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SPIROFORSKOLIN : ACID-CATALYSED REARRANGEMENT PRODUCT OF FORSKOLIN

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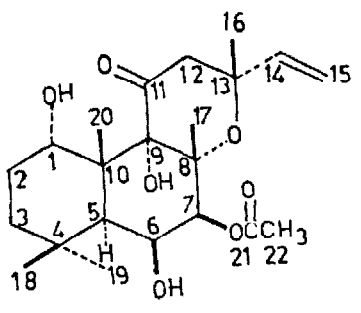
Abstract: Lewis acid induced carbocation mediated rearrangement of forskolin (1) afforded a spirolabdane, designated as spiroforskolin (2).

Forskolin (7β-acetoxy-8,13-epoxy-1α,6β,9α-trihydroxylabd-14-en-11-one, 1) isolated[1] from the Indian medicinal plant Coleus forskohlii has been intensively investigated[2] owing to its pronounced inotropic, antihypertensive, bronchospasmolytic activities[3]. It lowers intraocular pressure by topical application to glaucoma patients[4]. Forskolin, a highly oxygenated diterpenoid has been attractive target for synthesis[5,6,7] and transformation studies[8,9].

This paper reports a novel Lewis acid induced rearrangement of Forskolin (1) into a dihydrofuranone named as spiroforskolin (2). Forskolin, when treated with BF_3-Et_2O in dry benzene at 0-5° afforded 2 (yield 45%) via formation of less stable tertiary carbocation by the abstraction of C_9-OH and 1,2-nucleophilic migration of oxygen from C-8 to C-9 resulting in relatively stable C_8-carbocation, the return of OH from BF_3 then resulted in 2. The compound 2, mp 98-100°, analysed for $C_{22}H_{34}O_7$ (M^+, m/z 410, identical to that of forskolin) showed IR absorption at 1740 cm^{-1} (carbonyl of dihydrofuranone ring) whereas corresponding IR absorption for 1 was at 1705 cm^{-1} (tetrahydropyranone ring). The ^1H NMR spectrum[10] showed downfield shifts in the characteristic ABX pattern of vinylic protons (6.31, dd, C_{14}-H; 5.20, dd, C_{15}-H; 5.26, dd, C_{15}-H) and C_{13}-Me and upfield shift for C_8-Me (both methyls appeared at 1.6). Geminally coupled C_{12}-protons appeared at 3.05 (C_{12ax}-H, J=17 Hz) and 2.60 (C_{12eq}-H, J=17 Hz). The ^{13}C NMR spectrum[11] displayed a singlet at 93.4, characteristic of spirocarbon i.e. C-9 of 2, considering ^{13}C NMR of griseofulvin[12] as model. The mass spectrum of 2 showed[13] relatively facile loss of H_2O. A triacetate (m/z



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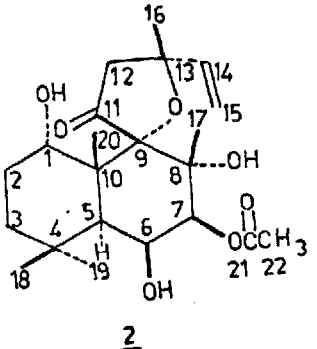

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494) was obtained by acetylation of 2 (Ac_2O, Py, 24 h. room temp.). Spiroforskolin (2) when kept in solution of methanol for 3-4 days slowly transformed back to forskolin, identical in all respect to the natural enantiomer, forskolin isolated from Coleus forskohlii ($[\alpha]_D^{20}$ -17° for both the samples). This slow reversal of 2 into 1 further confirmed the stereochemical assignments at C-8 of spiroforskolin, the C_8-Me being β-axially oriented as in the case of forskolin[14].

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References and Notes:

1. Bhat, S.V., Bajwa, B.S., Dornauer, H., deSouza, N.J. and Fehlhaber, H.W. Tetrahedron Letters 1977, 1669.

2. Forskolin-Its Chemical, Biological and Medical Potential, eds. deSouza, N.J., Dohadwalla, A.N. and Rupp, R.H. (Hoechst India Ltd) Bombay, 1986.

3. Seamon, K.B. Annual Report in Medicinal Chemistry 1984, 19, 293.

4. Caprioli, J. and Sears, M. The Lancet 1983, 1, 958.

5. Ziegler, F.E., Jaynes, B.H. and Saindane, M.T. J. Am. chem. Soc. 1987, 109, 8115.

6. Hashimoto, S., Sakata, S., Sonegawa, M. and Ikegami, S. J. Am. chem.Soc. 1988, 110, 3670.

7. Corey,E.J., Jardine,P.D. and Rohloff,J.C. J.Am.chem.Soc. 1988, 110,3672.

8. Saksena, A.K., Green, M.J., Shue, H.J., Wong, J.K. amd McPhail, A.T. Tetrahedron Letters 1985, 26, 551.

9. Khandelwal, Y., Moraes, G., deSouza, N.J., Fahlhaber, H.W. and Paulus, E.F. Tetrahedron Letters 1986, 27, 6249.

10. ^1H NMR(400 MHz, $CDCl_3$,ppm): 4.42 (d, C_1-H, J=6Hz), 1.30 (m, 1H, C_{2eq}-H), 2.05 (m, 1H, C_{2ax}-H), 1.11 (m, 1H, C_{3eq}-H), 1.72 (m, 1H, C_{3ax}-H), 2.20(d, 1H, C_5-H, J=2Hz), 4.42 (d, 1H, C_6-H, J=3.9Hz), 5.10 (d, 1H, C_7-H, J=3.9Hz), 2.60 (d, 1H, C_{12eq}-H, J_{gem}=17Hz), 3.05 (d, 1H, C_{12ax}-H, J_{gem}=17Hz), 6.31 (dd, 1H, C_{14}-H, J_{trans}=17Hz, J_{cis}=10Hz), 5.20 (dd, 1H, C_{15}-H, J_{cis}=10Hz, J_{gem}=1Hz), 5.26 (dd, 1H, C_{15}'-H, J_{trans}=17Hz, J_{gem}= 1Hz), 1.6 (s, 6H, C_{16}-H and C_{17}-H), 1.26 (s, 3H, C_{18}-H), 1.06 (s, 3H, C_{19}-H), 1.48 (s, 3H, C_{20}-H), 2.20 (s, 3H, C_{22}-H).

11. ^{13}C NMR (SFORD, NDC and DEPT spectra at 100.57 MHz, $CDCl_3$,ppm): 73.7 (C-1), 26.5 (C-2), 35.9 (C-3), 34.7 (C-4), 42.8 (C-5), 69.9 (C-6), 78.2 (C-7), 80.5 (C-8), 93.4 (C-9), 43.4 (C-10), 49.2 (C-12), 82.6 (C-13), 143.8 (C-14), 113.9 (C-15), 29.8 (C-16), 33.2 (C-17), 25.1 (C-18), 20.2 (C-19), 24.6 (C-20), 171.1 (C-21), 20.9 (C-22).

12. Levine, S.G., Hicks, R.E.,Gottleib, H.E. and Wenkert, E. J. Org. Chem. 1975, 40, 2540.

13. MS data (EIMS, 70 eV, m/z, %): 410 (M^+,14.1%), 392(M^+-H_2O, 30.2%), 224 (23%), 208 (15.5%), 207 (15.9%).

14. Prakash, O., Roy, R. and Dhar, M.M. J. Chem. Soc. Perkin Trans.II, 1986, 1779.

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