Tetrahedron Letters No.42, pp. 3099-3103, 1964. Pergamon Press Ltd.
Printed in Great Britain.

SOLVOLYSIS OF PSEUDODIOSGENIN 27-p-TOLUENESULFONATE[1]

Frederick C. Uhle

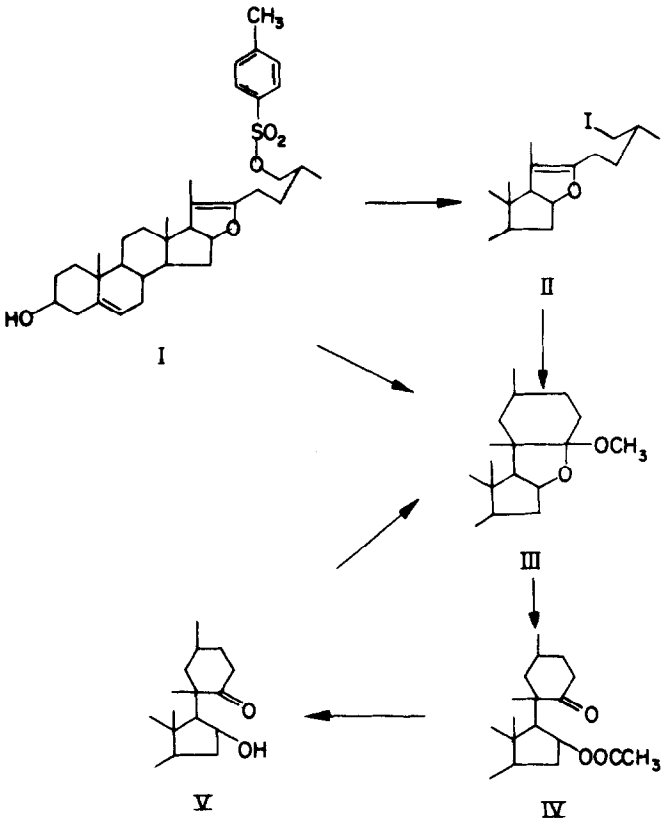
Department of Pharmacology, Harvard Medical School

Boston, Massachusetts 02115

(Received 4 August 1964)

Solvolytic ring closures currently elicit widespread theoretical and practical interest[2]. In contribution to this development, participation of the 20,22 double bond in solvolysis of pseudosapogenin 27-derivatives to afford hemiketals of novel structure has been observed. The transformation appears to represent the first example of a solvolytic cyclization involving a neighboring vinyl ether.

When pseudodiosgenin 3β,27-di-p-toluenesulfonate is allowed to react with water in refluxing aqueous acetone during several hours, the homoallylic 3β ester linkage is selectively hydrolyzed, providing 80% of pseudodiosgenin 27-p-toluenesulfonate (I)[3]. Prolonged exposure of I under these conditions resulted in only slow attack at the 27-position, with a major fraction of starting tosylate surviving unchanged after 95 hours. Buffered aqueous ethanol served as a more favorable medium, giving a mixture whose principal component no longer retained the α,β-unsaturated ether function.

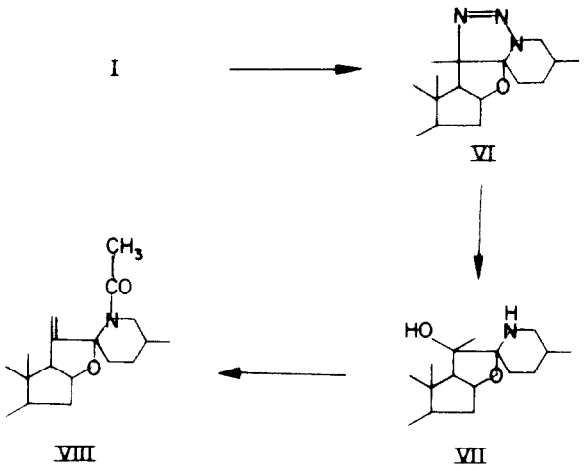


Search for definitive preparative conditions led to discovery that treatment of pseudodiosgenin 27-iodide (II)[3,4] with aqueous ethanolic silver nitrate, at ambient temperature, within a few minutes furnished 85% of the same hemiketal, conveniently isolated as the methyl ketal, m.p. 220-225°, [α] -3°, n.m.r. sharp peak at δ 3.21 p.p.m., OCH_3 7.00 (calcd. 7.24), and considered to be III[5].

Ethanolic acetic acid transformed III to the ethyl ketal, m.p. 166-171°, OC_2H_5 10.24 (calcd. 10.18), while aqueous acetic acid liberated the sparingly soluble hemiketal, m.p. 203-206°. Brief recrystallization from methanol sufficed for conversion of the hemiketal to the methyl ketal III; the ethyl ketal formed less readily.

Treatment of the 3β-acetate of III, m.p. 200-205°, with refluxing acetic acid yielded the acetoxy ketone IV, m.p. 187-189°, [α] -125°. Alkaline hydrolysis of IV gave the hydroxy ketone V, m.p. 182-187°, [α] -4°, carbonyl infrared absorption at 1700 cm^{-1}; oxime, m.p. 243-253°, [α] +9°. With a catalytic amount of p-toluenesulfonic acid in methanol, the hydroxy ketone V reverted to the methyl ketal III[6].

Additional evidence for the reactive nature of the pseudosapogenin dihydrofuranoid ring E was adduced when I was treated with potassium azide in dimethylformamide. Displacement of the p-toluenesulfonate function by azide ion proved to be followed by a 1,3-dipolar cycloaddition[8], affording 80% of the heptacyclic triazoline VI, m.p. 221-228° with ebullition, [α] -87°. Acidification of an ethanolic solution of VI with dilute hydrochloric acid effected prompt evolution of nitrogen, giving the hydrochloride, m.p. 255-275°, [α] -21°, of a secondary base, m.p. 212-217°, [α] -31°, formulated as a 20-hydroxy



solasodine derivative (VII). Treatment of the 3β,N-diacetate of VII, m.p. 245-249°, [α] +52°, with boiling acetic anhydride, or with p-toluenesulfonyl chloride in boiling pyridine, gave the $\Delta^{20,21}$ elimination product VIII, m.p. 215-225°, $=CH_2$ infrared absorption at 11.45 μ.

---

(1) Supported by the National Heart Institute, National Institutes of Health, United States Public Health Service (H-2205) and by the Eugene Higgins Trust. I am indebted to Dr. B. H. Walker, Upjohn Research Laboratories, for a gift of the diosgenin used as starting material.

(2) B. Capon, Quart. Rev., 18, 93 (1964).

(3) F. C. Uhle, J. Org. Chem., 27, 2797 (1962).

(4) F. C. Uhle, J. Am. Chem. Soc., 83, 1460 (1961).

(5) Satisfactory analytical values have been obtained for all compounds mentioned.

(6) Solvolysis experiments with kryptogenin 27-p-toluenesulfonate[4], with kryptogenin 27-iodide[4], and with 3β,16β-diacetoxy-27-chloro-25α-5-cholesten-22-one[7] to the present have detected no rearrangement products arising from 1,2 hydrogen migration. Thus, treatment of kryptogenin 27-iodide with methanolic silver nitrate has afforded 80-90% of bethogenin (16α-methoxydiosgenin), which, in acid medium, returns kryptogenin.

Formolysis of I with boiling formic acid in the presence of potassium formate has given 20% of a compound, m.p. 240-245°, [α] -57°, whose structure is not yet known.

(7) F. C. Uhle, J. Org. Chem., 27, 656 (1962); R. S. Miner, Jr., and E. S. Wallis, J. Org. Chem., 21, 715 (1956).

(8) R. Huisgen, Angew. Chem., 75, 618 (1963).

(9) M. E. Wall and H. A. Walens, J. Am. Chem. Soc., 80, 1984 (1958), have prepared an analogous $\Delta^{20,21}$-tigogenin acetate by thionyl chloride - pyridine dehydration of the 20β-hydroxy compound derived from chromic acid oxidation of cyclopseudotigogenin acetate; thionyl chloride proved ineffective in the present case.