[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MAINE]

Aluminum Chloride-Catalyzed Opening of the Steroidal Sapogenin Spiroketal System[1]

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Several representative steroidal sapogenins have been conveniently converted to the corresponding dihydrosapogenins employing the lithium aluminum hydride–aluminum chloride reagent. Dihydro derivatives of 11α-hydroxytigogenin, markogenin, and three previously described dihydrosapogenins were prepared by the new procedure. Lithium aluminum hydride reduction of tomatidine, in the presence of aluminum chloride, provided both isomers of dihydrotomatidine.

In 1939 Marker and Rohrmann reported the catalytic hydrogenation of sarsasapogenin (5β, Ia) to dihydrosarsasapogenin (5β, IIa).[2] Catalytic hydrogenation of steroidal sapogenins to dihydrosapogenins, using similar conditions,[3] has been described numerous times subsequent to Marker's discovery. Recently, the hydrogenation procedure has been carried out in the presence of perchloric acid.[4] Doukas and Fontaine[5] have employed an ethereal lithium aluminum hydride solution saturated with anhydrous hydrogen chloride or hydrogen bromide to achieve reduction. However, lithium aluminum hydride, either alone[5,6] or in the presence of hydrogen sulfide, sulfur dioxide, or *p*-toluenesulfonic acid is ineffective.[5]

The elegant mechanism proposed by Woodward, Sondheimer, and Mazur[7] to account for the acid-catalyzed interconversion of normal and isosteroidal sapogenins, involves rupture of the spiroketal system and eventual generation of a potential aldehyde at C-26 (*e.g.*, A).[8] In view of these experiments, current work in this laboratory and the novel lithium aluminum hydride–aluminum chloride reduction of acetals and ketals described by Eliel and Rerick[9] it appeared possible to generate an intermediate such as C or D by treating a steroidal sapogenin with ethereal aluminum chloride or boron trifluoride. Concomitant metal hydride reduction might then lead to a dihydrosapogenin.[10] A variety of steroidal sapogenins were, in fact, found to be converted in good yield to dihydro derivatives employing an ethereal mixture of lithium aluminum hydride and aluminum chloride.[9,11]

Addition of tigogenin acetate (Ib) to a cool mixture of the lithium aluminum hydride–aluminum chloride reagent in ether and recovery of the product after a 3 hr. reaction period afforded a 92.5% yield of dihydrotigogenin (IIb). Acetylation of the reaction product (IIb) gave a diacetate (IIc) which was identical with an authentic sample of tigogenin diacetate (IIc).[3a]

In order to verify the course of the reduction, two additional dihydrosapogenins of known composition were prepared. Diosgenin (IIIa) and desoxytigogenin (Id) were readily reduced to dihydrodiosgenin[5] (IVa) and dihydrodesoxytigogenin[12] (IId) respectively. Raney nickel desulfurization of tigogenin 3-ethylenethioketal (Ic)

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(2) R. E. Marker and E. Rohrmann, *J. Am. Chem. Soc.*, **61**, 846 (1939). Hydrogenation in acetic acid or in acidified ethanol solution followed by saponification of the oily product gave crystalline dihydrosarsasapogenin. However, hydrogenation did not take place in a neutral medium. The unusual reactivity of the steroidal sapogenin side chain in acid media prompted Marker and Rohrmann to propose the presently accepted spiroketal system.

(3) See for example: (a) R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith, and C. H. Ruof, *J. Am. Chem. Soc.*, **69**, 2167 (1947); (b) I. Scheer, R. B. Kostic, and E. Mosettig, *J. Am. Chem. Soc.*, **77**, 641 (1955); (c) M. E. Wall, S. Serota, and C. R. Eddy, *J. Am. Chem. Soc.*, **77**, 1230 (1955); (d) Y. Sato and H. G. Latham, Jr., *J. Am. Chem. Soc.*, **78**, 3150 (1956).

(4) R. K. Callow and P. N. Massy-Beresford, *J. Chem. Soc.*, 2645 (1958).

(5) H. M. Doukas and T. D. Fontaine, *J. Am. Chem. Soc.*, **75**, 5355 (1953). This procedure presents the obvious advantages of preserving nuclear unsaturation and eliminating a subsequent saponification step.

(6) The following references are cited in support of this observation: C. Djerassi, H. Martinez, and G. Rosenkranz, *J. Org. Chem.*, **16**, 1278 (1951); J. Romo, H. J. Ringold, G. Rosenkranz, and C. Djerassi, *J. Org. Chem.*, **16**, 1873 (1951); R. Yashin, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, **73**, 4654 (1951); J. Pataki, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, **73**, 5375 (1951); C. Djerassi, R. Yashin, and G. Rosenkranz, *J. Am. Chem. Soc.*, **74**, 422 (1952); C. Djerassi, E. Batres, M. Velasco, and G. Rosenkranz, *J. Am. Chem. Soc.*, **74**, 1712 (1952); H. J. Ringold, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, **74**, 3318 (1952); R. Hirschmann, C. S. Snoddy, C. F. Hiskey, and N. L. Wendler, *J. Am. Chem. Soc.*, **76**, 4013 (1954).

(7) R. B. Woodward, F. Sondheimer, and Y. Mazur, *J. Am. Chem. Soc.*, **80**, 6693 (1958).

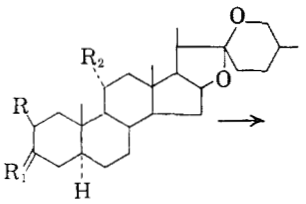
(8) C. Djerassi, O. Halpern, G. R. Pettit, and G. H. Thomas, *J. Org. Chem.*, **24**, 1 (1959), have provided additional experimental evidence in support of this hypothesis.

(9) E. L. Eliel and M. Rerick, *J. Org. Chem.*, **23**, 1088 (1958). We are grateful to these investigators for informing us of their experimental procedure prior to publication.

(10) The course of the reduction employing boron trifluoride etherate will be the subject of a subsequent communication.

(11) R. F. Nystrom, *J. Am. Chem. Soc.*, **81**, 610 (1959).

(12) R. E. Marker and E. Rohrmann, *J. Am. Chem. Soc.*, **61**, 1516 (1939).



Ia. R = R_2 = H; R_1 = $\overset{OH}{\underset{H}{}}$

b. R = R_2 = H; R_1 = $\overset{OCOCH_3}{\underset{H}{}}$

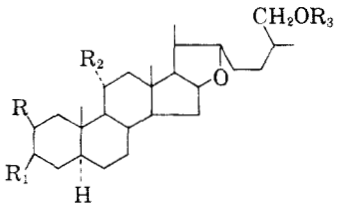
c. R = R_2 = H; R_1 = 

d. R = R_2 = H; R_1 = H_2

e. R = OH; R_1 = $\overset{OH}{\underset{H}{}}$; R_2 = H

f. R = H; R_1 = $\overset{OH}{\underset{H}{}}$; R_2 = OH

g. R = R_2 = H; R_1 = O



IIa. R = R_2 = R_3 = H; R_1 = OH

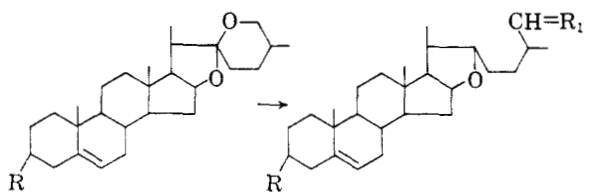
b. R = R_2 = R_3 = H; R_1 = OH

c. R = R_2 = H; R_1 = $OCOCH_3$; R_3 = $COCH_3$

d. R = R_1 = R_2 = R_3 = H

e. R = R_1 = OH; R_2 = R_3 = H

f. R = R_3 = H; R_1 = R_2 = OH

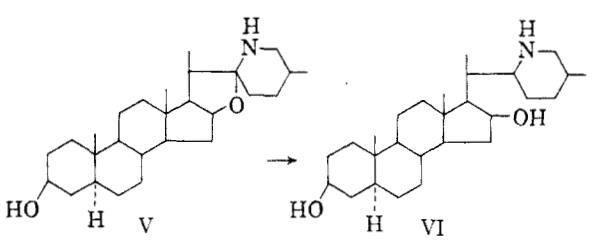


IIIa. R = OH

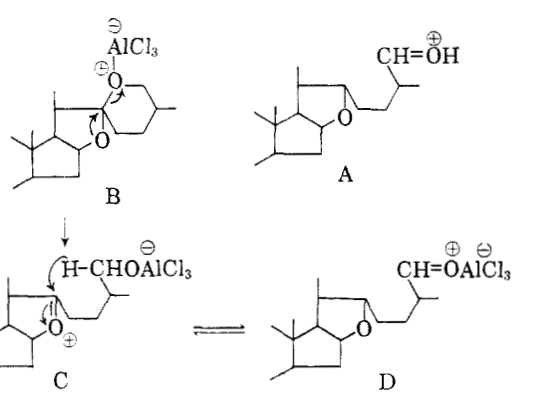
b. R = $OCOCH_3$

IVa. R = OH, R_1 = $\overset{OH}{\underset{H}{}}$

b. R = $OCOCH_3$, R_1 = 



V VI



B A

C D

provided a convenient source of desoxytigogenin (Id).

Lithium aluminum hydride–aluminum chloride reduction of markogenin (Ie → IIe) and 11α-hydroxytigogenin (If → IIf) gave, in each case, a previously unreported dihydro derivative. Similar reduction of the steroidal alkaloid tomatidine (V) afforded a preponderant amount of the higher melting (229–230°) isomer of dihydrotomatidine[13,14] (VI), accompanied by a smaller quantity of the isomer melting at 193–195°.

When a solution of diosgenin acetate (IIIb) in ethereal aluminum chloride was allowed to react with ethanedithiol, 3β-acetoxy-5-furostene 26-ethylenethioketal (IVb) was formed in high yield. Implication of a mechanistic pathway such as B → D in the aluminum chloride catalyzed lithium aluminum hydride reduction of the spiroketal moiety receives some support from the result of this experiment.[15]

EXPERIMENTAL[16]

The preparation of dihydrotigogenin (IIb) illustrates the general procedure employed to effect reduction in each of the subsequent examples.

Dihydrotigogenin (IIb). Anhydrous aluminum chloride (6.4 g.), in 50 ml. of dry ether, was added to a cool (ice bath) mixture of lithium aluminum hydride (0.45 g.) and dry ether (50 ml.). An ether (75 ml.) solution of tigogenin (0.50 g.) was then added, with stirring, over a 15-min. period. Stirring was continued an additional 45 min. at ice bath temperature followed by a 2 hr. period at reflux. After cooling, the mixture was treated cautiously with water and dilute hydrochloric acid. The resulting aqueous phase and suspended product was extracted with ether (5 × 100 ml.) and the combined ethereal extract washed with dilute sodium bicarbonate solution, dried (sodium sulfate), and concen-

(13) Y. Sato and H. G. Latham, Jr., *J. Am. Chem. Soc.*, **78**, 3146 (1956). An authentic specimen of VII was generously provided by Dr. Sato.

(14) It may be of some mechanistic importance that the yield of this isomer is reduced to *ca.* 10% when lithium aluminum hydride reduction of V is carried out in the absence of aluminum chloride.[13]

(15) Alternatively, reduction might simply take place at the stage illustrated by intermediate C. However, the possibility of a completely different initial mechanism being operative in the reduction reaction cannot be overlooked. Additional experimental evidence will be necessary before this point can be satisfactorily resolved.

(16) Melting points were observed on the Fisher-Johns apparatus unless otherwise noted, and are uncorrected. The microanalyses were provided by Dr. A. Bernhardt, Mülheim, Germany, and the optical rotation (chloroform solution) measurements by Drs. Wieler and Strauss, Oxford, England.

trated to a cream colored crystalline product; yield 0.42 g., m.p. 153–159°. Recrystallization from acetone gave colorless crystals of dihydrotigogenin melting at 165–166°, $[\alpha]_D^{16}$ 0.0°.[5,12]

The diacetate (acetic anhydride–pyridine, 1 hr. at 90–95°) melted at 115° and was identical (mixed melting point and infrared comparison) with an authentic specimen (m.p. 116–117°) of dihydrotigogenin diacetate (IIe).[5,17]

Desoxytigogenin (Id). In one experiment, a solution of tigogenone (Ig, 0.14 g.)[18] in ethanedithiol (3 ml.) was treated with 1 drop of 70–72% perchloric acid. Colorless crystals began to separate within several minutes. However, the reaction was allowed to proceed for 3 hr. at 25° before dilution with ether and 2*N* sodium hydroxide. The ethereal solution was washed successively with 2*N* sodium hydroxide and water before removing the dry (sodium sulfate) solvent *in vacuo*. Chromatography of the pale yellow colored crystalline residue, in 4:1 petroleum ether–benzene on 10 g. of Merck activated alumina, followed by elution with the same solvent, gave 0.15 g. of colorless product melting at 299–302°. Two recrystallizations from chloroform–ethyl acetate afforded a pure sample of tigogenin 3-ethylenethioketal (Ic) as needles, m.p. 307–309°,[19] $[\alpha]_D^{16}$ −67.7°.

Anal. Calcd. for $C_{29}H_{46}O_2S_2$: C, 70.97; H, 9.44; S, 13.07; mol. wt. 490.8. Found: C, 70.62; H, 9.70; S, 13.15; mol. wt. (Rast), 465.

Desulfurization of the ethylenethioketal Ic (0.027 g.) with W-4 Raney nickel[20] (0.5 ml.) was carried out in ethanol (30 ml.) employing a 4-hr. reflux period. The solvent was removed after filtering the hot reaction mixture through Celite. The crystalline residue recrystallized from ethanol as colorless plates (0.011 g.), m.p. 174–175°. Mixed melting point determination with an authentic sample (m.p. 174–175°) of desoxytigogenin (Id)[18] was undepressed.

Dihydroxydesoxytigogenin (IId). Conversion of desoxytigogenin (Id, 0.72 g.) to the *dihydro* derivative IId was readily accomplished. The crude oily product was chromatographed in petroleum ether on 10 g. of Merck acid washed alumina. Elution with petroleum ether–benzene (1:1) afforded 0.70 g. of pale yellow oil which crystallized upon trituration with acetone. Recrystallization from acetone gave colorless needles, m.p. 92–93°, $[\alpha]_D^{16}$ 0.0°.[12]

Dihydrodiosgenin (IVa). Reduction of diosgenin (IIIa, (0.50 g.) led to dihydrodiosgenin (0.45 g.). A sample recrystallized from acetone as colorless needles, m.p. 167–168°, $[\alpha]_D^{16}$ −28.9° (*cf.* ref. 5). The product gave a straw coloration with tetranitromethane. A mixed melting point with dihydrotigogenin (IIb) was 160–164°, while comparison infrared spectra (potassium bromide) were distinctly different.

Diosgenin acetate (IIIb, 0.50 g.) afforded 0.45 g. of dihydrodiosgenin melting at 163–165°. Recrystallization from acetone gave colorless needles, m.p. 165–167°.

Dihydromarkogenin (IIe). A 0.28 g. sample of markogenin[17] provided 0.25 g. of dihydromarkogenin which crystallized as colorless needles from acetone, m.p. 179–180°, $[\alpha]_D^{16}$ 0.0°.

Anal. Calcd. for $C_{27}H_{46}O_4$: C, 74.61; H, 10.67. Found C, 74.58; H, 10.61.

11α-Hydroxydihydrotigogenin (IIf). Almost quantitative conversion of 11α-hydroxytigogenin (If, 0.15 g.)[21] to the dihydro compound (IIf) was realized; yield 0.14 g. Recrystallization from acetone gave colorless rosettes of needles, m.p. 176–177°, $[\alpha]_D^{16}$ −13.0°.

Anal. Calcd. for $C_{27}H_{46}O_4$: C, 74.61; H, 10.67. Found: C, 74.74; H, 10.71.

Dihydrotomatidine (VI). Lithium aluminum hydride–aluminum chloride reduction of tomatidine (V, 0.50 g.) was carried out as previously described (*cf.* IIb). In this case, the reaction mixture was diluted with sodium hydroxide solution. Ether extraction and recovery of product in the usual manner afforded 0.35 g. of cream colored solid, m.p. 226–228°. Recrystallization from methanol-water gave colorless plates (0.20 g.) melting at 229–230°. Concentration of the mother liquors afforded the lower melting isomer (0.09 g.) as cream colored crystals, m.p. 193–195°. The isomer melting at 229–230° was found to be identical (mixture melting point determination and infrared comparison) with an authentic sample of the higher melting (230–233°) isomer of dihydrotomatidine.[13]

3β-Acetoxy-5-furostene 26-ethylenethioketal (IVb). A mixture of diosgenin acetate (IIIa, 0.5 g.), ethanedithiol (1 g., 0.9 ml.) and aluminum chloride (2 g.) in ether (5 ml.) was allowed to stand at room temperature over a 3-hr. period. Following dilution with benzene, the reaction mixture was washed successively with 2*N* sodium hydroxide and water. The residue obtained after removing the dry (sodium sulfate) solvent *in vacuo* was chromatographed in 1:1 petroleum ether–benzene on Merck activated alumina. Elution with the same solvent gave an oil which crystallized as needles from acetone; yield 0.38 g., m.p. 140°. The product was identified by mixed melting point determination and infrared comparison with an authentic sample of 3β-acetoxy-5-furostene 26-ethylenethioketal (m.p. 140–142°).[8]

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(17) This sample was kindly provided by Dr. M. E. Wall.

(18) M. E. Wall and S. Serota, *J. Am. Chem. Soc.*, **78**, 1747 (1956).

(19) Capillary tube melting point.

(20) A. A. Pavlic and H. Adkins, *J. Am. Chem. Soc.*, 68, 1471 (1946).

(21) A sample of this compound was generously provided by Dr. Carl Djerassi.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF KENTUCKY]

Amino Derivatives of Kojic Acid

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An investigation of the physiological properties of new compounds from kojic acid, 5-hydroxy-2-hydroxymethyl-4*H*-pyran-4-one has led to the synthesis of several amino derivatives which have not previously been reported. Secondary as well as tertiary aminomethyl groups were introduced into position 6 of kojic acid by use of the Mannich reaction. Factors which influence this reaction, as it applied to kojic acid, were also studied.

Our work on kojic acid derivatives is an extension of the program here to prepare a large number of aminophenols and aminobisphenols of various types, with the ultimate view of evaluating them as