; H, 9·0%.)

Action of methanolic HCl *on* IVa *to give* IVb. A mixture of IVa (200 mg) dissolved in MeOH (20 ml) and HCl (2 ml) was allowed to stand overnight at room temp. It was diluted with water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with $NaHCO_3$aq, H_2O, and the solvent removed, when a gummy residue was obtained. The compound (IVb) was purified by distillation at 120°/5 × 10^{-2} mm (120 mg). TLC on Si-gel (R_f 0·68, chf–EtOAc, 9:1). IR spectrum (liquid film): 3452, 1727, 1480, 1452, 1434, 1382, 1242, 1195, 1127, 1037, 987, 937, 897, 802, 760 cm^{-1}. The NMR spectrum shows the following peaks: 3·78 (3H; OCH_3), 2·2 (1H; due to OH; disappears on addition

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* Available on application to the authors.

of D_2O), doublets centered at 1·08 and 0·92 δ (3H each; J = 6 c/s) due to the secondary methyls on C-1 and C-11.

Methyl ester of IVa. To a soln of IVa (80 mg) in ether (30 ml) was added an excess of diazomethane and the reaction mixture allowed to stand over-night at room temp. The gummy residue (80 mg) obtained after removal of the ether was dissolved in Chf and passed through a column of Si-gel. On keeping the compound in the refrigerator a crystalline solid was obtained which was purified by sublimation at 90°/5 × 10^{-3} mm (IVc). TLC on Si-gel (R_f 0·82, chf–EtOAc, 9:1). IR spectrum (liquid film): 1738, 1447, 1386, 1356, 1248, 1127, 1081, 939, 849 cm^{-1}. (Found: C, 65·7; H, 9·5. $C_{18}H_{30}O_4$ requires: C, 66·2; H, 9·3%.)

Alkaline hydrolysis of IVa to IVd. A mixture of IVa (300 mg) dissolved in EtOH (6 ml) and 10% KOHaq (2 ml) was heated under reflux at 80° for 1½ hr. Most of the EtOH was removed under red. press. and the residue carefully acidified with 1NHCl, filtered, taken in CH_2Cl_2, washed with H_2O, and the solvent removed. The resulting gum crystallized after scratching with ether. It was further purified by sublimation at 130°/10^{-4} mm to give IVd (40 mg), m.p. 127°. TLC on Si-gel (R_f 0·48, toluene:ethyl formate:formic acid, 5:4:1). IR spectrum (nujol): 3486, 1688, 1311, 1256, 1131, 1106, 1076, 1056, 1006, 986, 974, 806, 718 cm^{-1}. (Found: C, 66·2; H, 10·0. $C_{15}H_{26}O_4$ requires: C, 66·6; H, 9·7%.)

Lactonization of IVd to II. To a soln of IVd (120 mg) in dry benzene (100 ml) was added powdered *p*-toluenesulphonic acid (100 mg), and the mixture refluxed for 22 hr in a Dean-Stark apparatus. It was then washed with $NaHCO_3$aq, H_2O, and the solvent removed. The semicrystalline residue (90 mg) on recrystallization from CH_2Cl_2–ether gave II (50 mg), m.p. 208°. TLC in Si-gel (R_f 0·69; toluene:ethyl formate:formic acid, 5:4:1). IR spectrum (nujol): 1729, 1709, 1464, 1379, 1319, 1229, 1190, 1160, 1079, 1040, 1019, 953, 914, 853, 803, 739, 730 cm^{-1}. (Found: C, 71·4; H, 9·6; $C_{15}H_{24}O_3$ requires: C, 71·4; H, 9·6%.)

Acid hydrolysis of zeylanine (III) *to desacetylzeylanine*. A mixture of zeylanine (500 mg) dissolved in MeOH (20 ml) and HCl (2 ml) was allowed to stand overnight at room temp. It was diluted with water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with $NaHCO_3$aq, H_2O and the solvent removed. The semicrystalline residue (400 mg) on recrystallization from CH_2Cl_2–ether gave desacetylzeylanine (230 mg), m.p. 217–220°. TLC on Si-gel (R_f 0·15, chf_3:EtOAc, 9:1). UV (EtOH): 205 and 249 mμ (log ε, 4·03 and 4·84). IR spectrum (nujol): 3436, 1735, 1306, 1261, 1216, 1200, 1156, 1136, 1088, 1046, 1026, 946, 908, 874, 781, 725 cm^{-1}. (Found: C, 68·9; H, 6·0. $C_{15}H_{16}O_4$ requires: C, 69·2; H, 6·2%.)

Acetylation of desacetylzeylanine to zeylanine. To a soln of desacetylzeylanine (50 mg) in pyridine (1 ml) was added Ac_2O (1 ml) and the reaction mixture left at room temp overnight. On dilution with water, a crystalline ppt separated which was collected, washed with water and recrystallized from CH_2Cl_2–ether to give III (26 mg), m.p. 175°. The identity was confirmed by mixed m.p., TLC, IR and UV. (Found: C, 67·7; H, 5·9. $C_{17}H_{18}O_5$ requires: C, 67·5; H, 6·0%.)

Dihydrozeylanicine. Zeylanicine (V; 500 mg) was dissolved in EtOH (50 ml) and hydrogenated at 26° using 10% Pd/C (100 mg). The reaction was stopped when 35 ml of H_2 (1 mole) was absorbed. After filtration of the catalyst, the solvent was removed and the residue (200 mg) crystallized from ether, m.p. 130–131°. TLC on Si-gel (R_f 0·17, chf:EtOAc, 19:1). UV(EtOH): 226 mμ (log ε, 3·82). IR spectrum (nujol): 1775, 1736, 1541, 1341, 1311, 1246, 1231, 1185, 1156, 1113, 1946, 1921, 951, 909, 846, 801, 786, 725, 706 cm^{-1}. (Found: C, 63·7; H, 6·3. $C_{17}H_{20}O_6$ requires: C, 63·7; H, 6·3%.)

Desacetylzeylanidine. A mixture of zeylanidine (300 mg) in MeOH (12 ml) and 5% methanolic KOH (3 ml) was allowed to stand overnight at room temp. This was acidified with dil. HCl and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with $NaHCO_3$aq, H_2O and then evaporated when a gummy residue (120 mg) was obtained, m.p. 210°. This on crystallization from CH_2Cl_2–ether gave desacetylzeylanidine (73 mg), m.p. 210°, UV(EtOH): 218 mμ (log ε, 3·75). IR spectrum (nujol): 3516, 1766, 1326, 1221, 1191, 1127, 1107, 1091, 1061, 943, 908, 821, 791, 740 cm^{-1}. (Found: C, 61·5; H, 5·7. $C_{15}H_{16}O_6$ requires: C, 61·6; H, 5·5%.)

Acetylation of desacetylzeylanidine to zeylanidine. To a soln of desacetylzeylanidine (25 mg) in pyridine (0·25 ml) was added Ac_2O (0·5 ml) and the mixture left at room temp overnight (20 hr). The reaction mixture was diluted with ice, when a semicrystalline ppt was formed. This was filtered off, washed with water and crystallized from CH_2Cl_2-ether to give VI (20 mg), m.p. 220°. The identity was confirmed by mixed m.p., TLC and IR.

Conversion of zeylanidine VI *to zeylanicine* V. A soln of VI (150 mg) in acetone (15 ml) and gl. AcOH (5 ml) was flushed with N for 20 min. To this was added dropwise with stirring $CrCl_2$ (7 ml)[1] and the stirring under N continued. It was diluted with water, extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with $NaHCO_3$aq, H_2O, dried over Na_2SO_4 and evaporated to dryness. The semicrystalline residue was recrystallized from CH_2Cl_2–ether to give V; (110 mg), m.p. 235°. Mixed m.p. with zeylanicine was undepressed. The identity was further confirmed by TLC and IR.

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