Synthesis of a Diosgenin Ring F Thia Counterpart

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Pseudodiosgenin 27-*p*-toluenesulfonate has been prepared and has been transformed to the 27-acetylthio ester. Alkaline hydrolysis, followed by treatment with hydrochloric acid, has given cyclopseudodiosgenin and diosgenin thia counterparts in which sulfur replaces the ring F ketal oxygen.

Synthesis of the azaoxaspirane steroid alkaloids solasodine, tomatidine, and 5β-tomatidine from pseudosapogenins proceeded through intermediate 27-*p*-toluenesulfonate esters which, without isolation, were transformed to 27-iodo derivatives.[1] Separation of the 27-iodides from products representing attack at both 3β- and 27-positions was effected by chromatography. Over-all conversion to pseudodiosgenin 27-iodide (16%) fell below that to the ring B saturated pseudoneotigogenin 27-iodide (40%) and pseudosarsasapogenin 27-iodide (46%) as a consequence of enhanced sensitivity to esterification of the pseudodiosgenin homoallylic 3β-hydroxyl group.

Subsequently, an improved preparation of pseudodiosgenin 27-iodide (53%) was developed through subjection of the pseudodiosgenin tosylation mixture, before treatment with sodium iodide, to selective hydrolysis of the 3β-tosyl ester linkage according to a procedure first devised for transformation of kryptogenin 3β,27-di-*p*-toluenesulfonate to kryptogenin 27-*p*-toluenesulfonate.[1] The demonstrated capacity of the intermediate pseudodiosgenin 27-*p*-toluenesulfonate to withstand several hours' heating in aqueous acetone solution characterized it as far more stable than had been expected and prompted an attempt to isolate the compound in crystalline form.

Tosylation of pseudodiosgenin with four equivalents of *p*-toluenesulfonyl chloride in pyridine at 0° gave 87% of the 3β,27-di-*p*-toluenesulfonate I. Hydrolysis of I in aqueous acetone (3:7) solution at reflux temperature during 90 minutes afforded pseudodiosgenin 27-*p*-toluenesulfonate (II) which crystallized directly from the reaction medium in 70% yield. Treatment of II with sodium iodide in butanone at 80° gave 80% of pseudodiosgenin 27-iodide.

Treatment of II with potassium thioacetate in dimethylformamide at 25° yielded 80% of the 27-acetylthio ester III. Cautious hydrolysis of III with two equivalents of potassium hydroxide in methanol at 25° during 15 minutes,[2] followed by acidification with three equivalents of hydrochloric acid, furnished the cyclopseudodiosgenin ring F thia counterpart IV.[3]

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

(2) Overnight alkaline hydrolysis of III gave a virtually insoluble precipitate, presumably the disulfide.

In an attempt to isolate the intermediate 27-mercapto compound, alkaline hydrolysis of III was interrupted with the requisite quantity of pivalic acid, affording precipitated material which gave color tests and infrared spectrum indicative of the presence of both 20(22)-double bond and free SH group.[4] Recrystallization at 0° led only to the hexacyclic IV, however, providing evidence that the 27-sulfhydryl function adds to the ring E cyclic vinyl ether much more readily than does the 27-hydroxyl group of the pseudosapogenins.

Treatment of IV with 0.3 *N* aqueous ethanolic hydrochloric acid at reflux temperature gave the diosgenin ring F thia counterpart V. The metastable IV, in which the C-20 methyl group occupies the anterior, α-position, is distinguished from V by its sparingly soluble nature, by its variable crystallizing habit and melting point, and by characteristic infrared absorption maxima.

Treatment of the 3β-acetate of V with boiling acetic anhydride in the presence of pyridine hydrochloride gave the 3β-acetate of III. The ring opening reaction, which parallels conversion of the sapogenins to their pseudo isomers, appears to proceed somewhat more smoothly with the thia counterpart.

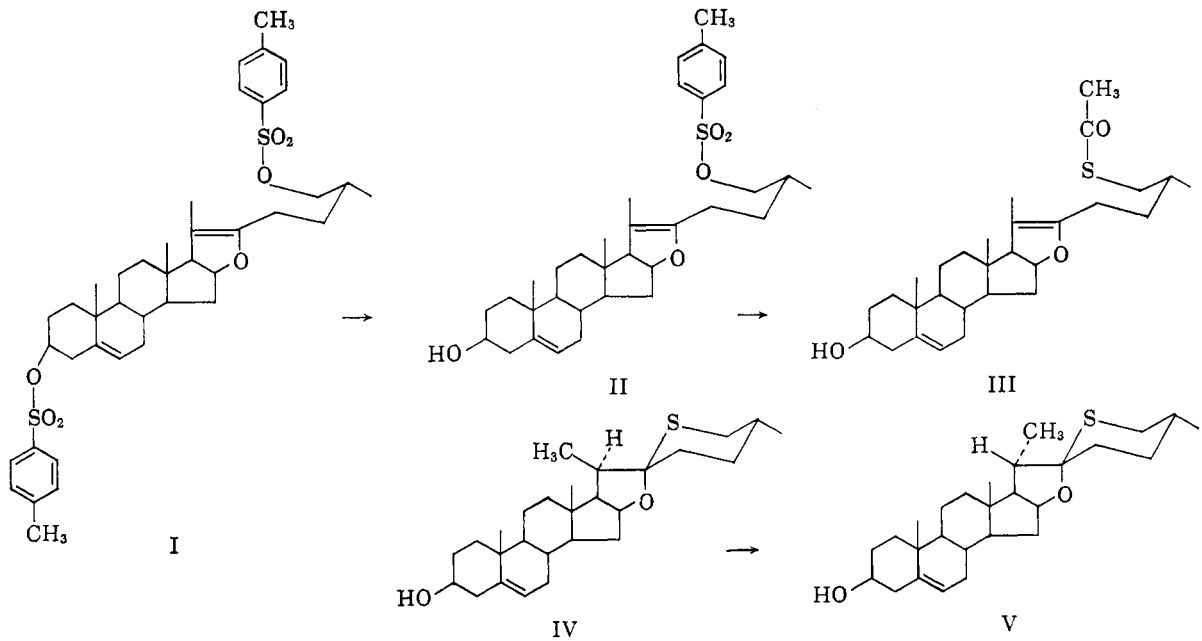
Experimental[5]

3β,27-Di-*p*-toluenesulfonyloxy-25α-5,20(22)-furostadiene (Pseudodiosgenin 3β,27-Di-*p*-toluenesulfonate) (I).—To a solution of 2.07 g. (0.005 mole) of pseudodiosgenin[1] in 20 ml. of anhydrous pyridine at 0° was added 3.8 g. (0.02 mole) of *p*-toluenesulfonyl chloride. After 20 hr. at 0°, 500 ml. of water was added to give a deposit which was collected, washed with water, and dissolved in chloroform. The chloroform extract was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. To a solution of the residue in 5 ml. of acetone (in which the product is very soluble) was added 95 ml. of isopropyl alcohol

(3) For discussion of cyclopseudosapogenin chemistry see L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 825–832; for nomenclature and numbering see p. 819.

(4) Sodium borohydride in aqueous isopropyl alcohol gave the same product.

(5) Melting points were observed on a calibrated micro hot stage. Microanalyses were performed by Dr. S. M. Nagy of the Massachusetts Institute of Technology, Cambridge, Massachusetts. Rotations, in chloroform at 25 ± 1°, were measured by Schwarzkopf Microanalytical Laboratories, Woodside 77, New York. Infrared spectra, in potassium bromide, were recorded with a Perkin-Elmer spectrophotometer, Model 137; only those bands of significance in interpretation are mentioned.



(in which the product is very sparingly soluble). After 48 hr. at 0°, the precipitate was collected by filtration to give 3.15 g. (87%); m.p. 80–85°. The analytical sample, from acetone–isopropyl alcohol, melted at 85–86°; $[\alpha]D$ −31°; infrared spectrum: 5.92 (medium) (vinyl ether), 6.25 (phenyl), 7.40, 8.45, 8.55 μ (OSO_2).

Anal. Calcd. for $C_{41}H_{54}S_2O_7$ (722.97): C, 68.11; H, 7.53; S, 8.87. Found: C, 67.89; H, 7.35; S, 9.02.

3β-Hydroxy-27-*p*-toluenesulfonyloxy-25α-5,20(22)-furostadiene (Pseudodiosgenin 27-*p*-Toluenesulfonate (II).—A solution of 362 mg. (0.0005 mole) of pseudodiosgenin 3β,-27-di-*p*-toluenesulfonate (I) and 15 ml. of water in 35 ml. of acetone was heated under reflux for 90 min. The product began to crystallize nicely as the colorless solution approached ambient temperature. After 20 hr. at 0°, the precipitate was collected by filtration to give 200 mg. (70%) of needles; m.p. 151–157°. One recrystallization from acetone brought the melting point to that of the analytical sample, 157–159°; $[\alpha]D$ −42°; infrared spectrum: 5.92 (medium) (vinyl ether), 6.25 (medium) (phenyl), 7.40, 8.45, 8.55 μ (OSO_2).

Anal. Calcd. for $C_{34}H_{48}SO_5$ (568.78): C, 71.79; H, 8.51; S, 5.64. Found: C, 71.64; H, 8.38; S, 5.49.

3β-Hydroxy-27-iodo-25α-5,20(22)-furostadiene (Pseudodiosgenin 27-Iodide) ($C_{27}H_{41}O_2I$) (524.51).—A mixture of 114 mg. (0.0002 mole) of pseudodiosgenin 27-*p*-toluenesulfonate (II), 60 mg. (0.0004 mole) of sodium iodide, and 2.5 ml. of butanone was heated under reflux for 1 hr. (Because of the low solubility of II in cold butanone, no reaction occurred at 25°, even with magnetic stirring during several days.) The mixture was diluted with 25 ml. of water to give a precipitate which was collected by filtration, washed with water, and dried. One recrystallization from dichloromethane–methanol gave 84 mg. (80%); m.p. 72–75°, followed by solidification in highly characteristic fashion to clusters of tiny needles which melted at 120–123°.[1]

3β-Hydroxy-27-acetylthio-25α-5,20(22)-furostadiene (III).—A mixture of 569 mg. (0.001 mole) of pseudodiosgenin 27-*p*-toluenesulfonate (II), 228 mg. (0.002 mole) of potassium thioacetate,[6] and 5 ml. of dimethylformamide[7] was magnetically stirred at 25°; after 3 hr. the starting material had completely dissolved. When the clear solution had been kept at 0° for 20 hr., 10 ml. of water was added to give a precipitate which was collected by filtration and washed with water. A solution of the product in chloroform was dried over anhydrous magnesium sulfate, filtered, and concentrated under diminished pressure. The residue was recrystallized from methanol to give 385 mg. (81%) of rosettes of long needles, m.p. 96–103°. The analytical sample, from methanol, melted at 103–106°; $[\alpha]D$ −31°; infrared spectrum: 5.90 μ (CH_3COS).

Anal. Calcd. for $C_{29}H_{44}SO_3$ (472.71): C, 73.68; H, 9.38; S, 6.78. Found: C, 73.44; H, 9.28; S, 6.67.

3β-Acetoxy-27-acetylthio-25α-5,20(22)-furostadiene.—A. A solution of 236 mg. (0.0005 mole) of 3β-hydroxy-27-acetylthio-25α-5,20(22)-furostadiene (III) and 0.5 ml. of acetic anhydride in 2 ml. of anhydrous pyridine was kept at 0° for 20 hr. The solution was diluted with water to give a precipitate which was collected and washed with water. A chloroform solution of the product was dried over anhydrous magnesium sulfate, filtered, and concentrated under diminished pressure. The residue was recrystallized from methanol to give large spars; m.p. 122–125°; $[\alpha]D$ −38°; infrared spectrum: 5.80, 8.05 (CH_3COO), 5.95 μ (CH_3COS).

Anal. Calcd. for $C_{31}H_{46}SO_4$ (514.75): C, 72.33; H, 9.01; S, 6.23. Found: C, 72.41; H, 9.07; S, 6.02.

B. A solution of 47 mg. (0.0001 mole) of 3β-acetoxy-20β-25α-22(27)-thia-5-furostene (V 3β-acetate) and 17.5 mg. (0.00015 mole) of pyridine hydrochloride in 2 ml. of acetic anhydride was heated at reflux temperature for 4.5 hr. The solution was diluted with 100 ml. of water to give a deposit which was collected by filtration and washed with water. A chloroform solution of the product was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was triturated with 10 ml. of petroleum ether (b.p. 30–60°) in which the product was freely soluble. The remainder from vacuum evaporation of the petroleum ether was crystallized twice from methanol to give 30 mg. (59%); m.p. 121–124°; melting point of a mixture with the diacetate prepared according to procedure A, 121–125°; infrared spectrum identical with that given by the product prepared according to procedure A.

As compared with the corresponding isomerization of dios-

(6) Prepared from thioacetic acid with aqueous potassium carbonate and recrystallized from absolute ethanol: *cf.* C. Ulrich, *Ann.*, **107**, 272 (1859); B. Bannister and F. Kagan, *J. Am. Chem. Soc.*, **82**, 3367 (1960).

(7) J. H. Chapman and L. N. Owen, *J. Chem. Soc.*, 579 (1950), in an exploratory study of the reaction of sulfonic acid esters with potassium thioacetate used refluxing acetone, or a refluxing mixture of acetone and ethanol, as solvent.

genin 3β-acetate, ring F opening of V 3β-acetate appears to proceed to completion during a shorter reaction period, with far less discoloration and resin formation. The crystallizing properties of III 3β-acetate are much superior to those of pseudodiosgenin diacetate.

3β-Hydroxy-20α-25α-22(27)-thia-5-furostene (IV).—To a solution of 94 mg. (0.0002 mole) of 3β-hydroxy-27-acetylthio-25α-5,20(22)-furostadiene (III) in 8 ml. of methanol was added 2 ml. of an aqueous methanol (1:9) solution containing 22.4 mg. (0.0004 mole) of potassium hydroxide. After the solution had been magnetically stirred for 15 min. at 25°, 0.1 ml. (0.0006 mole) of 6 *N* aqueous hydrochloric acid was added; a copious precipitate formed at once. The mixture was stirred for 15 min. at 25° and stored at 0° for 20 hr. The precipitate was collected by filtration, washed with a few drops of methanol, and dried. Recrystallization from acetone gave 70 mg. (84%) of needles. A second recrystallization from acetone gave plates; m.p. 195–208°; $[\alpha]_D$ −207°.

The melting point varies in an extraordinary way with the crystal form and with the rate of heating. From dichloromethane–methanol the compound crystallizes as small plates which, at least in part, rearrange to needles on the micro hot stage and melt at 182–205°. From isopropyl alcohol the substance usually separates as needles; from dichloromethane–ethanol as plates; from 90% aqueous acetic acid as plates. Rapid recrystallization from any solvent generally gives small, nondescript plates; the melting point may range from 182–210°. The infrared spectrum displays a rich finger print region with prominent bands associated with the spiroketal linkage at 10.35, 10.40, 10.80, 12.25, 12.90 μ.

Anal. Calcd. for $C_{27}H_{42}SO_2$ (430.68): C, 75.29; H, 9.83; S, 7.45. Found: C, 75.01; H, 9.74; S, 7.06.

In an attempt to isolate the intermediate 27-mercapto compound, potassium hydroxide hydrolysis of 94 mg. (0.0002 mole) of III, carried out as described above, was interrupted after 15 min. by addition of a solution of 45 mg. (0.00044 mole) of pivalic acid in 1 ml. of methanol. When the clear solution had been stirred for 3 min. at 25°, 10 ml. of water was added to completely precipitate the product. After 15 min. at 0°, the precipitate was collected by filtration, washed with water, and dried to give 80 mg.; m.p. 65–70°. A methanol solution of this material gave a purple color with sodium nitroferricyanide (sodium nitroprusside) and ammonium hydroxide. The infrared spectrum, which closely resembled that given by pseudodiosgenin, displayed the band of medium intensity at 5.92 μ characteristic of the ring E vinyl ether; few prominent bands were present in the finger print region.

The product was dissolved in 2 ml. of cold isopropyl alcohol. After 2 weeks at 0°, the precipitate, which had slowly deposited, was collected by filtration to give 60 mg.; m.p. 145–165°; the infrared spectrum was virtually identical with that of IV. Recrystallization from dichloromethane–methanol gave 40 mg., m.p. 160–190°.

The infrared spectrum of the product obtained by treatment of 47 mg. (0.0001 mole) of III with 20 mg. (0.0005 mole) of sodium borohydride in a mixture of 0.5 ml. of water and 2.5 ml. of isopropyl alcohol for 20 hr. was identical with that of the substance derived from brief potassium hydroxide hydrolysis, followed by neutralization with pivalic acid.

3β-Acetoxy-20α-25α-22(27)-thia-5-furostene.—A mixture of 86 mg. (0.0002 mole) of 3β-hydroxy-20α-25α-22(27)-thia-5-furostene (IV) and 5 ml. of acetic anhydride in 15 ml. of pyridine was kept at 25° for 20 hr. (The large volume of solvent was necessitated by the very sparingly soluble nature of the starting material which, even at this dilution, had completely dissolved only after the reaction mixture had been shaken intermittently during several hours.) The clear solution was diluted with 100 ml. of water to give a precipitate which, after 1 hr. at 0°, was collected by filtration and washed with water. A chloroform solution of the product was dried over anhydrous magnesium sulfate, filtered, and concentrated under diminished pressure. Recrystallization of the residue from dichloromethane–methanol gave 75 mg. (80%) of plates; m.p. 225–238°; $[\alpha]_D$ −212°; infrared spectrum: 5.80, 8.05 (acetoxy), 10.30, 10.85, 11.45, 12.25, 12.90 μ.

Anal. Calcd. for $C_{29}H_{44}SO_3$ (472.71): C, 73.68; H, 9.38; S, 6.78. Found: C, 73.37; H, 9.20; S, 6.81.

3β-Hydroxy-20β-25α-22(27)-thia-5-furostene (V).—A solution of 108 mg. (0.00025 mole) of 3β-hydroxy-20α-25α-22(27)-thia-5-furostene (IV) in 10 ml. of 0.3 *N* aqueous ethanolic (1:19) hydrochloric acid was heated under reflux for 1 hr. The solution was diluted with 5 ml. of water to precipitate the product which was collected by filtration, washed with water, and dried. Recrystallization from dichloromethane–methanol gave 82 mg. (76%) of plates; m.p. 210–220°. The analytical sample was prepared from acetone as large, glistening plates; m.p. 222–227°; $[\alpha]_D$ −226°; infrared spectrum: 10.40, 10.80, 10.90, 12.00 μ.

Anal. Calcd. for $C_{27}H_{42}SO_2$ (430.68): C, 75.29; H, 9.83; S, 7.45. Found: C, 75.19; H, 9.76; S, 7.35.

3β-Acetoxy-20β-25α-22(27)-thia-5-furostene.—A solution of 43 mg. (0.0001 mole) of 3β-hydroxy-20β-25α-22(27)-thia-5-furostene (V) and 1 ml. of acetic anhydride in 2 ml. of anhydrous pyridine was kept at 0° for 20 hr. The solution was diluted with 30 ml. of water to give a precipitate which was collected by filtration, washed with water, and dried. Recrystallization from dichloromethane–methanol gave hexagonal plates; m.p. 228–233°; $[\alpha]_D$ −203°; infrared spectrum: 5.80, 8.05 (acetoxy), 10.15, 10.40, 10.80, 12.10 μ.

Anal. Calcd. for $C_{29}H_{44}SO_3$ (472.71): C, 73.68; H, 9.38; S, 6.78. Found: C, 73.45; H, 9.33; S, 6.95.

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