A New Synthesis of Steroidal 3,5-Dieno[3,4-*b*]dithianes

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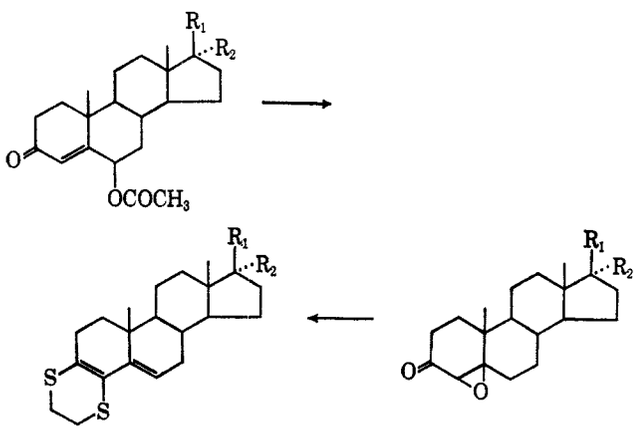
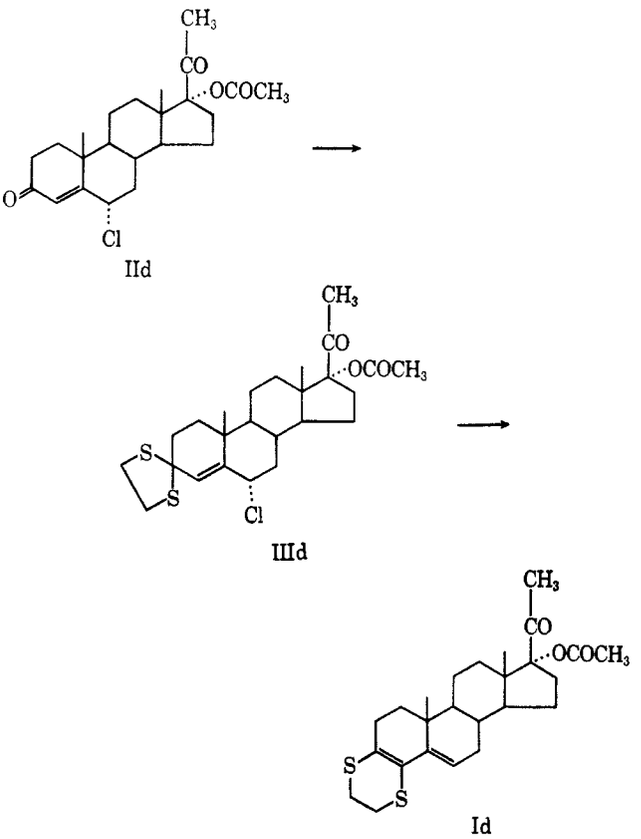
It has been observed that steroidal 6α-chloro-4-en-3-ones react with ethanedithiol under mild conditions to form the expected cyclic 3-ethylenethioketals III. The latter react with pyridine or pyridine hydrochloride in warm methanol, losing hydrogen chloride and rearranging to the six-membered 3,5-dieno[3,4-*b*]dithiane system I. 6β-Chloro-4-en-3-ones form these dithianes directly under the mild thioketalization conditions and it is suggested that the 3-ethylenethioketal is formed first, followed by very facile loss of the axial 6-chlorine atom and rearrangement through the allylic carbonium ion VI.

The first report of a steroidal 3,5-dieno[3,4-*b*]dithiane appeared in a 1960 publication of Fieser, Yuan, and Goto,[1] in which the structures of a variety of anomalous products from the reactions of cholestenolone acetates with ethanedithiol were deduced mainly through application of the then new nmr techniques. One of these products, formed in approximately 50% yield by reaction of equivalent amounts of 6β-acetoxy-4-cholesten-3-one and ethanedithiol in the presence of boron trifluoride etherate, was shown to be cholesta-3,5-dieno[3,4-*b*]dithiane (Ia). The only other reports of such dithianes are two papers and a patent of Tomoeda, *et al.*,[2] in which it is disclosed that steroidal 4β,5-epoxy-3-ones react with ethanedithiol and polyphosphoric acid in dioxane, yielding 40–50% of the dithianes (Ia–c). These workers substantiated the structure of Ia by desulfurizing it with Raney nickel to cholesta-3,5-diene.



Ia, $R_1 = C_8H_{17}$; $R_2 = H$
b, $R_1 = OAc$; $R_2 = H$
c, $R_1 = COCH_3$; $R_2 = OH$

In the course of investigations on steroidal ethylenethioketals, it was observed that 6α-chloro-17α-acetoxyprogesterone (IId) formed the expected 3-ethylenethioketal IIId in acetic acid, with hydrogen chloride as catalyst. When IIId was boiled in methanol containing a small amount of pyridine, a halogen-free compound was formed. Spectral and analytical properties identified the latter as a 3,5-dieno[3,4-*b*]dithiane (Id), analogous to Ia–c. Clearly, the reaction sequence involved dehydrohalogenation and rearrangement.



IId IIId Id

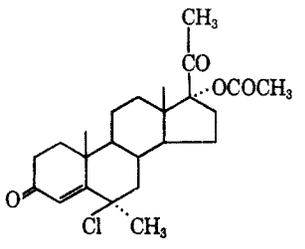
Further study showed that 6α-chlorotestosterone acetate (IIb) and 6α-chlorocholest-4-en-3-one (IIa) also reacted with ethanedithiol at room temperature, with either hydrogen chloride or pyridine hydrochloride as catalyst, giving good yields of 6α-chloro-3-ethylenethioketals of type III. Upon boiling of the chlorothioketals with pyridine hydrochloride in methanol, dithianes Ia, Ib, and Id were formed in 45–65% yield.

When 6β-chloro-4-en-3-ones were subjected to the thioketalization conditions (at 25°), no 6-chloro-3-ethylenethioketals were formed. The only isolable crystalline products were 40–70% of the 3,5-dieno-[3,4-*b*]dithianes. A general preparative method for the latter consisted in stirring the 6β-chloro ketone with ethanedithiol and pyridine hydrochloride in methanol for approximately 1 hr. This process was successful even when applied to the very crude 6β-chloro-17α-ethynyl-19-nortestosterone obtained from reaction of N-chlorosuccinimide with the 3-ethyl enol

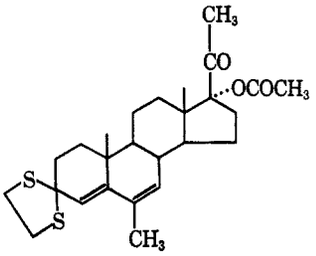
(1) L. F. Fieser, C. Yuan, and T. Goto, *J. Am. Chem. Soc.*, **82**, 1996 (1960).
(2) (a) M. Tomoeda, M. Ishizaki, H. Kobayashi, S. Kantomo, T. Koga, M. Inuzuka, and T. Furuta, *Chem. Pharm. Bull.* (Tokyo), **12**, 383 (1964); (b) *Tetrahedron*, **12**, 733 (1965). (c) M. Tomoeda, Japanese Patent 6338 (1966); *Chem. Abstr.*, **65**, 5505e (1966).

ether of 17α-ethynyl-19-nortestosterone, yielding 20% of the dithiane (Ie).

An attempted synthesis of a 6-methyldithiane by similar procedures failed. Only the 4,6-dienic 3-ethylenethioketal V could be isolated from reactions of ethanedithiol with 6α-methyl-6β-chloro-17α-acetoxyprogesterone (IV).



IV

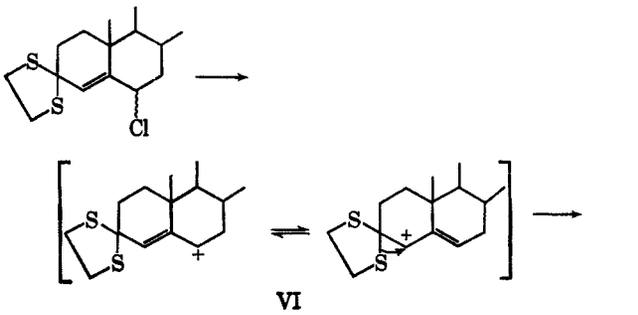


V

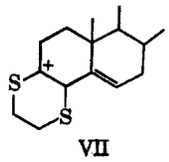
The action of pyridine hydrochloride in methanol on two 6β-chloro-4-en-3-ones was investigated with the hope that some aspects of the mechanism of formation of dithianes might be educed. In 1 hr at 25°, 6β-chloro-17α-acetoxyprogesterone was converted to approximately 10–15% of the corresponding 6-chloro-3-methyl enol ether and 25–30% of 6β-methoxy-17α-acetoxyprogesterone; 30–40% of the starting material was still unchanged. There was no evidence of 4,6-dien-3-one in the products. Clearly, dienone is not an intermediate in the formation of the dithiane, and this was further substantiated when 6-dehydro-17α-acetoxyprogesterone was found to give neither normal 3-ethylenethioketal nor dithiane, but only intractable oils.

However, 6α-methyl-6β-chloro-17α-acetoxyprogesterone (IV) was completely dehalogenated to 6-methyl-6-dehydro-17α-acetoxyprogesterone and 6α-methyl-6β-methoxy-17α-acetoxyprogesterone in 1 hr by pyridine hydrochloride in methanol at 25°, and these products apparently do not react with ethanedithiol to form a dithiane, as noted above.

It has been our experience that a wide variety of 4-en-3-ones react with ethanedithiol and pyridine hydrochloride in methanol at room temperature to give high yields of 3-ethylenethioketals, and this is probably also true of the 6β-chloro ketones as well as the 6α-chloro types. In each case, elimination of chlorine can lead to the allylic carbonium ion (VI), which is followed by rearrangement to the ion (VII) and loss of proton to form the diehiane. That the 6β-chloro-3-ethylenethioketals have not been isolated is apparently simply a consequence of the much easier solvolytic loss of axial 6β-chlorine as contrasted with equatorial 6α-chlorine, since each epimer yields roughly equivalent amounts of the various dithianes when the reaction mixtures are heated.



VI



VII

Experimental Section

Melting points are corrected (Fisher-Johns apparatus). Infrared spectra were taken on pressed potassium bromide pellets with a Beckman IR-5 spectrophotometer and ultraviolet spectra were taken in 95% ethanol solution with a Cary Model 11 spectrophotometer. Optical rotations were taken in chloroform solution at room temperature on a Rudolph Model 70 polarimeter. Nmr spectra were measured in deuteriochloroform solution using tetramethylsilane as internal standard on a Varian A-60 spectrometer. The usual designations, d = doublet, m = multiplet (center of signal), and singlets not specified by abbreviation, are employed, and chemical shifts are δ values. Solutions were dried with magnesium sulfate prior to evaporation under reduced pressure. Elemental analyses were performed by Midwest Microlab, Inc. of Indianapolis, Ind.

6α-Chloro-4-cholesten-3-one 3-Ethylenethioketal (IIIa).—A solution of 400 mg of 6α-chloro-4-cholesten-3-one,[3] 0.2 ml of ethanedithiol, and 0.15 ml of 1.4 *N* ethereal hydrogen chloride in 3 ml of acetic acid was maintained at 25° for 10 min and then diluted with 12 ml of methanol and chilled at 0°. Filtration afforded 400 mg of thioketal IIIa which was recrystallized from acetone, giving 350 mg of small white prisms: mp 133–134°; $[\alpha]_D$ +80°; λ_{max} 11.90, 12.90, 13.50 μ; the nmr spectrum gave peaks at δ 3.36 (m, 3-$C_2H_4S_2$), 4.55 (m, 6β-H), 6.18 (d, J = 1.5, 4-H).

Anal. Calcd for $C_{29}H_{47}ClS_2$: C, 70.35; H, 9.56. Found: C, 70.44; H, 9.54.

6α-Chlorotestosterone Acetate 3-Ethylenethioketal (IIIb).—A solution of 500 mg of 6α-chlorotestosterone acetate,[4] 0.35 ml of ethanedithiol, and 0.1 ml of 1.4 *N* ethereal hydrogen chloride in 1.5 ml of acetic acid was maintained at 25° for 10 min and then diluted with 13 ml of methanol and chilled at 0°. Filtration afforded 500 mg of thioketal IIIb as fine, white prisms. Recrystallization from ethyl acetate–methanol gave 380 mg: mp 154–155° dec; $[\alpha]_D$ +89°; λ_{max} 5.77, 11.90, 12.83, 13.49 μ; the nmr spectrum showed peaks at δ 0.84 (18-H_3), 1.08 (19-H_3), 2.05 (17β-OAc), 3.42 (m, 3-$C_2H_4S_2$), 4.61 (m, 6β-H), 6.22 (d, J = 1.5, 4-H).

Anal. Calcd for $C_{23}H_{33}ClO_2S_2$: C, 62.63; H, 7.54. Found: C, 62.85; H, 7.86.

6α-Chloro-17α-acetoxyprogesterone 3-Ethylenethioketal (IIId).—To a solution of 500 mg of 6α-chloro-17α-acetoxyprogesterone[5] and 0.3 ml of ethanedithiol in 1 ml of tetrahydrofuran was added a solution of 500 mg of pyridine hydrochloride in 3 ml of methanol. After this mixture had been held at 25° for 1 hr, it was chilled at 0° and filtered to afford 470 mg of thioketal IIId. This was recrystallized from methylene chloride–methanol, giving 420 mg of white prisms: mp 205–210° dec; $[\alpha]_D$ +69°; λ_{max} 5.76, 5.81, 11.88, 12.90, 13.48 μ; the nmr spectrum showed peaks at δ 0.65 (18-H_3), 1.07 (19-H_3), 2.05 (17α-OAC), 2.12 (21-H_3), 3.39 (m, 3-$C_2H_4S_2$), 4.60 (m, 6β H), 6.18 (d, J = 1.5, 4-H).

Anal. Calcd for $C_{25}H_{35}ClO_3S_2$: C, 62.17; H, 7.30. Found: C, 61.89; H, 7.38.

Cholesta-3,5-dieno[3,4-*b*]dithiane (Ia).—A solution of 500 mg of 6β-chloro-4-cholesten-3-one,[3] 0.25 ml of ethanedithiol, and 500 mg of pyridine hydrochloride in 3 ml of tetrahydrofuran and 5 ml of methanol was maintained at 25° for 1.5 hr; then 10 ml more of methanol was added and the mixture was stirred at 0° for 0.5 hr. Filtration afforded 400 mg of crude, pale yellow dithiane Ia. As has been reported,[1,2] this compound was extremely difficult to purify. Precipitation from ether with methanol gave 250 mg of a microcrystalline solid: mp 150–157° (best lit.[2] value, mp 161–162.5°); $[\alpha]_D$ −131°; λ_{max} 240

(3) D. H. R. Barton and E. Miller, *J. Am. Chem. Soc.*, **72**, 370 (1950).
(4) A. D. Cross, H. Carpio, and H. J. Ringold, *J. Med. Chem.*, **6**, 198 (1963).
(5) H. J. Ringold, E. Batres, A. Bowers, J. Edwards, and J. Zderic, *J. Am. Chem. Soc.*, **81**, 3485 (1959).

(ε 11,200), 292 mμ (ε 13,600); λ_{max} 6.33, 11.93, 13.17 μ; the nmr spectrum gave peaks at δ 3.15 (3,4-$C_2H_4S_2$), 5.89 (m, 6-H).

17β-Acetoxyandrosta-3,5-dieno[3,4-*b*]dithiane (Ib). A.—A solution of 750 mg of 6β-chlorotestosterone acetate,[4] 0.5 ml of ethanedithiol, and 600 mg of pyridine hydrochloride in 15 ml of methanol was stirred at 25° for 1 hr and at 0° for 30 min. Filtration afforded 600 mg of dithiane Ib which was recrystallized from ethyl acetate–methanol, giving 410 mg of white prisms, mp 200–202° (lit.[2a] mp 201–203°). The spectral properties[1,2] unequivocally identified this as a dithiane. Infrared spectra gave λ_{max} 5.75, 6.36, 11.96, 13.12 μ; the nmr spectrum showed peaks at δ 0.82 (18-H_3), 1.00 (19-H_3), 2.03 (17β-OAc), 3.15 (3,4-$C_2H_4S_2$), 5.93 (6-H).

B.—A mixture of 500 mg of the crude 6α-chlorothioketal IIIb, 700 mg of pyridine hydrochloride, and 75 ml of methanol was refluxed for 30 min and then stored at 0°. Filtration afforded 220 mg of dithiane Ib, which upon recrystallization as described in A gave 200 mg, mp 197–200°; the infrared spectrum was identical with that of the material obtained in A.

17α-Acetoxypregna-3,5-dieno-[3,4-*b*]dithian-20-one (Id). A.—A mixture of 1.0 g of 6β-chloro-17α-acetoxyprogesterone,[5] 0.7 ml of ethanedithiol, 1 g of pyridine hydrochloride, and 20 ml of methanol was stirred at 25° for 90 min, refluxed for 20 min, and then stored at 0°. Filtration afforded 850 mg of dithiane Id which was recrystallized from ethyl acetate, giving 780 mg of white prisms: mp 243–244°; [α]D −158°; λ_{max} 239 (ε 10,900), 292 mμ (ε 12,400); λ_{max} 5.76, 5.81, 6.37, 11.93, 13.19 μ; the nmr spectrum gave peaks at δ 0.65 (18-H_3), 1.00 (19-H_3), 2.03 (17α-OAc), 2.10 (21-H_3), 3.15 (3,4-$C_2H_4S_2$), 5.93 (6-H).

Anal. Calcd for $C_{25}H_{34}O_3S_2$: C, 67.24; H, 7.67. Found: C, 67.17; H, 7.60.

B.—A mixture of 500 mg of the 6α-chlorothioketal IIId and 700 mg of pyridine hydrochloride in 100 ml of methanol was refluxed for 1 hr, by which time the thioketal had completely dissolved. The solution was boiled down to 50 ml and chilled at 0° to afford 340 mg of dithiane Id, mp 242–244°; the infrared spectrum was identical with that of the material obtained in A.

17α-Ethynylestra-3,5-dieno[3,4-*b*]dithian-17β-ol (Ie).—A solution of 12.4 g of the 3-ethyl enol ether of 17α-ethynyl-19-nortestosterone[6] (crude, mp 172–175°) in 200 ml of acetone was stirred at 0° while 7.5 g of sodium acetate in 75 ml of water was added rapidly, followed by 7.5 g of N-chlorosuccinimide (in one portion).[7] The suspended enol ether dissolved rapidly; 3.2 ml of acetic acid was added and the mixture was kept at 0° for 40 min and then poured into 1500 g of ice plus water. The gummy precipitate was filtered off, dissolved in ether and dried. Evaporation of the ether solution gave crude 6β-chloro-17α-ethynyl-19-nortestosterone which was dissolved in 120 ml of methanol, and to this was added 7.2 ml of ethanedithiol and 8 g of pyridine hydrochloride. After this reaction mixture had been maintained at 25° for 16 hr it was boiled for 5 min and then diluted with 600 ml of water. Evaporation removed methanol and most of the excess ethanedithiol while precipitating crude dithiane which was extracted with methylene chloride. The methylene chloride residue was developed on a chromatographic column of neutral alumina (grade I), from which ether elution afforded a total of 6.0 g of tacky solid. This was recrystallized from methanol and then from ether, giving 3.1 g of dithiane Ie: mp 174–175° (after drying at 60–65° for 6 hr under vacuum to remove the solvated ether); [α]D −318°; λ_{max} 241 (ε 10,700), 293 mμ (ε 13,760); λ_{max} 2.85, 3.07, 6.37, 11.91 μ; the nmr spectrum showed peaks at δ 0.87 (18-H_3), 2.58 (17α-C≡CH), 3.15 (3,4-$C_2H_4S_2$), 5.93 (6-H).

Anal. Calcd for $C_{22}H_{28}OS_2$: C, 70.98; H, 7.58. Found: C, 71.09; H, 7.72.

17α-Ethynyl-17β-acetoxyestra-3,5-dieno[3,4-*b*]dithiane.—Refluxing of 100 mg of the 17β-ol (Ie) for 2.5 hr in 10 ml of acetic anhydride containing 1% of pyridine gave the 17β-acetate as fine, white flakes, recrystallization from methylene chloride–acetone gave mp 258–261°; [α]D −242°; λ_{max} 238 (ε 8700), 292 mμ (10,400); λ_{max} 3.07, 5.77, 6.37, 11.90 μ; the nmr spectrum showed peaks at δ 0.88 (18-H_3), 2.02 (17β-OAc), 2.59 (17α-C≡CH), 3.15 (3,4-$C_2H_4S_2$), 5.93 (6-H).

Anal. Calcd for $C_{24}H_{30}O_2S_2$: C, 69.60; H, 7.27. Found: C, 69.30; H, 7.55.

(6) H. J. Ringold, C. Djerassi, A. Bowers, and M. Velasco, U. S. Patent 3,138,589 (June 1964).

(7) L. H. Knox, J. A. Zderic, J. P. Ruelas, C. Djerassi, and H. I. Ringold, *J. Am. Chem. Soc.*, **82**, 1230 (1960).

6α-Methyl-6β-chloro-17α-acetoxyprogesterone (IV).—A solution of 2.5 g of the 3-ethyl enol ether of 6α-methyl-17α-acetoxyprogesterone[8] in 50 ml of acetone was stirred at 0°; to it was added 15 ml of water, and then consecutively 1.0 g of sodium acetate, 1.95 g of N-chlorosuccinimide, and 1 ml of acetic acid.[7] After 1 hr the clear solution was slowly diluted with 150 ml of water and then filtered to afford 1.75 g of pale yellow prisms of IV. This compound readily lost hydrogen chloride, forming 6-methyl-6-dehydro-17α-acetoxyprogesterone,[9] but was recrystallized from ether with 50% recovery to pale yellow prisms: mp 165–170° dec (stage preheated to 160°); [α]D −9°; λ_{max} 5.75, 5.81, 5.94, 6.21, 14.31 μ; the nmr spectrum showed peaks at δ 0.75 (18-H_3), 1.51 (19-H_3), 1.82 (6α-CH_3), 2.05 (17α-OAc), 2.08 (21-H_3), 6.12 (4-H).

Anal. Calcd for $C_{24}H_{33}ClO_4$: Cl, 8.42. Found: Cl, 8.02.

6-Methyl-6-dehydro-17α-acetoxyprogesterone 3-Ethylenethioketal (V).—A solution of 500 mg of IV, 0.3 ml of ethanedithiol, and 1 ml of 1.4 *N* ethereal hydrogen chloride in 3 ml of acetic acid was maintained at 25° for 90 min and then diluted with 150 ml of water. Evaporation removed excess dithiol and yielded a glassy solid which, after isolation and drying, was recrystallized from ether, giving 200 mg of V: white prisms; mp 210–215°; [α]D +62°; λ_{max} 249 mμ (ε 16,600); λ_{max} 5.76, 5.81, 10.34, 11.41 μ;[10] the nmr spectrum gave peaks at δ 0.69 (18-H_3), 0.93 (19-H_3), 1.82 (6-CH_3), 2.03 (17α-OAc), 2.08 (21-H_3), 3.42 (m, 3-$C_2H_4S_2$), 5.51 (m, 7-H), 5.72 (4-H).

Solvolysis of 6α-Methyl-6β-chloro-17α-acetoxyprogesterone.—A mixture of 500 mg of IV and 500 mg of pyridine hydrochloride in 4 ml of methanol plus 3 ml of methylene chloride was stirred at 25° for 70 min. The resulting clear solution was diluted with ether, washed with water, dried, and evaporated to a glassy froth. Recrystallization from methanol gave, as a first crop, 200 mg of 6-methyl-6-dehydro-17α-acetoxyprogesterone:[9] mp 210–214°; λ_{max} 288 mμ; λ_{max} 5.77, 5.82, 6.02, 6.13, 6.31 μ; the nmr spectrum showed peaks at δ 0.73 (18-H_3), 1.11 (19-H_3), 1.87 (6-CH_3), 2.05 (17α-OAc), 2.09 (21-H_3), 5.90 (4-H), 6.00 (m, 7-H). A second crop of crystalline material (150 mg) was shown to be 6α-methyl-6β-methoxy-17α-acetoxyprogesterone,[11] λ_{max} 234 mμ; the infrared spectrum was identical with that of an authentic sample;[11] peaks appeared at δ 0.72 (18-H_3), 1.30 and 1.32 (6α-CH_3 and 19-H_3), 2.05 (17α-OAc), 2.09 (21-H_3), 3.04 (6β-OCH_3), 5.98 (4-H), with weak signals of 6-methyl-6-dehydro-17-acetoxyprogesterone visible in the nmr spectrum.

Solvolysis of 6β-Chloro-17α-acetoxyprogesterone.—A mixture of 1 g of the 6β-chloro ketone[5] and 1 g of pyridine hydrochloride in 5 ml of methanol and 5 ml of methylene chloride was stirred at 25° for 1 hr and then diluted with ether, washed with water, and evaporated to a glass which showed no significant absorption at 280–290 mμ (no 4,6-dien-3-one). Crystallization from acetone afforded 100 mg of 3-methoxy-6-chloro-17α-acetoxypregna-3,5-dien-20-one:[12] λ_{max} 5.75, 5.80, 6.08, 6.17, 12.93 μ; the nmr spectrum gave peaks at δ 0.66 (18-H_3), 0.99 (19-H_3), 2.04 (17α-OAc), 2.09 (21-H_3), 3.64 (3-OCH_3), 5.57 (4-H). On dissolving the tacky acetone mother liquor residue in a few milliliters of methanol, 100 mg of the starting material (containing 10–15% of a methoxy compound) crystallized rapidly and was filtered off. Dilution of the filtrate with a small quantity of hexane and ether, followed by storage at 0°, afforded 400 mg of a 1:1 mixture of unreacted 6β-chloro ketone and 6β-methoxy-17α-acetoxyprogesterone.[13] Peaks in the nmr spectrum ascribed to the latter were at δ 0.70 (18-H_3), 1.30 (19-H_3), 2.04 (17α-OAc), 2.09 (21-H_3), 3.18 (6β-OCH_3), 3.68 (m, 6α-H), 5.80 (4-H), identical with the shifts of 6β-methoxy-17α-acetoxyprogesterone prepared by a different process,[14] and in

(8) F. B. Colton, U. S. Patent 2,980,711 (April 1961).

(9) H. J. Ringold, J. P. Ruelas, E. Batres, and C. Djerassi, *J. Am. Chem. Soc.*, **81**, 3712 (1959); R. M. Dodson and P. E. Sollman, U. S. Patent 2,891,-079 (June 1959).

(10) The infrared spectrum is identical with that of a sample of V (*Anal.* Calcd for $C_{26}H_{36}O_3S_2$: C, 67.78; H, 7.87. Found: C, 67.53; H, 8.03.) prepared earlier in these laboratories by A. Segal directly from 6-methyl-6-dehydro-17α-acetoxyprogesterone.

(11) P. B. Sollman and R. M. Dodson, *J. Org. Chem.*, **26**, 4180 (1961). A sample was kindly supplied by Dr. P. B. Sollman of G. D. Searle and Co.

(12) K. Ysuda, *Chem. Pharm. Bull.* (Tokyo), **11**, 1167 (1963); *Chem. Abstr.*, **59**, 12864*h* (1963).

(13) R. Sciaky, *Gazz. Chim. Ital.*, **91**, 545 (1961).

(14) Prepared by R. Mallory of these laboratories by the action of cupric bromide in methanol on 17α-acetoxyprogesterone, a process described in ref 11.

good agreement with the reported chemical shifts of two other 6β-methoxy-4-en-3-ones.[15]

(15) S. Julia, B. Decouvelaere, and F. Engelmann [*Bull. Soc. Chim. France*, 2277 (1966)] reported the following for 6β-methoxy-4-cholesten-3-one and 6β-methoxy-4-androstene-3,17-dione, respectively: δ 1.28, 1.31 (19-H_3); 3.19, 3.23 (6β-OCH_3); 3.65, 3.73 (t, 6α-H); 5.77, 5.83 (4-H).

Registry No.—Ia, 2066-13-9; Ib, 2944-79-8; Id, 13871-44-8; Ie, 13871-45-9; IIIa, 13871-46-0; IIIb, 13970-31-5; IIId, 13871-47-1; IV, 13871-48-2; V, 13871-49-3; 17α-ethynyl-17β-acetoxyestra-3,5-dieno-[3,4-*b*]dithiane, 13970-30-4.

Terpenoids. LX.[1] Revised Structures of the Cactus Triterpene Lactones Stellatogenin and Thurberogenin[2]

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A combination of chemical and spectral evidence is presented demonstrating that the pentacyclic triterpene lactones, thurberogenin and stellatogenin, previously believed to have structures I and II, respectively, are in fact correctly represented as III (thurberogenin) and IV (stellatogenin). By optical rotatory dispersion measurements on appropriate derivatives, the C-19 stereochemistry of III and IV has been shown to be the same (19α side chain) as in betulinic acid (XIII) and other lupane derivatives. The results of certain previously described experiments which appeared to support the earlier structural assignments (I and II) for thurberogenin and stellatogenin, respectively, are discussed and shown to be in accord with the revised structures.

Earlier papers in this series described the isolation and characterization of the title compounds from the cactus species *Lemaireocereus stellatus*[3] and *Lemaireocereus thurberi*,[4] respectively. Thurberogenin and stellatogenin were shown to possess the structural feature, unprecedented at that time among naturally occurring triterpenes,[5] of a lactone ring,[3,4] and thurberogenin was correlated with stellatogenin by the demonstration that the latter could be converted in a facile manner to the former, without skeletal rearrangement, by dehydrative elimination of a side-chain tertiary hydroxyl group.[3]

On the basis of biogenetic considerations and of a series of chemical transformations, structures I and II were proposed for thurberogenin and stellatogenin, respectively.[6] Subsequent confirmation for the presence of the lupane skeleton came from interrelation of a thurberogenin degradation product (XXIII) with one of known structure derived from betulinic acid (XIII).[7] (See Chart I.)

At the time that these structure assignments were made, nuclear magnetic resonance and mass spectrometry had not yet been employed in triterpene chemistry. Recently, we had occasion to examine the nmr and mass spectra of certain thurberogenin and stellatogenin derivatives, which showed that the earlier assignments were untenable. We have now accumulated a combination of chemical and spectral data that permits the conclusive assignment of structures III and IV to thurberogenin and stellatogenin, respectively. It is our present purpose to set forth the evidence which dictates these findings, as well as to discuss some of the chemical transformations reported previously[6,7] in the light of the structures now known to be correct.

For the sake of convenience much of the experimental and spectral information was obtained from thurberogenin derivatives. Since the relationship of stellatogenin to thurberogenin has been rigorously demonstrated,[3] any structural conclusions concerning the latter compound apply as well to the former.

It can be seen that the difference between the originally proposed (I) and revised (III) structures for thurberogenin involves the position and nature (*i.e.*, tertiary *vs.* secondary) of the hydroxylic terminus of the lactone bridge. Important information on this point comes from the nmr spectrum of dihydrothurberogenone (now known to have structure V), obtained from thurberogenin by catalytic hydrogenation of the side chain and oxidation of the C-3 hydroxyl function.[6] A complex resonance integrating for one proton is observed at δ 4.60, indicative of the grouping $H\overset{|}{C}OR$. This function must involve the lactonic hydroxyl group, since the other two oxygens above in V are carbonyls, *and the hydroxyl group involved in lactone formation must therefore be secondary.*

Supporting spectral evidence for this conclusion was obtained in the following manner. Lithium aluminum hydride reduction of dihydrothurberogenin (III with saturated side chain) cleaves the lactone ring and furnishes a triol VI, readily esterifiable with acetic anhydride–pyridine.[6] The acetylation product VIa, originally thought to be a diacetate, shows a molecular ion peak in the mass spectrum at *m/e* 586 as well as a prominent fragment ion at 526 (M − CH_3COOH), indicating it to be in fact a *triacetate* ($C_{36}H_{58}O_6$). The

(1) Paper LIX: T. Nakano, M. Hasegawa, T. Fukumaru, S. Tobinaga, C. Djerassi, L. J. Durham, and H. Budzikiewicz, *Tetrahedron Letters*, 365 (1967). The preseut article represents also part XIV in the series "Triterpenes" by B. Tursch, *et al.* (for preceding paper, see *Tetrahedron Letters*, 2129 (1967)).

(2) Financial support from the National Institutes of Health (Grant No. GM-06840) is gratefully acknowledged.

(3) C. Djerassi, L. H. Liu, E. Farkas, A. E. Lippman, A. J. Lemin, L. E. Geller, R. N. McDonald, and B. J. Taylor, *J. Am. Chem. Soc.*, **77**, 1200 (1955). In the same paper the isolation of stellatogenin from still another cactus genus is described.

(4) C. Djerassi, L. E. Geller, and A. J. Lemin, *ibid.*, **75**, 2254 (1953).

(5) The list of pentacyclic triterpenes reported to contain lactone rings has grown somewhat in recent years. For a compilation, as well as for reviews of structural progress in this field, see T. G. Halsall and R. T. Aplin in "Progress in the Chemistry of Organic Natural Products," Vol. 22, L. Zechmeister, Ed., Springer-Verlag, Vienna, 1964, pp 153–202, as well as P. Boiteau, B. Pasich and A. R. Ratsimamanga, "Les Triterpénoides," Gauthier-Villars, Paris, 1964.

(6) C. Djerassi, E. Farkas, L. H. Liu, and G. H. Thomas, *J. Am. Chem. Soc.*, **77**, 5330 (1955).

(7) C. Djerassi and R. Hodges, *ibid.*, **78**, 3534 (1956).