ELAEODENDROGENIN, ELAEODENDROSIDE B AND C: NEW CARDIAC STEROIDS FROM ELAEODENDRON GLAUCUM

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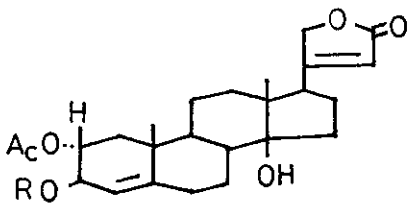
Abstract-A new cardiac steroid named elaeodendrogenin and two new cardiac glycosides named elaeodendroside B and C having an unusual sugar linkage were isolated from seeds of Elaeodendron glaucum Pers. The structure of elaeodendrogenin was elucidated to be Ia on the basis of chemical and spectral data. A newly developed procedure for cleavage of a glycoside having a doubly linked sugar was applied to characterization of elaeodendroside B and C. In consequence, the probable structures of these two stereoisomers were deduced to be VI.

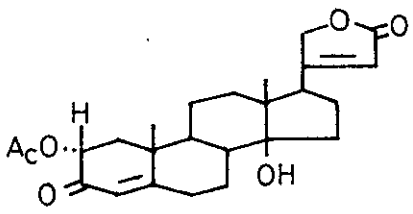
In the preceding paper we reported the isolation of cardiac steroids from seeds of Elaeodendron glaucum Pers. (Celastraceae)[2] and the structural elucidation of elaeodendroside A having an unusual glycoside linkage by X-ray crystallography.[3] The present paper describes the structures of elaeodendrogenin, elaeodendroside B and C which have been separated by the similar method previously reported.[3]

First, elaeodendrogenin (Ia) was isolated as colorless leaflets (from acetone-ether). mp 258-262°, $[\alpha]_D^{20}$ -21.1° (c=0.10 in $CHCl_3$). Inspection of the high-resolution mass spectrum and elemental analysis permitted us to assign a molecular formula $C_{25}H_{34}O_6$ to Ia. On the ^1H NMR spectrum[4] Ia exhibited the singnals at δ: 0.91 (3H, s, 18-CH_3), 1.15 (3H, s, 19-CH_3), 2.11 (3H, s, $OCOCH_3$), 2.76 (1H, m, 17α-H), 4.20 (1H, d, J=10 Hz, 3α-H), 4.80 (1H, m, 2β-H), 4.88 (2H, dd, J=15, 2 Hz, 21-CH_2), 5.22 (1H, br s, 4-H), 5.88 (1H, br s, 22-H). Usual acetylation with acetic anhydride and pyridine yielded the diacetate (Ib) as colorless leaflets

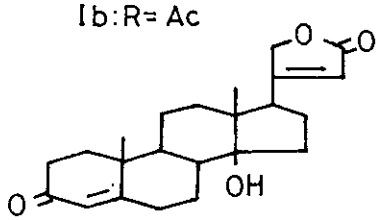
(from ether). mp 225-230°, $[\alpha]_D^{20}$-45.5° (c=0.06 in $CHCl_3$), ^1H NMR δ: 2.03 (3H, s, $OCOCH_3$), 2.06 (3H, s, $OCOCH_3$), 5.12 (1H, br s, 4-H), 5.15 (1H, m, 2β-H), 5.40 (1H, d, J=9 Hz, 3α-H). Nuclear Overhauser effect (NOE) (ca. 30%) between 19-CH_3 and 2-H and coupling constants ($J_{3,4}$=0 Hz, $J_{3,2}$=10 Hz) supported to assign the 2α,3β-glycol 2-monoacetate structure to Ia.[3,5] Being treated with manganese dioxide, Ia was readily converted to the Δ^4-3-ketone (II). mp 260-263°, $[\alpha]_D^{25}$+38.2° (c=0.17 in $CHCl_3$), UV λ_{max}^{MeOH} 235 nm. In addition, NOE (ca. 20%) was also observed between 19-CH_3 and 2-H. CD curve of II in methanol showed a negative Cotton effect with an extremum at 325 nm. These data strongly implied the presence of an acetoxyl group at the 2α-position.[6] Indeed, the structure of II was definitely established by direct comparison with the synthetic sample, obtainable from anhydroperiplogenone (III)[7] by lead tetraacetate oxidation and subsequent epimerization of 2β-acetoxyanhydroperiplogenone (IV) with potassium acetate in boiling acetic acid.[8] On the basis of these evidences elaeodendrogenin was unequivocally identified as Ia.



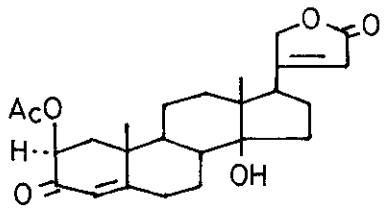
Ia: R= H
Ib: R= Ac



II



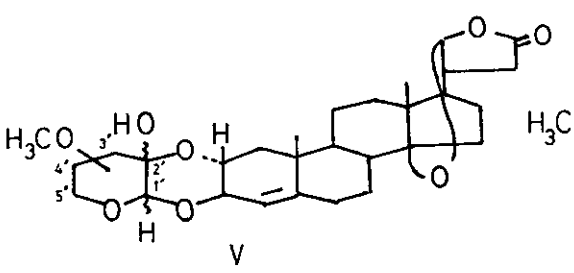
III



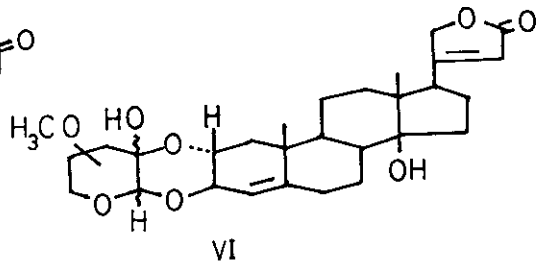
IV

Secondly, elaeodendroside B was obtained as colorless amorphous substances (from methanol-ethyl acetate), mp 252-257° (decomp.), $[\alpha]_D^{26}$+32.7° (c=0.15 in $CHCl_3$) and also elaeodendroside C as colorless amorphous substances (from methanol-ether), mp 233-236°, $[\alpha]_D^{21}$+6.0° (c=0.20 in $CHCl_3$). Elaeodendroside B ^1H NHR δ: 0.90(3H, s, 18-CH_3), 1.12 (3H, s, 19-CH_3), 2.75 (1H, m, 17α-H), 3.47 (3H, s, OCH_3), 4.20 (1H, m, 2β-H), 4.55 (1H, d, J=9 Hz, 3α-H), 4.55 (1H, s, 1'-H), 4.89 (2H, dd, J=18, 2 Hz, 21-CH_2), 5.21 (1H, br s, 4-H), 5.88 (1H, br s, 22-H). ^{13}C NMR δ:

70.5 or 67.7 (2-C), 82.3 (3-C), 92.2 (2'-C), 96.3 (1'-C). Elaeodendroside C ^{1}H NMR δ: 0.90 (3H, s, 18-CH_3), 1.13 (3H, s, 19-CH_3), 2.75 (1H, m, 17α-H), 3.42 (3H, s, OCH_3), 4.20 (1H, m, 2β-H), 4.50 (1H, d, J=9 Hz, 3α-H), 4.62 (1H, s, 1'-H), 4.89 (2H, dd, J=18, 2 Hz, 21-CH_2), 5.22 (1H, br s, 4-H), 5.88 (1H, br s, 22-H). ^{13}C NMR δ : 70.2 or 68.6 (2-C), 80.0 (3-C), 90.7 (2'-C), 96.1 (1'-C). A molecular formula $C_{29}H_{40}O_8$ could be assigned to both compounds by means of high-resolution mass spectrometry with chemical ionization using methane as a reactant gas. These were stable for acid treatment and resisted significantly against periodate oxidation and enzymatic hydrolysis. On treatment with acetic anhydride and pyridine in a sealed tube for 8 days at 35°[9] elaeodendroside B and C gave the monoacetate, respectively, ^{1}H NMR δ: 2.15 (3H, s, $OCOCH_3$). In contrast both were transformed into Ib in a reasonable yield when refluxed in acetic anhydride and pyridine. Comparison of their ^{1}H NMR and ^{13}C NMR spectra with those of elaeodendroside A[3] or acetyl-gomphoside[9] strongly indicated that the two compounds would be the cardiac glycosides having an unusual double linkage at both C-2 and C-3. Being refluxed with sodium carbonate in methanol, elaeodendroside B and C were converted into the isocardenolide (V).[10] mp 263-265° (decomp.), Mass m/e: 516, ^{1}H NMR δ: 3.40 (3H, s, OCH_3), 4.20 (1H, m, 2β-H), 4.50 (1H, d, J=10 Hz, 3α-H), 4.70 (1H, s, 1'-H), 5.20 (1H, br s, 4-H), 5.85 (1H, d, J=5 Hz, 21-H). These evidences lent a support to the assumption that the two new glycosides would be sterically isomeric and represented as VI.



V



VI

Several attempts for obtaining genins from the analogous cardiac glycosides resulted in failure, providing the artifacts as main products.[11-13] The newly developed degradation procedure, however, is rather mild and simple to obtain an acetylated genin. Kitagawa et al.[14,15] reported a novel method for cleavage of the glucuronoside linkage in saponins with acetic anhydride and pyridine. To the best of our knowledge this is the first reported degradation procedure applicable to the steroidal glycoside having a doubly linked sugar.

Further studies on the complete structures of elaeodendroside B and C and the mechanism for cleavage of their glycoside linkage are being conducted in these laboratories and the details will be reported elsewhere in the near future.

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REFERENCES AND NOTES

1 Present address, Fujisawa Pharmaceutical Co. Ltd., Osaka, Japan.

2 Seeds were collected in India in March, 1975.

3 S.M. Kupchan, I. Uchida, K. Shimada, B.Y. Fei, D.M. Stevens, A.T. Sneden, R.W. Miller, and R.F. Bryan, Chem. Commun., 1977, 255.

4 All NMR spectra were obtained in $CDCl_3$ using TMS as an internal standard.

5 S.M. Kupchan, J.L. Moniot, C.W. Sigel, and R.J. Hemingway, J. Org. Chem., 36, 2611 (1971).

6 S.L. Patashnik, H.L. Kimball, and S. Burstein, Steroids, 2, 19 (1963).

7 D. Satoh and T. Wada, Yakugaku Zasshi, 80, 1314 (1960).

8 R.L. Clarke, K. Dobriner, A. Mooradian, and C.M. Martini, J. Am. Chem. Soc., 77, 661 (1955).

9 P. Brown, J. von Euw, T. Reichstein, K. Stöckel, and T.R. Watson, Helv. Chim. Acta, 62, 412 (1979).

10 A.F. Krasso, M. Binder, and Ch. Tamm, Helv. Chim. Acta, 55, 1352 (1972).

11 R.G. Coombe and T.R. Watson, Austr. J. Chem., 17, 92 (1964).

12 F. Brüschweiler, K. Stöckel, and T. Reichstein, Helv. Chim. Acta, 52, 2276 (1969).

13 G. Hesse, Angew. Chem., 61, 339 (1949).

14 I. Kitagawa, Y. Ikenishi, M. Yoshikawa, and K.S. Im, Chem. Pharm. Bull. (Tokyo), 25, 1408 (1977).

15 I. Kitagawa and M. Yoshikawa, Heterocycles, 8, 783 (1977).

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