Forskolin: A Convenient Degradation to 14,15-Dinor-8,13-epoxy-1α,6β,7β,9α-tetrahydroxylabd-12-en-11-one 7-Acetate 1,9-Carbonate *via* β-Elimination of an Aldoxime

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The title compound (**6**) was obtained by an unprecedented β-elimination of the aldoxime (**4**).

The possible clinical utility of forskolin (coleonol) (**1**) has generated considerable interest in its chemical modifications[1] and total synthesis.[2] In an attempted dehydration of the aldoxime (**4**) we obtained the dihydropyran-4-one (**6**) rather than the nitrile (**5**). We are prompted to report this facile degradation of forskolin since (**6**) may serve as an important relay compound in synthetic routes to forskolin.

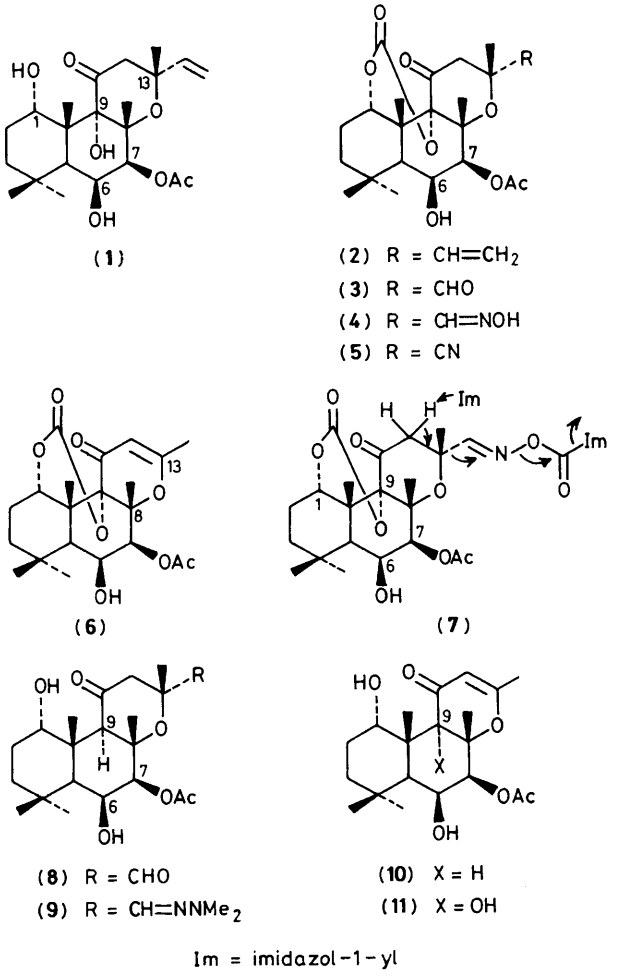
Ozonolysis of forskolin 1,9-carbonate (**2**)[1] in CH_2Cl_2–MeOH (Me_2S work-up) provided the aldehyde (**3**), m.p. 237—238 °C, $[\alpha]_D^{26}$ −77° ($CHCl_3$). Treatment of (**3**) with $NH_2OH{\cdot}HCl$ in pyridine readily gave the aldoxime (**4**), m.p. 277—280 °C (decomp.), $[\alpha]_D^{26}$ −44.5° ($CHCl_3$). An extremely mild procedure for the dehydration of aldoximes uses treatment with 1,1′-carbonyl-di-imidazole in CH_2Cl_2 at room temperature.[3] When the aldoxime (**4**) was subjected to these reaction conditions, the sole product isolated was the dihydropyran-4-one (**6**), m.p. 264—265 °C, $[\alpha]_D^{26}$ −142° ($CHCl_3$) in >90% yield [^{1}H n.m.r. (200 MHz, $CDCl_3$), 5.5 (d, 1H, $J_{ax.\ eq.}$ 4.0 Hz, 7α-H), 5.44 (br. m, 1H, 1β-H), 5.4 (s, 1H, olefinic), 4.6 (br. m, 1H, 6α-H), 2.2 (s, 3H, COMe), 2.0 (s, 3H, Me), 1.8 (s, 3H, Me), 1.58 (s, 3H, Me), 1.3 (s, 3H, Me), and 1.05 (s, 3H, Me)]. T.l.c. of the reaction mixture indicated transient formation of a more polar product [presumably the activated aldoxime (**7**)] followed by appearance of the less polar (**6**) as the only detectable product. Since all attempts to isolate the nitrile (**5**) were unsuccessful, we propose that (**6**) is formed by β-elimination of the activated aldoxime (**7**) as depicted. Although Beckman fragmentations of α-hydroxy and α-keto oximes are well known,[4] such a reaction [*viz.* (**7**) → (**6**)] to our knowledge has not been reported earlier.

The formation of (**6**) appears to be particularly favoured by the relief of 1,3-diaxial interaction of the methyl groups at C-8 and C-13. Thus attempted oxidation of the aldehyde (**3**) with AgO in Me_2SO also provided (**6**) as one of the products (yield ~10%). Further, treatment of the 9-deoxy aldehyde (**8**) with H_2NNMe_2 gave the 9-deoxy analogue (**10**), m.p. 186—189 °C [^{1}H n.m.r. (100 MHz, CD_3COCD_3), 5.08 (s, 1H, olefinic), 4.95 (d, 1H, $J_{ax.\ eq.}$ 4.0 Hz, 7α-H), 4.55 (br. m, 1H, 1β-H), 4.45 (br. m, 1H, 6α-H), 3.32 (s, 1H, 9α-H), 2.2 (s, 3H, COMe), 1.85 (s, 3H, Me), 1.7 (s, 3H, Me), 1.43 (s, 3H, Me), 1.25 (s, 3H, Me), and 0.95 (s, 3H, Me)], as a minor product (<10% yield) besides the desired hydrazone (**9**). We have not explored the mechanistic aspects or generality of these β-elimination reactions.

In preliminary experiments to reconstitute forskolin (**1**), reaction of (**6**) with $(CH_2{=}CH)_2Cu(CN)Li_2$[5] followed by basic hydrolysis[1] failed to provide 7-deacetyl forskolin or its 13-epimer. All attempts at conjugate addition of thiols to (**6**) also met with failure.

Basic hydrolysis of (**6**) followed by selective acetylation of the 7β-OH provided the forskolin analogue (**11**) in 60% yield. We shall describe full details of this work (including biological results) and other reactions of (**6**) elsewhere.†

† All new compounds described gave satisfactory spectral and analytical data.



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