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The Acid-catalyzed Rearrangement of Laurinterol Derivatives[1]

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In our studies of the chemistry of laurinterol (I) and debromolaurinterol (II),[2] we observed an interesting behavior upon the acid-catalyzed reaction of these compounds. The treatment of I and II (or their acetates, III and IV) with *p*-toluenesulfonic acid (TSA) in acetic acid at 50°C afforded aplysin (V) and debromoaplysin (VI) respectively.[2,3] In contrast, debromolaurinterol acetate (IV) gave cyclopentene VII in a good yield upon treatment with TSA in acetic anhydride under comparable conditions.[4] In this paper we will describe the acid-catalyzed rearrangement of laurinterol methyl ether (VIII) and debromolaurinterol methyl ether (IX).

The treatment of VIII with TSA in acetic acid at 50°C led to only the recovery of the starting material. However, when treated with 10% sulfuric acid in acetic acid at 50°C for 3 hr, VIII afforded two isomeric cyclopentenes, X and XI, with a concomitant *racemization*, in a ratio of about 3.5 : 1. In accordance with the assigned structure, X, $C_{16}H_{21}OBr$ (M^+ 308, 310), mp 123—124°C, $[\alpha]_D \pm 0°$, showed in its NMR spectrum the presence of two olefinic methyl groups (δ 1.46 and 1.69) instead of the one tertiary methyl and cyclopropane ring in VIII. On the other hand, the isomer XI (M^+ 308, 310), mp 93°C, $[\alpha]_D \pm 0°$, λ_{max} 290 and 284 mμ (ε 4100 and 4000), exhibited in its NMR spectrum signals due to two tertiary methyl (δ 0.82 and 0.93) and a secondary methyl group (δ 0.98; d, J=6 Hz) as well as to an olefinic proton (δ 5.41). On osmium tetroxide oxidation, XI gave the

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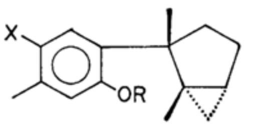
[1] Part XIV of "Constituents from Marine Plants." Part XIII: T. Irie, A. Fukuzawa, M. Izawa and E. Kurosawa, *Tetrahedron Letters*, **1969**, 1343.

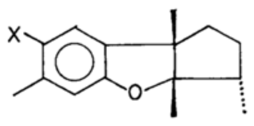
[2] T. Irie, M. Suzuki, E. Kurosawa and T. Masamune, *ibid.*, **1966**, 1837.

[3] T. Irie, M. Suzuki and Y. Hayakawa, This Bulletin, **42**, 843 (1969).

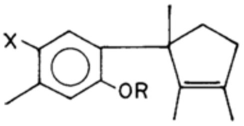
[4] *Cf.* Part XIII of this series.



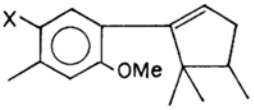
I X=Br, R=H
II X=R=H
III X=Br, R=Ac
IV X=H, R=Ac
VIII X=Br, R=Me
IX X=H, R=Me



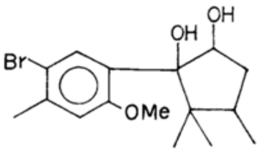
V X=Br
VI X=H



VII X=H, R=Ac
X X=Br, R=Me
XIII X=H, R=Me



XI X=Br
XIV X=H



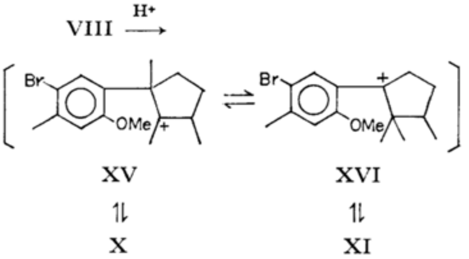
XII

corresponding glycol (XII), whose structure was supported by the presence of only one proton on a carbon bearing the hydroxyl group (δ 4.91; dd, J=8 and 6Hz) and the absence of a methyl group adjacent to the hydroxyl.

Similarly, debromolaurinterol methyl ether (IX) gave the corresponding isomeric cyclopentenes, XIII and XIV, in a ratio of about 3 : 1 on treatment under the conditions described above.

The prolonged treatment (15 hr) of VIII with the same catalyst produced X and XI in a ratio of about 5 : 1, but no other product could be obtained. The reaction of VIII with 0.5% sulfuric acid in acetic acid proceeded slowly and afforded X and XI in a ratio of about 1.5 : 1 after 72 hr. An examination of the latter reaction process by TLC indicates that, while X increases gradually the quantity of XI reaches its maximum after a few hours and then decreases, an equilibrium being finally attained between only X and XI. In fact, X and XI, on treatment with 10% sulfuric acid in acetic acid at 50°C for 15 hr, have formed a *ca.* 7 : 1 equilibrium mixture.

This observation can be explained by assuming that VIII undergoes protonation leading to the cleavage of the cyclopropane ring to yield a carbonium cation, XV, which, by a reversible reaction involving the migration of the methyl group, forms a cation, XVI.⁵⁾ These cations, XV and XVI, will then produce the cyclopentenes, X and XI respectively.



Experimental⁸⁾

Laurinterol Methyl Ether (VIII). To a solution of I (180 mg) and dimethyl sulfate (400 mg) in dry acetone (20 m*l*), potassium carbonate (800 mg) was added, and then the mixture was refluxed for 3 hr. After the removal of the unchanged potassium carbonate by filtration, the solution was made alkaline by the addition of a dilute sodium hydroxide solution. The solvent was then removed by distillation under diminished pressure, and the residue was extracted with ether. The ether solution was washed successively with water, the dilute sodium hydroxide solution, and a saturated sodium chloride solution, and dried over sodium sulfate. A crude crystalline substance obtained after the removal of the ether was purified by recrystallization from methanol to give VIII (160 mg); mp 96—97°C; M^+ 308, 310; $[\alpha]_D$ +18.0° (c, 1.25; Chf); ν_{max}^{Chf} 1602, 1490, 1240, 1165, 1065, 1043, 960, 890, 845 cm^{-1}; NMR, δ 0.43 (1H, s), 0.53 (1H, s), *ca.* 1.0 (1H, m) 1.30 (6H, s), 2.35 (3H, s), 3.77 (3H, s), 6.61 (1H, s), 7.53 (1H, s). (Found: C, 62.27; H, 6.69%. Calcd for $C_{16}H_{21}OBr$: C, 62.14; H, 6.85%).

Debromolaurinterol Methyl Ether (IX). Debromolaurinterol (II, 65 mg) was methylated with dimethyl sulfate and potassium carbonate in dry acetone as has been described above. The crude product was

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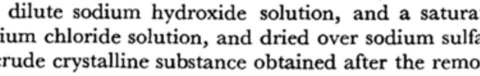
5) This type of methyl migration has recently been reported [Y. Hirata *et al.*, Preprints for the 22nd Annual Meeting of the Chemical Society of Japan (Tokyo, 1969)]. However, when isolaurene (XVII)⁶⁾ is treated with 10% sulfuric acid in acetic acid, both the methyl and the *p*-tolyl group migrate to give XVIII. It is well known that the migratory aptitude of the *o*-anisyl group is small;⁷⁾ the above observation is in accord with this view.



XVII XVIII

6) T. Irie, T. Suzuki, Y. Yasunari, E. Kurosawa and T. Masamune, *Tetrahedron*, **25**, 459 (1969).

7) *Cf.* P. de Mayo, "Molecular Rearrangements," Interscience Publishers, New York (1963), p. 22.

8) Mps are uncorrected. The NMR spectra were taken in CCl_4, with TMS as an internal standard, on a Hitachi H-60 Spectrometer.

purified by column chromatography on silica gel to give IX (50 mg); oil; M^+ 230 ($C_{16}H_{22}O$); $[\alpha]_D$ $-17.6°$ (*c*, 1.42; Chf); ν_{max}^{Chf} 1613, 1575, 1503, 1250, 1165, 1140, 1060, 1040, 820 cm^{-1}; NMR, δ *ca.* 0.5 (2H, m), *ca.* 1.0 (1H, m), 1.31 (3H, s), 1.35 (3H, s), 2.32 (3H, s), 3.79 (3H, s), 6.58 (1H, br. s), 6.60 (1H, br. d, J=7.5 Hz), 7.32 (1H, d, J=7.5 Hz).

Rearrangement of Laurinterol Methyl Ether (VIII). *a*) A solution of VIII (301 mg) in 10% sulfuric acid in acetic acid (10 m*l*) was stirred at 50°C for 3 hr. To the ice-cold reaction mixture water (*ca.* 20 m*l*) was added, and then the whole was extracted with ether. The ether solution was washed successively with water, a 5% sodium hydrogen carbonate solution, and a saturated sodium chloride solution, and dried over sodium sulfate. After the removal of the solvent, the residual oil (297 mg) was chromatographed over silica gel - Celite (10 : 1) to yield X (205 mg) and XI (68 mg).

X: mp 123—124°C, M^+ 308, 310 ($C_{16}H_{21}OBr$); $[\alpha]_D$ ±0°; λ_{max}^{EtOH} 288 and 282 mμ (ε 3200 and 3400); NMR, δ 1.37 (3H, s), 1.46 (3H, s), 1.69 (3H, s), 2.31 (3H, s), 3.72 (3H, s), 6.56 (1H, s), 6.95 (1H, s). (Found: C, 62.25; H, 6.86%).

XI: mp 93°C, M^+ 308, 310 ($C_{16}H_{21}OBr$); $[\alpha]_D$ ±0°; λ_{max}^{EtOH} 290 and 284 mμ (ε 4100 and 4000); NMR ,δ 0.82 (3H, s), 0.93 (3H, s), 0.98 (3H, d, J=6 Hz), 2.34 (3H, s), 3.69 (3H, s), 5.41 (1H, m), 6.60 (1H, s), 7.03 (1H, s). (Found: C, 62.32; H, 6.85%).

b) When 0.5% sulfuric acid in an acetic acid solution was used, the reaction was slow; after stirring at 50°C for 72 hr, the starting material disappeared (TLC), and X (50%) and XI (35%) were obtained after the usual work-up.

Rearrangement of Debromolaurinterol Methyl Ether (IX). A solution of IX (251 mg) in 10% sulfuric acid in acetic acid (10 m*l*) was stirred at 50°C for 3 hr. After treatment as above, there was obtained an oily product (217 mg) which was subsequently purified by silica gel chromatography to yield XIII (105 mg) and XIV (45 mg).

XIII: oil, M^+ 230 ($C_{16}H_{22}O$); $[\alpha]_D$ ±0°; NMR, δ 1.39 (3H, s), 1.47 (3H, s), 1.68 (3H, s), 2.27 (3H, s), 3.73 (3H, s), 6.48 (1H, d, J=8 Hz), 6.53 (1H, s), 6.73 (1H, d, J=8 Hz).

XIV: oil, M^+ 230 ($C_{16}H_{22}O$); $[\alpha]_D$ ±0°; NMR, δ 0.81 (3H, s), 0.92 (3H, s), 1.01 (3H, d, J=6 Hz), 2.30 (3H, s), 3.67 (3H, s), 5.35 (1H, m), 6.50 (1H, s), 6.51 (1H, d, J=8 Hz), 6.73 (1H, d, J=8 Hz).

Glycol XII. To a solution of XI (128 mg) in benzene (4 m*l*), osmium tetroxide (102 mg) and pyridine (0.1 m*l*) were added. After the mixture had stood for 3 days at room temperature, pale brown precipitates (180 mg) were separated and collected by filtration. This crude product was dissolved in dichloromethane (3 m*l*) and was added to a solution of mannitol (800 mg) and potassium hydroxide (100 mg) in water (10 m*l*). The whole was stirred at room temperature for 45 hr, the reaction mixture was then extracted with dichloromethane, and the organic layer was washed with water and dried. After the removal of the solvent, the residual oil (101 mg) was purified by chromatography over silica gel to give pure XII (64 mg): ν_{max} 3500, 1105, 1045 cm^{-1}; NMR, δ 0.49 (3H, s), 0.82 (3H, s), 0.82 (3H, d, J=7 Hz), 2.34 (3H, s), 3.77 (3H, s), *ca.* 3.4 (1H, br. m), *ca.* 4.3 (1H, br. m), 4.91 (1H, dd, J=8 and 6 Hz), 6.65 (1H, br. s), 7.45 (1H, s).

Acid-catalyzed Equilibration of X and XI. Pure X and pure XI (50 mg) were each dissolved in 10% sulfuric acid in acetic acid (10 m*l*), and the mixture was stirred at 50°C for 15 hr. The reaction mixture was then worked-up as has been described above, and the composition of the products was determined by column and/or thin-layer chromatography. From each of the cyclopentenes, X and XI were obtained in a ratio of *ca.* 7 : 1.

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