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OXIDATION/REDUCTION STUDIES WITH FORSKOLIN

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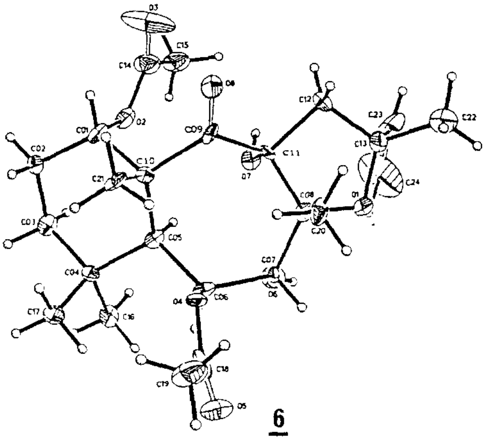
Abstract : Oxidation/reduction reactions were carried out with forskolin and its derivatives. The structures of the skeletally rearranged products obtained are reported.

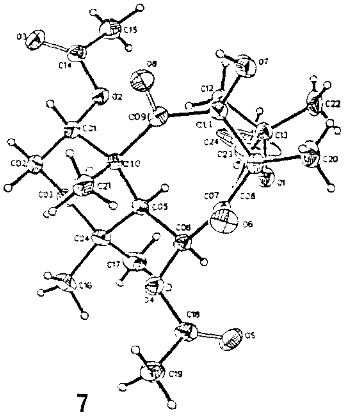
Forskolin[1] (1), a labdane diterpenoid isolated from an Indian plant *Coleus forskohlii* in our laboratories, displays interesting biological properties[2,3]. In continuation of our studies on structure-activity relationships[4], we desired to investigate the influence of the stereochemistry of the hydroxy groups on biological activity. In this paper we report the results of oxidation/reduction reactions carried out with forskolin, 1-acetylforskolin (2), and 1,6-diacetyl-7-deacetylforskolin[1b] (3).

Jones oxidation of 3 at 0° gave two products, to which the structures 4 (1,6-diacetyl-7-deacetoxy-7-oxoforskolin, m/z 450, mp 156-158°C) and 5[5] (mp 150-151°C), a rearranged compound, were assigned. In the PMR (CDCl$_3$) spectrum of 5, 6α-CH and 5α-CH appear as singlets at δ5.80 and δ3.5 respectively. 15-CH (trans) and 15-CH (cis) appear at δ5.88 and δ5.17, in contrast to the resonances at δ5.28 and δ5.0 respectively for the same protons in 4. This result may be rationalized through a shielding effect of the 7C=0 group. The assignments for 5 were further confirmed by NOE studies. On irradiation of 5α-CH, positive NOE effects on 6α-CH and 4α-CH$_3$ were observed, while irradiation of 10ß-CH$_3$ showed positive NOE effect on 1ß-CH, 5α-CH (indirect effect because the irradiation of 10ß-CH$_3$ effected also 3α-CH) and 4ß-CH$_3$. NOE effects of 4α-CH$_3$ were observed on 5α-CH and 6α-CH, and NOE effects of 4ß-CH$_3$ were observed on 6α-CH and 10ß-CH$_3$. The stereochemistry of the B/C ring junction could not be assigned at this stage.

Reduction of the rearranged product 5 (m/z 450) with one equivalent of sodium borohydride in pyridine at 0°C yielded two products 6[6] (mp 218-220, m/z 452) and 7[7] (mp 199-201, m/z 450) respectively. The PMR spectrum of 6 showed a triplet at δ3.96 for 7-CH, which collapsed to a doublet (J=4Hz) after D$_2$O exchange. The 6-CH proton appeared as a doublet at δ5.92 (J=4Hz) and the 5α-CH as a singlet at δ3.36, suggesting a cis relationship between protons 5 and 6 and a trans-relationship between protons 6 and 7. The features were confirmed by an X-ray analysis of 6, which further showed the stereochemistry of the B/C ring junction. Surprisingly, an X-ray analysis of 7, while confirming the assignments made for 6α-CH and 5α-CH based on NMR decoupling experiments and NOE effects between 4α-CH_3, 5α-CH, and 6α-CH, showed that the B/C ring junction was different from that in 6.



6



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The results for 6 are in contrast to those reported by Saksena et al.[9] wherein the B/C ring junction in the rearranged product obtained by them has a stereochemistry opposite to that seen in 6. Since 6 is a reduced product of 5, it may be assumed that the B/C ring junction in 5 has the same stereochemistry as that in 6.

Reduction of 4 (m/z 450) also yielded two products 7 (m/z 450) and 8 (mp 140-142°, m/z 452). For compound 8, a singlet at δ3.52 was observed accounting for 9-CHOH,[11] which on irradiation showed positive NOE effects of 1β-CH and 12β-CH.

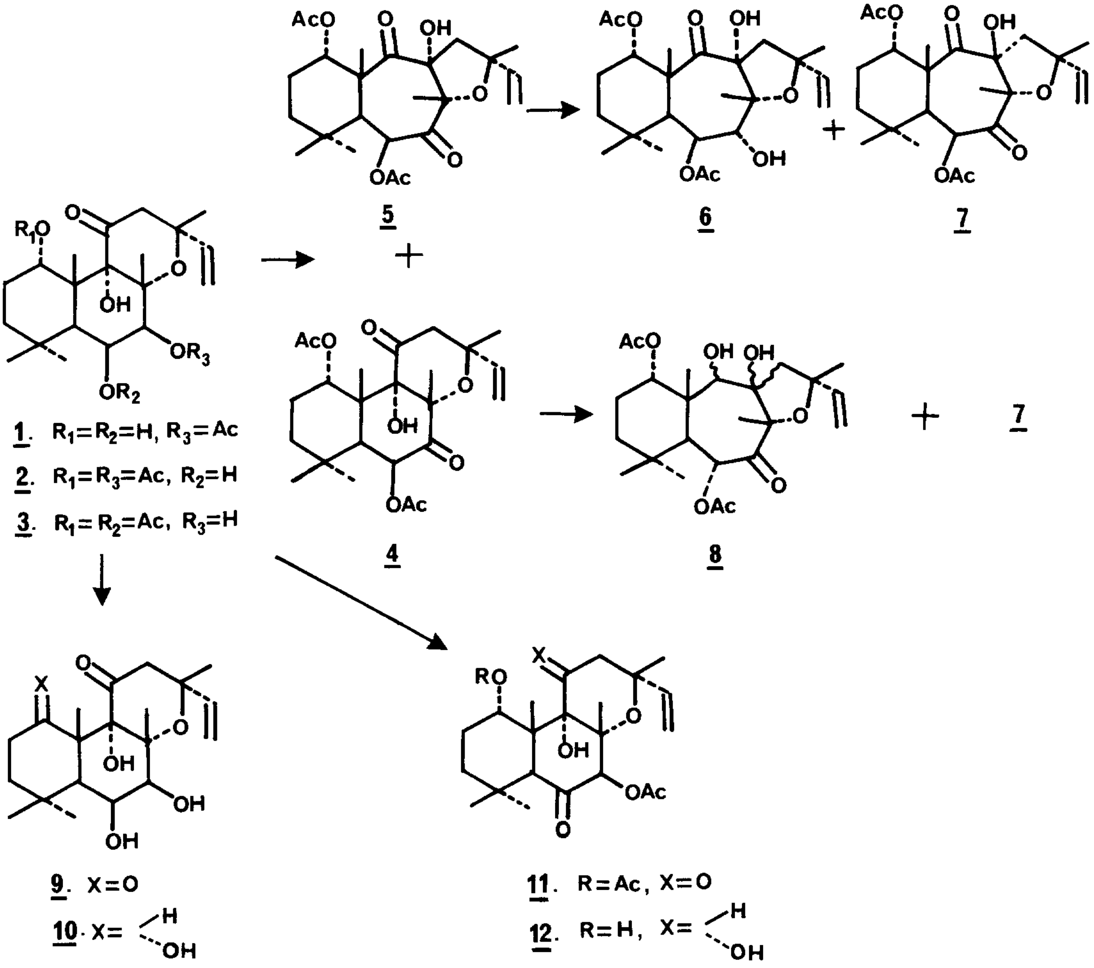
These effects can be interpreted only with the rearranged skeleton in 8[8]. The appearance of 6β-CH as a doublet at δ6.0 (J=6Hz) and 5α-CH as a doublet at δ2.48 (J=6Hz) indicated that 5-CH and 6-CH are trans oriented.

A possible mode of formation of 7 from 4 is proposed in scheme 2. Retro-aldol rearrangement of 4 generates 13, which cyclises to yield the less strained skeleton 5. Base-catalysed rearrangement of 5 gives 7,which has been experimentally verified by treatment of 5 with pyridine, and reduction of 5 yields 6. The stereochemistry of the B/C ring junctions in compound 5 and 8 remains to be unequivocally confirmed.

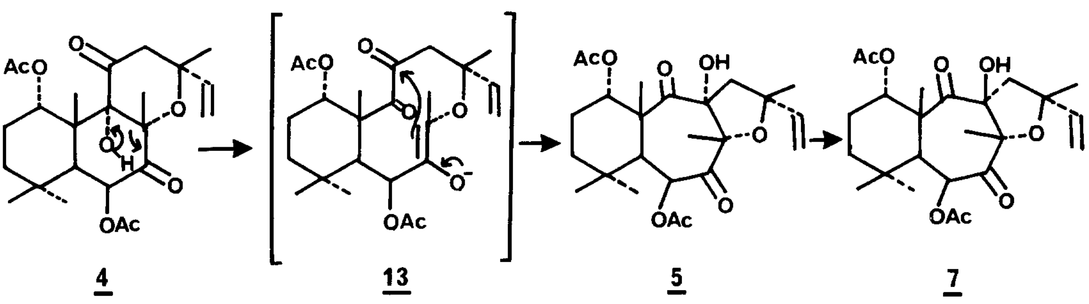
In contrast to the above results obtained by reduction of a 7-oxoforskolin derivative, sodium borohydride-pyridine reduction of the 1-oxo-forskolin derivative 9 (mp 158-160°C), prepared by Jones oxidation of forskolin at 0°C and subsequent hydrolysis, resulted in the selective formation of 7-deacetylforskolin (10)[1a]

Treatment of the 6-oxoforskolin derivative 11 (mp 148-150°C), obtained by Jones oxidation of 1-acetylforskolin at 28°C, with sodium borohydride in pyridine produced a highly complex mixture. Reduction of 11 with sodium borohydride in ethanol, however, resulted in selective reduction of the 11-keto function to give the 11α-

SCHEME-1



SCHEME-2



hydroxy forskolin derivative 12[10] (mp 227-230°C). In the PMR spectrum of 12, assignment of the resonance at δ4.64 (J_1=6Hz, J_2=3.6Hz) was made to 11β-C$\underline{H}$OH on the basis of its chemical shift, its coupling constants with 12α-C$\underline{H}$ δ2.5(dd, J_{gem}=16Hz, J_2=6Hz) and the singlet peaks observed for 5α-C$\underline{H}$ (δ3.36) and 7α-C$\underline{H}$ (δ5.5).

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5. PMR (270 MHz, $CDCl_3$): δ6.05 (dd, J_{cis}=11Hz, J_{trans}=18Hz, vinylic-$\underline{H}$), 5.88 (dd, J_{gem}=1Hz, J_{trans}=18Hz, vinylic-$\underline{H}$) 5.17 (dd, J_{gem}=1Hz, J_{cis}=11Hz, vinylic-$\underline{H}$), 5.8 (s, 6-C$\underline{H}$), 4.93 (bs, 1β-C$\underline{H}$), 3.5 (s, 5α-C$\underline{H}$) 2.91 (d, J_{gem}=14Hz, 12α-C$\underline{H}$), 2.09 (s, COC$\underline{H}_3$), 1.96 (d, J_{gem}=14Hz, 12β-C$\underline{H}$), 1.94 (s, $COCH_3$), 1.68 (s, 10β-C$\underline{H}_3$), 1.43(s, 8β-C$\underline{H}_3$), 1.4 (s, 13β-C$\underline{H}_3$), 1.15 (s, 4α-C$\underline{H}_3$), 1.01 (s, 4β-C$\underline{H}_3$).
6. PMR (90 MHz $CDCl_3$)δ6.14 (dd, J_{cis}=10.8Hz, J_{trans}=17Hz, vinylic-$\underline{H}$), 5.92 (d, J=4Hz, 6α-C$\underline{H}$), 5.18 (dd, J_{gem}=1Hz, J_{trans}=vinylic-$\underline{H}$), 4.98 (dd, J_{gem}=1Hz, J_{cis}=10.8Hz, vinylic-$\underline{H}$), 4.92 (m, 1β-C$\underline{H}$), 3.96 (t, 7α-C$\underline{H}$ collapsed to d (J=4Hz) on D_2O shake), 3.56 (s, 5α-C$\underline{H}$), 2.86 (d, J_{gem}=14Hz, 12α-CH), 2.04 (s, COC$\underline{H}_3$), 2.0 (s, $COCH_3$), 1.56, 1.46, 1.16, 1.12, 0.98 (s, 5 X C$\underline{H}_3$).
7. PMR (270 MHz, $CDCl_3$)δ6.35 (d, J=5Hz 6α-C$\underline{H}$), 6.26 (dd, J_{cis}=10Hz, J_{trans}=17Hz, vinylic-$\underline{H}$), 5.32 (dd, J_{gem}=1Hz, J_{trans}=17Hz, vinylic-$\underline{H}$), 5.18 (dd, J_{gem}=1Hz, J_{cis}=10Hz, vinylic-$\underline{H}$), 4.92 (bs, 1β-C$\underline{H}$), 3.78 (d, J_{gem}=14Hz, 12α-C$\underline{H}$), 3.16 (d, J=5Hz 5α-C$\underline{H}$), 2.17 (s, CO$\underline{C}H_3$), 1.99 (s, COC$\underline{H}_3$), 1.99 (d, J_{gem}=14Hz, 12β-C$\underline{H}$), 1.63 (s, 13β-C$\underline{H}_3$), 1.48 (s, 8β-C$\underline{H}_3$), 1.39 (s, 10β-C$\underline{H}_3$), 1.21 (s, 4β-C$\underline{H}_3$), 1.15 (s, 4α-C$\underline{H}_3$)
8. PMR (270 MHz, $CDCl_3$): δ6.0 (d, J=6Hz, 6β-C$\underline{H}$), 5.92 (dd, J_{cis}=10Hz, J_{trans}=17Hz vinylic-$\underline{H}$) 5.12 (dd, J_{gem}=0.5Hz, J_{trans}=17Hz vinylic-$\underline{H}$), 5.03 (dd, J_{gem}=0.5Hz, J_{cis}=10Hz), 4.76 (bs, 1β-C$\underline{H}$), 3.52 (s, 9 –C$\underline{H}$) 2.47 (d, J=6Hz, 5α-C$\underline{H}$), 2.47 (d, J_{gem}=14Hz, 12α-C$\underline{H}$), 2.22 (d, J_{gem}=14Hz, 12β-C$\underline{H}$), 2.13 (s, COC$\underline{H}_3$), 2.1 (s, $COCH_3$), 1.48 (s, 8β-C$\underline{H}_3$, 10β-C$\underline{H}_3$, 13β-C$\underline{H}_3$),1.07 (s, 4α-C$\underline{H}_3$), 1.02 (s, 4β-C$\underline{H}_3$).
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10. PMR (90MHz, $CDCl_3$):δ5.88 (dd, J_{trans}=16Hz, J_{cis}=10.8Hz, vinylic-$\underline{H}$), 5.48 (s, 7α-C$\underline{H}$) 5.12 (dd, J_{trans}=16Hz, J_{gem}=1Hz, vinylic-$\underline{H}$), 4.94 (dd, J_{cis}=10.8Hz, J_{gem}=1Hz, vinylic-$\underline{H}$), 4.64 (dd, J_1=6Hz, J_2=3.6Hz, 11β-C$\underline{H}$), 4.10 (m, 1β-C$\underline{H}$), 3.36 (s, 5α-C$\underline{H}$), 2.5 (dd, J_{gem}=16Hz, $J_{11,12}$=6Hz, 12α-C$\underline{H}$), 2.2 (s, COC$\underline{H}_3$), 1.72, 1.55, 1.28, 1.28, 1.0, (s, 5 X C$\underline{H}_3$).
11. A β-orientation is not unequivocally assignable to 9-C$\underline{H}$OH because of the undefined stereochemistry of the B/C ring junction.

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