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COLEONOLIC ACID, A REARRANGED URSANE TRITERPENOID FROM COLEUS FORSKOHLII

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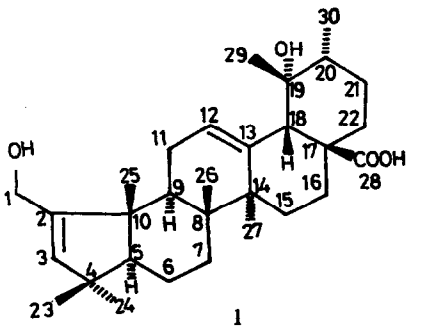
Abstract : Coleonolic acid, a novel rearranged pentacyclic triterpenoid isolated from the roots of Coleus forskohlii has been characterized as 2-hydroxymethyl A(1)nor-urs-19α-hydroxy-2(3),12(13)-dien-28-oic acid. The stereostructure has been determined by two-dimensional COSY, COSYLR, COSYDQF, XHDEPT, COLOC and NOE difference NMR experiments.

Indian medicinal plant Coleus forskohlii Briq. (Labiatae) has been extensively investigated by us[1] and others[2] mainly due to the isolation of a unique labdane diterpenoid Coleonol (Forskolin) which showed remarkable biological activity and potential as future drug for glaucoma, congestive cardiomyopathy and asthma[3]. We now report isolation and stereostructure of a novel triterpenoid with a rearranged ursane skeleton as the first representative of a new class.

The compound named coleonolic acid (**1**) was isolated from dichloromethane extract of the roots of Coleus forskohlii as white crystals, mp 245° and analysed for $C_{30}H_{46}O_4$ (M^+ 470). The spectral studies[4] (1D-^{1}H, ^{13}C NMR, IR and MS) of **1** and its acetate **2** revealed it to be Δ^{12} ursane triterpenoid having two trisubstituted double bonds, one-COOH, one-CH_2OH and one tertiary-OH groups. The fully decoupled and DEPT spectra of **1** showed 30 signals including seven Me, eight CH_2, six CH and nine quaternary carbons indicating the ring A to be five-membered bearing a -CH_2OH attached to trisubstituted double bond. Furthermore, the signals for the ring junction carbons (C-5 and C-10) of **1** and its acetate **2** were found significantly downfield shifted than the values of the carbons in normal ursane or oleananes[5]. Based on the spectral data, structure **1** was postulated for coleonolic acid. For the unambiguous assignment of the proposed structure and stereochemistry, detailed two-dimensional NMR studies on the acetyl derivative **2** using COSY, COSYLR, COSYDQF, XHDEPT, COLOC and NOE difference experiments were undertaken.

A 2D COSY ^{1}H NMR spectrum of **2** in $CDCl_3$ is shown as a contour plot in figure 1. The signals at δ 4.70 and 4.56 were unambiguously assigned to both the CH_2OAc protons which showed cross peaks with each other and with the signal at δ 5.41 indicating allylic correlation with one of the olefinic protons. Moreover, long range correlations were observed in the COSYLR spectrum for the signal at 5.41 with two methyls at 0.94 and 1.02 which in turn showed cross peaks with each other. The methyl signals at 0.94 and 1.02 were found to be for Me-23 & Me-24 by nOe difference spectra (Figure 2). These observations provided the preferred placement of the double



1

bond at C-2,3 position and linking of H-3 with Me-23 and Me-24. The downfield signal at 5.31 which could be attributed to the other olefinic proton, gave cross peaks at 2.02 and 2.22 and an allylic correlation with the signal at 2.51 only. The signals at 2.02 and 2.22 were due to methylene protons from 2D XHDEPT spectrum (Figure 3), whereas long range allylic correlation at 1.41 was for methine proton. The evidence for the fixation of double bond at C-12,13 position was further reinforced by the irradiation of methyl signal at 1.20 which showed nOes with Me-30 (a doublet at 0.95) and with signals at 2.51 and 5.31. These observations provided the unambiguous assignment of Me-29and linking of H-12 with H-18 and Me-29 respectively. Similarly, the linking of the protons from C-15 to C-16 and C-20 to C-22 were determined.

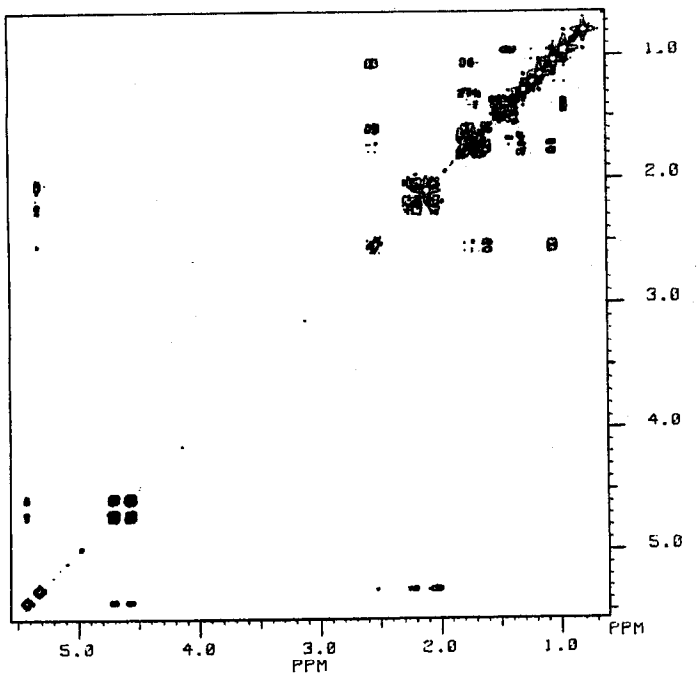


Figure 1. A 2D COSY spectrum of 2

The 2D XHDEPT spectrum permitted the unambiguous ^{13}C chemical shift assignments of the corresponding carbons in relation to the previously assigned proton chemical shifts. The assignment of C-5 was done on the basis of the remaining methine carbon signal at 63.0 and then extracting its ^{1}H NMR chemical shift (1.40) in the $\omega 1$ dimension. This unambiguous assignment of H-5 then provided the linking of protons from C-5 to C-7 in the 2D COSY spectrum.

The correlation for the quaternary carbons (C-4, C-8, C-10, C-14, C-17 and C-19) were achieved by long range ^{1}H-^{13}C (COLOC) spectrum. For example, the carbon signal at 73.1 showed long range correlation with the proton at 2.51 (H-18) which can now be assigned unambiguously to C-17. In a similar manner the signal at 42.7 gave correlation with H-5 confirming the assignment of C-4. The chemical shifts for the ring junction carbons (C-5 and C-10) were found to be downfield shifted accordingly from the values of corresponding carbons of ursolic acid[5]. These evidences inferred the structure **2**.

Irradiation of Me-23 showed nOes for Me-24 and Me-25 only. The nOe of Me-25 with Me-26 and Me-23 indicated all these methyls to be axially β-oriented. Since no nOe was observed for H-5 with Me-25, thereby confirming trans A/B ring junction. Similarly irradiation of Me-26

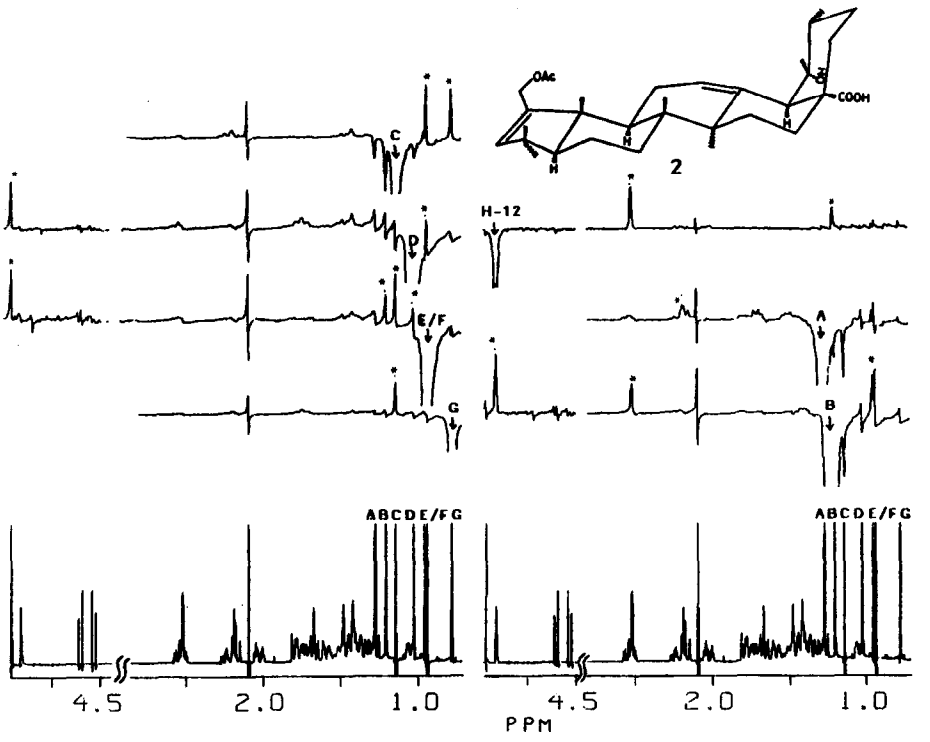


*Figure 2. Homonuclear proton nOe difference spectra at positions indicated ↓ ; enhancements indicated *, over 1D spectra.*

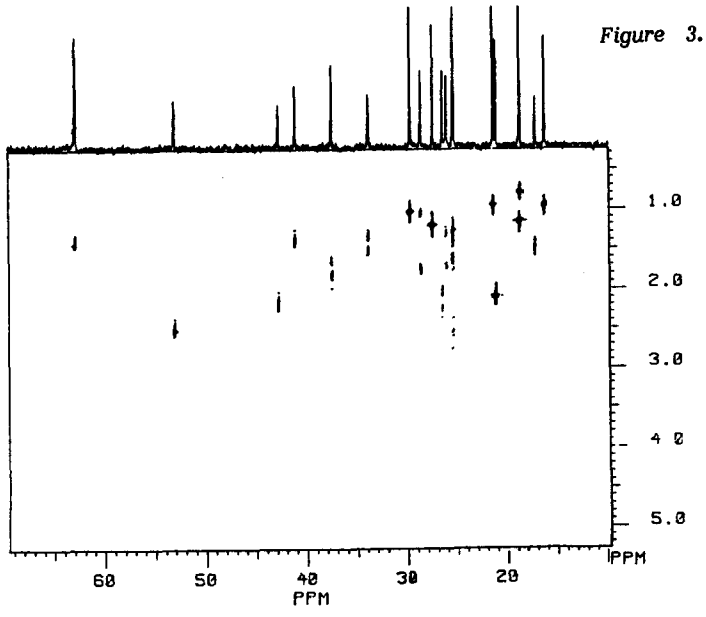


Figure 3. A section of contour plot of XHDEPT spectrum of 2

showed nOe for M-25 only and the couplings between H-9 and H_2-11 suggested[4] the axial geometry and confirmed trans B/C ring fusion. The nOe of Me-27 with H-9 suggested axial α-geometry. Similarly nOe of Me-29 with H-18, H-12 and Me-30, while nOe of Me-30 for Me-29 only, indicated cis D/E ring fusion, a typical of ursane triterpenoid. These nOe difference experiments

also confirmed the placement of OH at C-19 α-position.

All the NMR studies confirmed the structure **1** as 2-hydroxymethyl A(1) nor-urs-19α-hydroxy-2(3),12(13)-dien-28-oic acid. Coleonolic acid as first member of ring-A rearranged ursane triterpenoid is biogenetically derived from 2,3-dihydroxyursane via oxidative cleavage across the C-2, C-3 bond to form an intermediary dialdehyde which through aldol type condensation, dehydration and reduction would generate **1**.

Acknowledgements

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References and Notes

1. Tandon, J.S., Dhar, M.M., Ramakumar, C. and Venkatesan, K., Indian J. Chem., **15B**, 880, 1977.
2. Bhat, S.V., Bajwa, B.S., Dornauer, H. , deSouza, N.J. and Fehlhaber, H.W., Tetrahedron Letters, 1669, 1977.
3. Seamon, K.B., Ann. Rep. Med. Chem., **19**, 293, 1984.
4. ^{1}H NMR of the acetate **2**: 0.77 (s, Me-26), 0.94 (s, Me-23), 0.95 (d, 6.5, Me-30), 1.02 (s, Me-24), 1.14 (s, Me-25), 1.20 (s, Me-29), 1.27 (s, Me-27), 1.00 (m, H-15), 1.75 (m, H-15), 1.30-1.58 (m, H-6), 1.79 and 1.60 (m, H-7), 1.33 (m, H-22), 1.39 (m, H-20), 1.46 and 1.58 (m, H-21), 1.40 (brs, H-5), 1.60 (m, H-16), 2.18 (dd, 4.7, 11.2, H-9), 2.02 (ddd, 4.1, 4.7, 16.4, H-11'), 2.22 (ddd, 3.5, 11.2, 16.4, H-11), 2.30 (ddd, 4.7, 12.9, 13.5, H-16'), 2.51 (s, H-18), 4.70 (dd, 1.2, 14.1, H-1), 4.56 (dd, 1.2, 14.1, H-1'), 5.41 (brs, H-3), 5.31 (dd, 4.1, 3.5, H-12), 2.09 (s, Me-32) : ^{13}C NMR of **2** : 17.2 (C-6), 16.1 (C-30), 18.6 (C-25 and C-26), 20.9 (C-32), 21.3 (C-23), 25.2 (C-27), 29.6 (C-24), 27.4 (C-29), 28.7 (C-15), 25.5 (C-16), 26.1 (C-21), 26.5 (C-11), 33.9 (C-22), 41.2 (C-20), 41.7 (C-14), 41.3 (C-10), 42.9 (C-9), 42.6 (C-4), 47.9 (C-8), 37.4 (C-7), 50.8 (C-17), 53.3 (C-18), 63.0 (C-5), 62.8 (C-1), 73.1 (C-19), 129.2 (C-12), 138.4 (C-13), 137.5 (C-3), 148.9 (C-2), 170.7 (C-31), 183.8 (C-28). IR of **1** : 3340 (OH), 2900 , 1680 (CO), 1450, 1375, 1230, 1155, 1005. Mass spectrum of **1** m/z : 470 (M^{+}), 452, 437, 425, 329, 284, 270, 257, 246, 239, 231, 219, 206, 201, 199, 145, 135, 123, 119, 107, 105, 91, 81, 79, 55, 43.
5. Wehrli, F.W. and Nishida, T., Forschritte Chem. Org. Naturstoffe, **36**, 1, 1979.

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