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SEVEN-MEMBERED CYCLIC TRANSITION STATE IN THE ALKOXY-RADICAL INDUCED INTRAMOLECULAR HYDROGEN ABSTRACTION OF 26-HYDROXY-FUROSTANS

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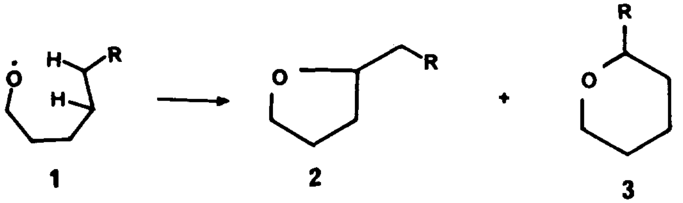
Summary: The photolysis of 26-hydroxy-furostan (5) and (8) in the presence of $Pb(OAc)_4/I_2$ *afforded spirostan sapogenins (4) and (7) respectively in 80% yield. This cyclization takes place by an uncommon 1,6-hydrogen shift involving a 7-membered transition state as demonstrated by using specifically deuterium labeled compounds.*

Intramolecular free radical hydrogen abstraction has been widely used in preparative organic chemistry.[1] The reaction is originated by thermal or photolytic homolysis of an appropriate bond of the molecule to give rise to carbon,[2] nitrogen,[3] or oxygen[1] radicals. The most important reactions of this type are those initiated by oxy-radicals (1, R=Alkyl)(Scheme 1) in which the hydrogen is preferentially abstracted from the γ-carbon atom[4] through a six-membered cyclic transition state leading finally to tetrahydrofuranic derivatives (2, R=Alkyl). Tetrahydropyranic derivatives (3, R=Alkyl) are occasionally obtained in small yields[5] (8%). Tetrahydropyrans are obtained in fair to good yields only in cases of rigid systems[6] where the δ-hydrogen is activated and closely positioned to the oxy-radical, or in the not rigidly fixed 1,3- and 1,5-hydroxyl ethers[7] (1, R=O-Alkyl).

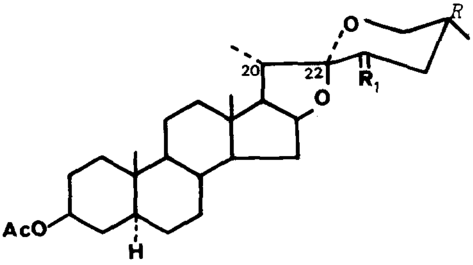


SCHEME 1

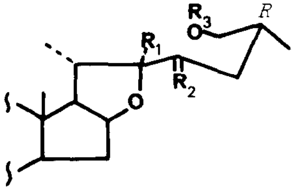
Seven-centered cyclic transition states have been postulated to explain the formation of tetrahydropyranic derivatives. However, evidence of this assumption has never been reported.

G.R. Pettit et al.[8] studied the electron impact mass spectra of furostanic compounds of type (5-d_1) and reported that the deuterium atom at C-22 was abstracted by the C-26 radical ionized alcohol via a seven centers transition state. Taking into account the correlation between free radical chemistry and electron impact mass spectrometry,[9] we report here the photochemical intramolecular cyclization of the 26-hydroxy-furostans (5) and (8) to spirostan sapogenins (4) and (7) via a seven-membered transition state.

The 26-hypoiodite (6), readily prepared by reaction of (22R,25R)-5α-furostan-3β,26-diol 3-acetate (5) (1 mmol) ("dihydrotigogenin 3-acetate") with $Pb(OAc)_4$ (3 mmoles) and I_2 (1 mmol) in cyclohexane, decomposed homolitically by irradiation with 2x100 w tungsten-filament lamps at reflux temperature for 20 min. to afford (20S,22R,25R)-5α-spirostan-3β-yl acetate ("tigogenin acetate") (4) in 80% yield. In a similar way (22R,25S)-5α-furostan-3β,26-diol 3-acetate



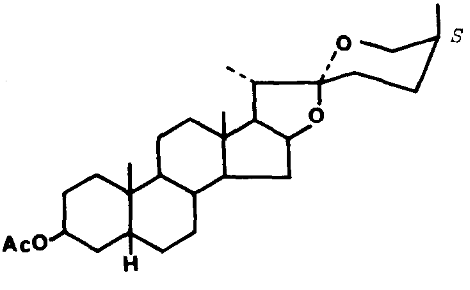
4 $R_1 = H_2$
4-d$_2$ $R_1 = D_2$



	R_1	R_2	R_3
5	H	H_2	H
5-d$_1$	D	H_2	H
5-d$_2$	H	D_2	H
5-d$_3$	D	D_2	H
6	H	H_2	I

("dihydrosarsasapogenin 3-acetate") (8) gave sarsasapogenin acetate (7) also in 80% yield.

Whilst at first glance the formation of the tetrahydrofuranic ring seems to indicate a seven-membered transition state, a 1,5-hydrogen shift from C-23, as shown in Scheme 2, cannot be discharged. In fact, 1,5-hydrogen transfer from C-23 would lead to (9), which after being disproportioned is stabilized through the loss of HI to give the vinyl ether (10) which cyclizes spontaneously to the spiroketal (4).[10]



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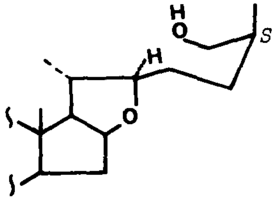

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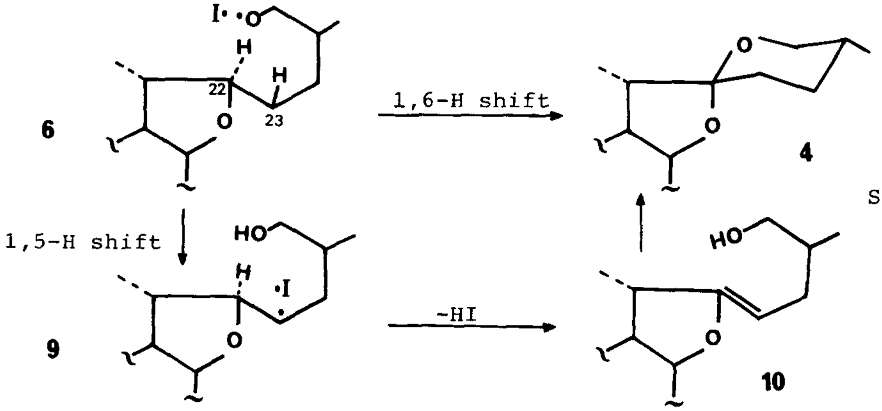
In order to distinguish between both possible mechanisms, we have performed this intramolecular cyclization with suitable C-22 and C-23 deuterium labeled furostans.

Platinum (IV) oxide catalyzed hydrogenation of 23,23-d_2-tigogenin acetate (4-d_2, d_0 4%, d_1 22%, d_2 68%, d_3 6%)[11] afforded 23,23-d_2-dihydrotigogenin 3-acetate (5-d_2) with total retention of the deuterium atoms. Reaction of (5-d_2) with $Pb(OAc)_4/I_2$ as described previously for unlabeled compound (5) gave 23,23-d_2-tigogenin acetate (4-d_2, d_0 4%, d_1 23%, d_2 68%, d_3 5%) in 80% yield showing that a 1,6-hydrogen shift is operating.[12]

As the hydrogen-deuterium kinetic isotopic effect (KH/KD) for intramolecular cyclization involving alkoxy-radicals is known to be large[9] we have prepared the 22,23,23-d_3-dihydrotigogenin 3-acetate (5-d_3, d_0 2%, d_1 9%, d_2 29%, d_3 55%, d_4 5%) by catalytic hydrogenation of 23,23-d_2-tigogenin acetate (4-d_2) (H_2/PtO_2 in AcOD for 5h)^{14}. The ^1H n.m.r. spectrum of (5-d_3) lacks the signal corresponding to the H-22 indicating that a deuterium atom has been incorporated at C-22. Photolysis of (5-d_3) in the presence of $Pb(OAc)_4/I_2$ gave the 23,23-d_2-tigogenin acetate (4-d_2, d_0 6%, d_1 24%, d_2 65%, d_3 5%) (80% yield). The fact that only one deuterium atom (at C-22) is lost (a 6-center process would involve the loss of two deuterium atoms) proves that this intramolecular cyclization takes place by a 1,6-hydrogen (or deuterium) shift through a seven-membered transition state.



SCHEME 2

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References and Notes:

1 a) J. Kalvoda and K. Heusler, Synthesis, 1971, 501; K. Heusler and J. Kalvoda in Organic Reactions in Steroid Chemistry, vol. 2, eds. J. Fried and J.A. Edwards, Van Nostrand Reinhold, New York, 1971, p. 237; b) K. Heusler and J. Kalvoda, Angew. Chem. Int. Ed. Engl., 1964, 3, 525.

2 C.A. Grob and H. Kammuller, Helv. Chim. Acta, 1957, 40, 2139.

3 M.E. Wolff, Chem. Reviews, 1963, 63, 55; R. Hernández, A. Rivera, J.A. Salazar, and E. Suárez, J. Chem. Soc., Chem. Comm., 1980, 958.

4 A.L. Nussbaum and C.H. Robinson, Tetrahedron, 1962, 17, 35.

5 M. Lj. Mihailovic, Z. Cekovic, and J. Stankovic, J. Chem. Soc., Chem. Comm., 1969, 981; M. Lj. Mihailovic, M. Jakovljevic, and Z. Cekovic, Tetrahedron, 1969, 25, 2269; M. Lj. Mihailovic, Z. Cekovic, and D. Jeremic, Tetrahedron, 1965, 21, 2813.

6 A. Bowers and E. Denot, J. Amer. Chem. Soc., 1960, 82, 4956; H. Immer, M. Lj. Mihailovic, K, Schaffner, D. Arigoni, and O. Jeger, Helv. Chim. Acta, 1962, 45, 753.

7 M. Lj. Mihailovic and M. Miloradovic, Tetrahedron, 1966, 22, 723.

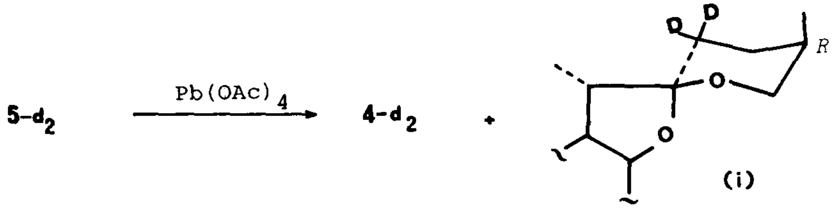
8 P. Brown, A.H. Albert, G.R. Pettit, J. Amer. Chem. Soc., 1970, 92, 3212; *ibid*, J. Org. Chem., 1973, 38, 2197.

9 M.M. Green, Tetrahedron, 1980, 36, 2687.

10 A similar mechanism has been proposed to explain olefin formation during alkyl hypoiodite decomposition (see reference 1b, p. 532).

11 W.H. Faul, A. Failli, and C. Djerassi, J. Org. Chem., 1970, 35, 2571; R.K. Callow, V.H.T. James, O. Kennard, J.E. Page, P.N. Paton, and L.R. di Sanseverino, J. Chem. Soc. (C), 1966, 288.

12 When iodine was omitted the reaction became sluggish giving, after 4h at reflux temperature, a mixture of 23,23-d_2-tigogenin acetate (4-d_2) and its (22S)-stereoisomer (i, d_0 6%, d_1 28%, d_2 60%, d_3 6%) in a ratio of 3:1 with an overall yield of 40%. Noteworthy, compound (i)



[3.28, 3.42, 4.00, 4.14 (each m, $W_{1/2}$ =6 Hz, 26-H_2), axial 25-Me]^{13} was readily isomerized to the more stable (22R)-spirostane (4-d_2) with catalytic amounts of iodine at reflux temperature for 1h with total retention of the two deuterium atoms. This explains the absence of the (22S)-stereoisomer (i) when the intramolecular cyclization is accomplished in the presence of iodine.

13 A.G. González, R. Freire, M.G. Garcia-Estrada, J.A. Salazar, and E. Suárez, Tetrahedron, 1972, 28, 1289.

14 Additional proofs that a deuterium atom was incorporated at C-22 were obtained by identical hydrogenation of tigogenin acetate (4); the monodeuterated compound obtained (5-d_1, d_0 4%, d_1 80%, d_2 12%, d_3 4%) also lacks the 22-H signal in its ^1H n.m.r. spectrum. The deuterium distribution data in the labeled dihydrocompounds 5-d_1 and 5-d_3 are approximated inasmuch as ions $[M-1]^+$ and $[M-2]^+$ could not be completely eliminated from the mass spectra (see K. Biemann in Mass Spectrometry, Organic Chemical Applications, McGraw-Hill Inc., New York, 1962, p. 209). We are presently investigating the mechanism of this catalytic hydrogenation.

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