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IDENTITY OF COLEONOL WITH FORSKOLIN: STRUCTURE REVISION OF A BASE-CATALYSED REARRANGEMENT PRODUCT

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Abstract: The identity of coleonol and forskolin is shown through structure revision of a rearrangement product isolated earlier from coleonol and is confirmed by direct comparison of authentic coleonol with forskolin 1; in addition, coleonol-B should be correctly represented by structure 4.

Forskolin 1, a labdane diterpenoid isolated from an Indian medicinal herb Coleus Forskohlii, is central among a group of novel 11-oxomanoyl oxide derivatives isolated at the Hoechst Laboratories.[1] The strongly positive inotropic, antihypertensive, and adenylate cyclase stimulant properties of 1 have provided a rich source for pharmacological studies.[2] More recently, forskolin was shown to lower intraocular pressure[3a] and it displayed bronchospasmolytic activity[3b] in man suggesting its potential for clinical utility.

Coleonol, which was isolated earlier from the same plant by Tandon et.al. was assigned structure 2.[4] This compound elicited similar pharmacology as described above for forskolin.[5] The only feature where coleonol and related compounds were reported to differ from the forskolin group is in the C-7 oxo substituent having an α-configuration in the former.[6] A good deal of confusion has arisen since both structures 1 and 2 are based on independent X-ray analyses.[4,7] In addition, a recent comparison of physicochemical properties of coleonol and forskolin was claimed to show the non-identity of the two natural products.[8] We now report our results which unequivocally establish that coleonol and forskolin are one and the same entity represented by the common structure 1.

Vigorous hydrolysis of coleonol with ethanolic KOH has been reported to yield a rearrangement product, $C_{20}H_{32}O_6$, m.p. 171°, $[\alpha]_D$ +33.4° ($CHCl_3$) to which structure 3 was assigned.[4] Coleonol-B was also reported to yield the same compound 3.[9] The i.r. spectrum of 3 lacked a carbonyl absorption and its reacetylation gave a monoacetate which was different from 2. While the inverted configuration at C-13 could be rationalized (β-elimination followed by internal conjugate addition), the hemiketal linkage between the C-1 hydroxyl (α or β) and the 11-keto group in structure 3 appeared quite unlikely to us on steric grounds.

Treatment of forskolin[10] with KOH as described for coleonol[4] gave a single crystalline product, $C_{20}H_{32}O_6$ (m/e 368), m.p. 176-77°, $[\alpha]_D$ +35.4° ($CHCl_3$). From the similarity of the i.r. spectrum and extremely close physical constants to those reported

for 3, it appeared that we had obtained the same product as had been obtained from coleonol.[4] The complete structure and stereochemistry of 10 were established unequivocally[11,12] by single crystal X-ray analysis. The structure was solved by direct methods.[13] Atomic positional[14] and thermal parameters (anisotropic C, Cl, O; fixed H contributions) were refined by full-matrix least-squares calculations to R = 0.096 over 2164 [$I > 2.0\sigma(I)$] reflections recorded on an Enraf-Nonius CAD-3 automated diffractometer (Ni-filtered Cu-K radiation, λ= 1.5418 Å; θ-2θ scans, $\theta_{max.}$ = 67°) as described previously.[15] A view of the solid-state conformation of the hydrogen-bonded crystallographically independent pair of molecules in the asymmetric crystal unit is provided in the Figure.

A possible mode of formation of 10 is presumably triggered by an α-ketol rearrangement[16] with migration of the 8,9-bond (6 → 10). The retro-aldol, aldol process would account for inversion at C-1 leading to the less hindered equatorial 1β-OH. The hemiketal formation involving the 7β-OH group is preferred over the 6β-OH for the latter would have given a relatively more strained trans-fused tetrahydrofuran ring.

We now turn our attention to coleonol. An authentic sample of coleonol[5b] was found (after purification)[17] to be identical in all respects to forskolin 1. Treatment of coleonol with ethanolic KOH as above gave the same rearrangement product 10 that we isolated from forskolin. Therefore the proposed structure 3[4] for the coleonol-derived rearrangment product should be corrected to 10.

Structure 5 was assigned to coleonol-B.[9] Mild alkaline hydrolysis of both forskolin 1 and coleonol gave the same tetraol 6.[1] Treatment of 6 with $(EtO)_3C.CH_3$/p-TsOH in DMSO[19] gave the cyclic orthoester 11. Aqueous acid hydrolysis of each sample then gave the same 6β-monoacetate, $C_{22}H_{34}O_7$ (m/e 410), m.p. 210° (acetone/n-hexane)[9] identical in all respects to 4.[18] As the spectral characteristics for 4[20] and coleonol-B are the same, we ascribe structure 4 to the latter.

In view of these results, we urge that all the compounds isolated from Coleus Forskohlii propounded to have the 7α-oxo configuration[6] be critically examined and their structures be revised if necessary.

Acknowledgements: We would like to thank Dr. A.K. Ganguly for his keen interest in the problem and kind help in obtaining authentic coleonol.[5b] We also thank Dr. D. Liotta for providing a decoupled p.m.r. spectrum (300 MHz) of 10 and Drs. B. Pramanik, T.M. Chan, and M.S. Puar for all other high resolution spectral data.

References and Notes:

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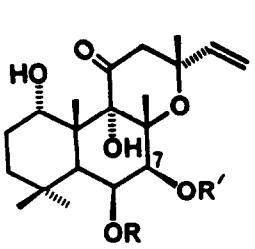
5. (a) M.P. Dubey, R.C. Srimal, S. Nityanand, and B.N. Dhawan, J. Ethnopharmacol., 3, 1-13 (1981); (b) We are grateful to Dr. S. Nityanand for a gift of authentic coleonol (m.p. 220-22°).[4,8]



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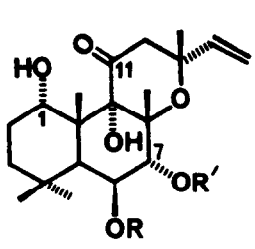
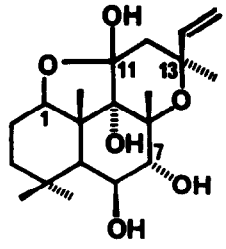
4 R=Ac;R′=H
6 R=R′=H



2 R=H;R′=Ac
5 R=Ac;R′=H



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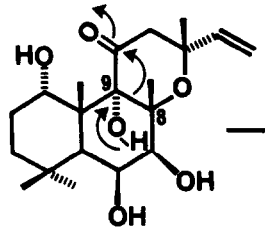

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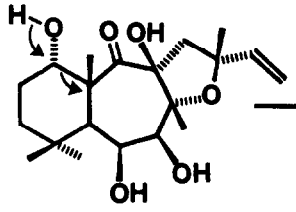

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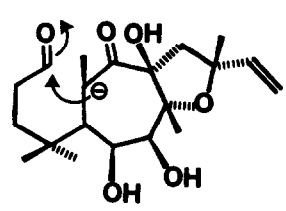

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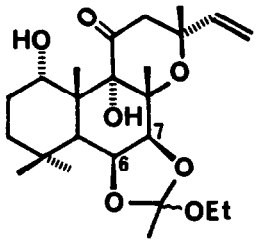

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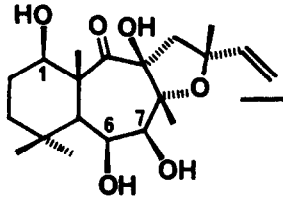

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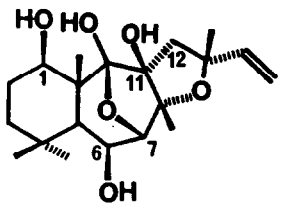

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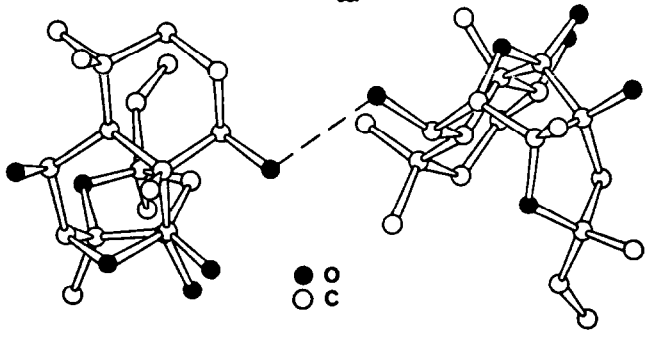

FIGURE

6. J.S. Tandon, P. Painuly, S.B. Katti, and S. Singh, Indian J. Chem., 23B, 67 (1984); and references cited therein.
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9. J.S. Tandon, P.K. Jauhari, R.S. Singh, and M.M. Dhar, Indian J. Chem., 16B, 341 (1978); The statement that coleonol-C likewise also gave 3 is not supported by the data given in this same paper; p.m.r. and i.r. clearly do not match.
10. Chemistry of forskolin as reported[1] and in our own laboratories is in complete agreement with the assigned structure 1.[1,7] Authentic forskolin was obtained from Calbiochem-Behring Corp., San Diego, CA 92112, U.S.A.
11. 10 p.m.r. (400 MHz; $CDCl_3$): 1.0 (s, CH_3), 1.3 (s, CH_3), 1.52 (s, CH_3). 1.58 (s, $2CH_3$'s), 1.9 (d, J_{gem} = 14 Hz, 12-H), 3.18 (d, J_{gem} = 14 Hz, 12-H), 3.78 (d, $J_{7,6}$ = 2.0 Hz, 7-H), 4.1 (dd, $J_{6,7}$ = 2.0 Hz, $J_{6,5}$ = 4 Hz, 6α-H), 4.2 (dd, $J_{a,e}$ = 6 Hz, $J_{a,a}$ = 10 Hz, 1α-H), 5.1 (dd, J_{gem} = 1 Hz, J_{cis} = 10 Hz, vinylic-H), 5.15 (dd, J_{gem} = 1 Hz, J_{trans} = 17 Hz, vinylic-H), 6.05 (dd, J_{cis} = 10 Hz, J_{trans} = 17 Hz, vinylic-H).
12. Crystal Data: $C_{20}H_{32}O_6.0.5CHCl_3$, M = 428.16, orthorhombic, space group $P2_12_12_1$, a = 13.868(1), b = 28.498(3), c = 10.633(2) Å, U = 4202.3 Å^3, Z = 8, $D_{calc.}$ = 1.353 g cm^{-3}.
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14. Atomic coordinates for this work have been deposited with the Cambridge Crystallographic Data Centre, Lensfield Road, Cambridge CB2 1EW.
15. R.W. Miller and A.T. McPhail, J. Chem. Soc., Perkin Trans. 2, 1527 (1979).
16. Advanced Organic Chemistry, J. March, McGraw Hill (1968), p. 802; this rearrangement is presumably made more favorable by the relief of steric compression of the 1,3-diaxial methyl groups at C-8 and C-10.
17. The sample of coleonol[5b] which contained two minor impurities (~5%), was purified on silica gel plates (40% EtOAc/n-hexane) and recrystallized from EtOAc, m.p. 232-33°, $[\alpha]_D^{26}$ -18.4° (1%, $CHCl_3$); forskolin, m.p. 233° (EtOAc), $[\alpha]_D^{26}$ -18.7° (1%, $CHCl_3$); m.m.p. 232-33°. The two compounds had superimposable p.m.r. (400 MHz; $CDCl_3$): 1.03 (s, CH_3), 1.25 (s, CH_3), 1.34 (s, CH_3), 1.44 (s, CH_3), 1.7 (s, CH_3), 2.17 (s, $O.CO.CH_3$), 2.5 (d, J_{gem} = 17 Hz, 12β-H), 3.2 (d, J_{gem} = 17 Hz, 12α-H), 4.46 (dd, $J_{e,e}$ = 3 Hz, $J_{e,a}$ = 4 Hz, 1β-H), 4.56 (dd, broad W1/2 = 7 Hz, 6α-H), 4.98 (dd, J_{gem} = 1 Hz, J_{cis} = 10 Hz, vinylic-H), 5.3 (dd, J_{gem} = 1 Hz, J_{trans} = 17 Hz, vinylic-H), 5.48 (d, $J_{a,e}$ = 4 Hz, 7α-H), 5.92 (dd, J_{cis} = 10 Hz, J_{trans} = 17 Hz, vinylic-H), 6.4 (s, C_9-OH).
18. 4, m.p. 208-10° has also been isolated as a natural product by the Hoechst group.[1] It was correlated with forskolin by Al_2O_3 catalysed 7 → 6 acetoxy migration.[1b]
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20. 4 p.m.r. (200 MHz; $CDCl_3$): 1.0 (s, CH_3), 1.08 (s, CH_3), 1.42 (s, CH_3), 1.43 (s, CH_3), 1.64 (s, CH_3), 1.64 (s, CH_3), 2.13 (s, $O.CO.CH_3$), 2.56 (d, J_{gem} = 16 Hz, 12β-H), 3.2 (d, J_{gem} = 16 Hz, 12α-H), 4.3 (d, $J_{a,e}$ = 5 Hz, 7α-H), 4.7 (broad, W1/2 = 7 Hz, 1β-H), 5.02 (dd, J_{gem} = 1 Hz, J_{cis} = 12 Hz, vinylic-H), 5.21 (dd, J_{gem} = 1 Hz, J_{trans} = 18 Hz, vinylic-H), 5.78 (dd, $J_{e,a}$ = 4 and 5 Hz, 6α-H), 6.16 (dd, J_{cis} = 12 Hz, J_{trans} = 18 Hz), 6.47 (s, C_9-OH).

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