[CONTRIBUTION FROM CHEMICAL RESEARCH AND DEVELOPMENT DIVISION, SCHERING CORPORATION]

Steroid Amines. Fungicides Derived from Δ^5-3β-Hydroxybisnorcholenic Acid (Fernholz Acid)

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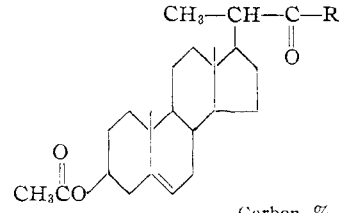
Several amines, and their quaternary derivatives, prepared from Δ^5-3β-acetoxybisnorcholenic acid, have been found to possess the ability to inhibit the growth of *Candida albicans*.

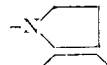
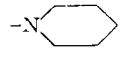
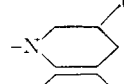
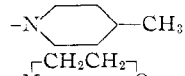
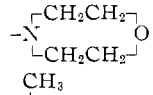
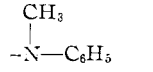
The preparation and antimicrobial effects of a number of aminosteroids have been reported. Webb and co-workers,[1] and Dodgson and Haworth[2] prepared derivatives of bile acids and cholesterol, none of which was especially effective either as antibacterial agents[1] or as amoebicides.[2] Barnett, Ryman and Smith synthesized some amino derivatives of cholesterol with appreciable antibacterial properties.[3] Kull and co-workers[4] have described the action of several amino pregnenes and aminoandrostenes against a wide variety of microörganisms. 20-Amino-3β-hydroxy-5-pregnene hydrochloride and 3-keto-21-(1-piperidyl)-$\Delta^{4,17}$-pregnadiene hydrochloride were effective in inhibiting the growth of *Candida albicans* at concentrations of 10 mg. %. The remaining steroids displayed less pronounced activity. Louw, Backer and Strating[5] reported recently the preparation of Δ^5-3β-hydroxy-22-[N,N-diethylamino]-bisnorcholene and the corresponding dimethylamino compound, both derived from Fernholz acid, according to the method (I → III) elaborated in the next paragaph. They reported no microbiological studies.

Prior to the report of Louw[5] we prepared a group of amines from Δ^5-3β-acetoxybisnorcholenic acid which inhibit the growth of *Candida albicans* at low concentration. Δ^5-3β-Acetoxybisnorcholenic acid (I) which is available through the ozonolysis of stigmasteryl acetate,[6] has been converted, by treatment with thionyl chloride, into the corresponding acid chloride which, with the appropriate secondary amine, afforded an amide II (Table I). Reduction of the amide with lithium aluminum hydride in the conventional way[7] yielded the corresponding amine III (Table II), with attendant loss of the acetate group at C-3. The amine then was converted to the methiodide IV (Table III) in the usual way.

The reduction of the amide from N-methylaniline took an unexpected course. Instead of the anticipated amine there was isolated a neutral substance, free from nitrogen, which was shown to be Δ^5-3β,22-dihydroxybisnorcholene.[8] Subsequently

TABLE I



-R	M.p., °C.	$[\alpha]^{25}D$ (CHCl$_3$)	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
-N(CH$_3$)$_2$	238–240	−35.8°	75.13	75.00	9.94	10.01
-N(C$_2$H$_5$)$_2$	174–175	−16.0[a]	75.80	75.81	10.22	9.99
-N(*n*-C$_3$H$_7$)$_2$	152–153	−29.0	76.38	76.71	10.47	10.42
-N(CH$_2$CH$_2$OH)$_2$	230.5–231	−24.2	70.70	70.78	9.54	9.31
	212–214	−38.5	76.15	76.32	9.81	9.67
	202–204	−39.5	76.44	76.40	9.95	9.67
	173–174	−36.4	76.71	76.82	10.09	10.08
	176–179	−34.2	76.71	76.67	10.09	10.43
	232–233	−37.9	73.48	73.64	9.47	9.23
	182–184	+ 0.7	77.94	78.20	9.07	9.02

[a] In methyl alcohol.

* Deceased, January 19, 1955.

(1) M. Webb, *et al.*, *J. Chem. Soc.*, 665 (1946); 2767 (1951).

(2) D. P. Dodgson and R. D. Haworth, *ibid.*, 67 (1952).

(3) J. Barnett, B. Ryman and F. Smith, *ibid.*, 524, 526, 528 (1946).

(4) F. C. Kull, *et al.*, *J. Invest. Dermatol.*, **21**, 227 (1953); see also R. A. Micheli and C. K. Bradsher, THIS JOURNAL, **77**, 4788 (1955).

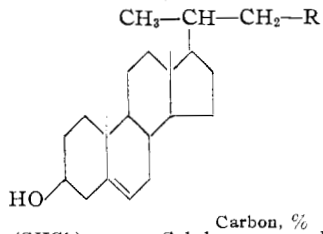
(5) D. F. Louw, J. Strating and H. J. Backer, *Rec. trav. chim.*, **73**, 667 (1954).

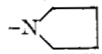
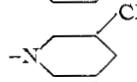
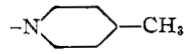
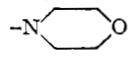
(6) E. Fernholz, *Ann.*, **507**, 128 (1933).

(7) A review of this reaction appears in an article by V. Micovic and M. Mihailovic, *J. Org. Chem.*, **18**, 1190 (1953).

(8) A. V. McIntosh, *et al.*, THIS JOURNAL, **70**, 2955 (1948).

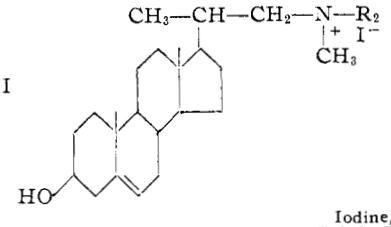
TABLE II

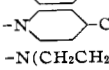
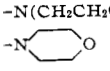


R	M.p., °C.	$[\alpha]^{25}D$ (CHCl₃)	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
$-N(CH_3)_2$	171–172	−14.5°	80.15	80.38	11.49	11.53
$-N(C_2H_5)_2 \cdot HCl$	326–327 d.		Cl, 8.36	8.62	N, 3.30	3.27
$-N(n\text{-}C_3H_7)_2 \cdot HCl$	302–303 d.	− 8.4[a]	Cl, 7.86	7.67	N, 3.10	2.95
$-N(n\text{-}C_4H_9)_2 \cdot HCl$	274–275 d.	− 5.5[a]	Cl, 7.37	7.47	N, 2.92	2.77
	155–156	−10.8	80.98	81.15	11.24	11.36
	200–201	− 5.0	81.14	81.07	11.35	11.23
	179–180	− 3.3	81.29	81.27	11.45	11.34
	192–194	− 2.5	81.29	80.95	11.45	11.35
$-N(CH_2CH_2OH)_2$	238–245	+23.4[b]	74.41	74.00	10.81	10.65
	219–222	− 6.0	77.75	78.04	10.79	10.79

[a] In methyl alcohol. [b] In ethyl alcohol.

TABLE III



−N R₂	M.p., °C.	$[\alpha]^{25}D$	Iodine, % Calcd.	Found
$-N(CH_3)_2$	298–300 d.	−30.8 (DMF)	25.31	24.96
$-N(C_2H_5)_2$	245.5–246 d.	−22.5 (CH_3OH)	23.97	24.43
$-N(n\text{-}C_3H_7)_2$	235 d.	−21.6 (CH_3OH)	22.76	23.03
$-N(n\text{-}C_4H_9)_2$	210–211 d.	−20.6 (C_2H_5OH)	21.67	21.32
	280 d.	−22.6 (CH_3OH)	24.06	24.43
	275–276 d.	−24.5 (C_2H_5OH)	23.43	23.77
	277–278 d.	−26.6 (DMF)	22.84	22.78
	278–279 d.	−27.0 (DMF)	22.84	23.26
$-N(CH_2CH_2OH)_2$	277–278 d.	−20.6 (C_2H_5OH)	22.60	22.42
	269–270 d.[a] 275–277		23.35	22.87

[a] Double m.p.

there appeared the description of a method for the preparation of aldehydes from acids involving conversion of the acid to the corresponding N-methylanilide, followed by lithium aluminum hydride reduction with $^1/_3$ to $^1/_2$ mole of reducing agent.[9] The use of a larger excess of reducing agent converted the aldehyde to the alcohol, as we observed. This abnormal course of reaction, from conditions designed to produce the amine, also has been observed as the principal reaction path with amides derived from pyrrole, indole, carbazole and, to some extent, tetrahydroquinoline.[7]

The amine III derived from piperidine (Δ⁵-3β-hydroxy-22-[N-piperidino]-bisnorcholene) was reduced catalytically to the corresponding allobisnorcholane (V), and was oxidized by the Oppenauer procedure to Δ⁴-3-keto-22-[N-piperidino]-bisnorcholene (VI). Amines also were prepared from cholic acid and Δ⁵-3β-acetoxyandrostene-17β-carboxylic acid. Cholic acid was converted into the 3,7,12-triformate[10] which then was transformed by the previously illustrated method to 3α,7α,12α-trihydroxy-24-[N-piperidino]-cholane methiodide.[11] From Δ⁵-3β-acetoxyandrostene-17β-carboxylic acid, Δ⁵-3β-hydroxy-17-[(N-piperidino)-methyl]-androstene and its methiodide were synthesized similarly.

None of the amides of Fernholz acid possessed significant antimonilial activity. The amines, on the other hand, were effective at low concentrations. The most active members of the group, 3β-hydroxy-22-[N-piperidino]-allobisnorcholane, Δ⁵-3β-hydroxy-22-[N-piperidino]-bisnorcholene and Δ⁵-3β-hydroxy-22-[N-pyrrolidino]-bisnorcholene were effective in inhibiting *Candida albicans* in the concentration range 0.1–1.0 mg. %.[12] However, these substances were both toxic and irritating. Several of the methiodides retained the activity of the parent amines and displayed greatly reduced toxicity. The methiodide of Δ⁵-3β-hydroxy-22-[N-piperidino]-bisnorcholene inhibited *Candida albicans* in the concentration range 0.25–0.5 mg. % and was relatively non-toxic and non-irritating to mucous membranes. The quaternaries from cholic acid and Δ⁵-3β-acetoxyandrostene-17β-carboxylic acid possessed much lower orders of activity against *Candida albicans*.

(9) F. Weygand, *et al.*, *Angew. Chem.*, **65**, 525 (1953).

(10) F. Cortese and L. Bauman, THIS JOURNAL, **57**, 1393 (1935).

(11) *Cf.* L. F. Fieser and W. Huang, *ibid.*, **75**, 6306 (1953).

(12) Inhibition of growth of *Candida albicans* was determined by conventional methods. Various concentrations of the compounds under test were incorporated in tryptose agar containing 5% serum, and after the agar had hardened the surface was streaked with 24-hour cultures. Growth was recorded after 48 hours incubation at 37°. Details of the bacteriological investigation will be published elsewhere. We are indebted to Dr. J. Ilavsky, Messrs. E. Foley, W. Morgan, F. Vitale, J. Stevenson and Misses G. Greco and M. Bronit for the description of the procedure and the reported activities.

Experimental[13]

Δ^5-3β-Acetoxybisnorcholenoyl Chloride.[14]—To a suspension of 24 g. (0.062 mole) of Δ^5-3β-acetoxybisnorcholenic acid (I, Fernholz acid 3-acetate) in 500 ml. of dry benzene was added 12 ml. of thionyl chloride and one drop of pyridine. The resulting mixture was stirred until solution of the acid was complete (*ca.* 3 hours), whereupon the benzene was removed *in vacuo* at 30°. The residue was dissolved in 100 ml. of dry benzene and concentrated once again *in vacuo* at 30°. The crystalline Δ^5-3β-acetoxybisnorcholenoyl chloride was employed in the succeeding step without further purification.

Amides from Δ^5-3β-Acetoxybisnorcholenoyl Chloride.—The acid chloride thus prepared was dissolved in 300 ml. of dry benzene and was treated with 0.155 mole of the appropriate secondary amine. The reaction mixture was allowed to stand overnight, and was then washed with water, dilute sulfuric acid, dilute sodium carbonate solution and dried over anhydrous magnesium sulfate. The dried solution was concentrated with the occasional addition of heptane until precipitation from the boiling solution ensued. The resulting mixture was cooled and the precipitate was removed by filtration (the amides from dipropylamine and dibutylamine did not crystallize readily from heptane and the residues from concentration of the benzene solutions were employed in the subsequent reactions without further purification). Recrystallization of the amides could be effected from methylene chloride–hexane and yields based on I were in the range 80–90%.

Amines from Lithium Aluminum Hydride Reduction of Amides.—To a suspension of 2.5 g. of lithium aluminum hydride in 100 ml. of anhydrous ether was added a solution of 10 g. of amide in 100 ml. of anhydrous tetrahydrofuran and the resulting mixture was refluxed with stirring overnight. The reaction mixture was cooled and 25 g. of acetone was added dropwise with stirring, followed by 25 ml. of water. The precipitated alumina was removed by filtration with Filter Aid and the precipitate was leached several times with methylene chloride. The filtrate and methylene chloride extracts were combined, dried and concentrated. Crystallization of the residue was effected from methylene chloride–hexane solution in most instances. The amines derived from diethylamine, dipropylamine and dibutylamine were taken up in dry ether and precipitated as hydrochlorides with anhydrous hydrogen chloride. The hydrochlorides were recrystallized from ethanol. Yields from the reduction were in the range 80–90%.

Reaction of Amines with Methyl Iodide.—The amine (1.0 g.) was refluxed with 10 ml. of methyl iodide until a heavy precipitate formed. The precipitate was redissolved by the addition of methanol and reflux was continued for one hour. The solvents were removed by distillation and the methiodides were recrystallized from ethanol.

Δ^5-3β-Acetoxy-22-[N-piperidino]-bisnorcholene.—To a solution of 1.0 g. of Δ^5-3β-hydroxy-22-[N-piperidino]-bisnorcholene in 10 ml. of anhydrous pyridine was added 2 ml. of acetic anhydride. The reaction mixture was allowed to stand overnight at room temperature and was then poured into ice-water. The resulting precipitate (1.1 g.) was removed by filtration and recrystallized from methylene chloride–hexane; m.p. 171–172.5°, $[\alpha]^{25}D$ −7.8° ($CHCl_3$).

Anal. Calcd. for $C_{29}H_{47}O_2N$: C, 78.86; H, 10.73. Found: C, 78.58; H, 10.51.

The methiodide melted at 288–289° dec., $[\alpha]^{25}D$ −28.6 (ethanol).

Anal. Calcd. for $C_{30}H_{50}O_2NI$: I, 21.75. Found: I, 21.45.

3β-Hydroxy-22-[N-piperidino]-allobisnorcholane.—To a solution of 5 g. of Δ^5-3β-hydroxy-22-[N-piperidino]-bisnorcholene in 100 ml. of glacial acetic acid was added 1.0 g. of Adams platinum catalyst and the resulting mixture was hydrogenated at room temperature and atmospheric pressure. When uptake of hydrogen ceased, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was refluxed for one-half hour with 200 ml. of 5% methanolic potassium hydroxide, whereupon water was added and the resulting precipitate was collected on a filter by suction. The precipitate was washed well with water and recrystallized from methanol. There resulted 4.4 g., m.p. 190–191°, $[\alpha]^{25}D$ + 49.6° ($CHCl_3$).

Anal. Calcd. for $C_{27}H_{47}ON$: C, 80.73; H, 11.80. Found: C, 80.71; H, 11.98.

The methiodide melted at 282–287° dec., $[\alpha]^{25}D$ + 10.6° (dimethylformamide).

Anal. Calcd. for $C_{28}H_{50}ONI$: I, 23.35. Found: I, 23.04.

Δ^4-3-Keto-22-[N-piperidino]-bisnorcholene.—To a solution of 2 g. of Δ^5-3β-hydroxy-22-[N-piperidyl]-bisnorcholene in 30 ml. of anhydrous acetone and 60 ml. of anhydrous benzene was added a solution of 3.5 g. of aluminum isopropylate in 50 ml. of anhydrous benzene. The reaction mixture was refluxed with stirring for 48 hours. At the end of the reflux period the reaction mixture was cooled and washed with 10% sodium hydroxide and water. The resulting solution was dried and concentrated *in vacuo* to a solid residue. Recrystallization from acetone afforded 1.02 g., m.p. 155–157°, resolidified and remelted 168–171°, ϵ_{242} 15,500 (methanol), $[\alpha]^{25}D$ +119.7° ($CHCl_3$).

Anal. Calcd. for $C_{27}H_{43}ON$: C, 81.55; H, 10.90. Found: C, 81.43; H, 10.58.

3α,7α,12α-Trihydroxy-24-[N-piperidino]-cholane Methiodide.—Cholic acid was converted to the triformate according to Cortese and Bauman.[5] The triformate (16.1 g.) was dissolved in 500 ml. of anhydrous ether, and to the solution were added 10 ml. of thionyl chloride and one drop of pyridine. The reaction mixture was allowed to stand at room temperature overnight. The ether was then removed *in vacuo*, 100 ml. of anhydrous benzene was added to the residue and the resulting solution was again concentrated *in vacuo*. The residue was taken up in 200 ml. of benzene and 25 ml. of piperidine was added. After the reaction mixture had remained at room temperature overnight it was washed well with water, dilute sulfuric acid and again with water. The solution then was dried and concentrated, and the residue was dissolved in 100 ml. of anhydrous tetrahydrofuran. The resulting solution was added to a suspension of 15 g. of lithium aluminum hydride in 150 ml. of anhydrous ether and the reaction mixture was refluxed with stirring overnight. Then 100 ml. of acetone was added dropwise, followed by 30 ml. of water. The precipitated alumina was removed by filtration with Filter Aid and the precipitate was leached several times with methylene chloride. The filtrate and extracts were combined and evaporated to a residue, which was taken up in anhydrous ether. Anhydrous hydrogen chloride was passed into the solution until precipitation was complete. Filtration afforded 11.9 g. of 3α,7α,12α-trihydroxy-24-[N-piperidino]-cholane hydrochloride, m.p. 304–305°, $[\alpha]^{25}D$ +29° (ethanol).

Anal. Calcd. for $C_{29}H_{52}O_3NCl$: Cl, 7.12. Found: Cl, 6.90.

Five grams of amine hydrochloride was dissolved in methanol and a solution of 2 g. of potassium hydroxide in methanol was added. The reaction mixture was diluted with water and extracted with methylene chloride. The combined extracts were washed with water, dried and concentrated to an oily residue. The residue was dissolved in 25 ml. of methyl iodide and the resulting solution was refluxed for one-half hour. The methyl iodide was boiled off and replaced with methanol. Water was then added to induce crystallization. Filtration of the precipitate afforded 4.65 g. of methiodide, m.p. 234–237°. Recrystallization from methanol–water raised the m.p to 236–238°, $[\alpha]^{25}D$ +28° (ethanol).

Anal. Calcd. for $C_{30}H_{54}ONI$: I, 21.03. Found: I, 20.94.

Δ^5-3β-Hydroxy-17-[(N-piperidino)-methyl]-androstene Methiodide.—To a mixture of 8.0 g. of Δ^5-3β-acetoxyandrostene-17β-carboxylic acid in 400 ml. of anhydrous ether were added 10 ml. of thionyl chloride and one drop of pyridine. The reaction mixture was allowed to stand at room temperature overnight and then was concentrated *in vacuo*. The residue was dissolved in 100 ml. of anhydrous benzene and again concentrated *in vacuo*. The residue was then taken up in 200 ml. of anhydrous benzene and 15 ml. of piperidine was added. After standing overnight at room temperature the reaction mixture was processed according to the previously elaborated procedure. The

(13) All melting points are corrected. Analyses and optical data were obtained by the Microanalytical and Physical Chemistry Departments of these laboratories.

(14) A. Wettstein, *Helv. Chim. Acta*, **24**, 311 (1941).

amide was crystallized from a benzene–heptane mixture; yield 8.4 g., m.p. 192–195°.

The amide (7.9 g. in 100 ml. of anhydrous tetrahydrofuran) was then treated with 8 g. of lithium aluminum hydride in 100 ml. of ether as described in the general procedure. The resulting Δ^5-3β-hydroxy-17-[(N-piperidino)-methyl] androstene separated as a gel from methylene chloride–hexane. After repeating this process several times there was obtained 6.7 g., m.p. 132–136°, $[\alpha]^{25}D$ −50.7° ($CHCl_3$).

Anal. Calcd. for $C_{25}H_{41}ON$: C, 80.80; H, 11.12. Found: C, 80.69; H, 11.51.

A solution of 1.5 g. of amine in 30 ml. of methyl iodide was refluxed for one-half hour. Sixty ml. of ethanol then was added and the methyl iodide was removed by distillation. A small amount of insoluble material was filtered from the hot solution, and the filtrate was concentrated until crystallization began. From the cooled mixture there was obtained 1.25 g. of the methiodide, m.p. 280–282° dec. Recrystallization from methanol raised the m.p. to 282–283° dec., $[\alpha]^{25}D$ −32.1° (ethanol).

Anal. Calcd. for $C_{26}H_{44}ONI$: I, 24.71. Found: I, 24.68.

Δ^5-3β,22-Dihydroxybisnorcholene from the N-Methyl Anilide of Δ^5-3β-Acetoxybisnorcholenic Acid by Lithium Aluminum Hydride Reduction.—To a solution of 1.57 g. of the N-methyl anilide of Δ^5-3β-acetoxybisnorcholenic acid in 240 ml. of anhydrous tetrahydrofuran was added 5.0 g. of lithium aluminum hydride and the reaction mixture was refluxed overnight. The excess reagent was decomposed in the usual way and the precipitated alumina was removed by filtration. The precipitate was leached with methylene chloride and the extracts were combined with the filtrate. The resulting solution was dried and concentrated. Addition of hexane induced crystallization. There resulted 0.95 g. of Δ^5-3β,22-dihydroxybisnorcholene, m.p. 199–200°, $[\alpha]^{25}D$ −58.6° ($CHCl_3$) [lit. m.p.[3] 196–205° (hemihydrate), $[\alpha]^{25}D$ −55.4° ($CHCl_3$)].

Anal. Calcd. for $C_{22}H_{36}O_2$: C, 79.46; H, 10.92. Found: C, 79.04; H, 11.05.

The product was not basic (no precipitate in ethereal hydrogen chloride), was free from nitrogen, and showed no carbonyl bands in the infrared (strong hydroxyl absorption was observed).

BLOOMFIELD, N. J.

[CONTRIBUTION FROM THE MEDICINAL CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES, RESEARCH DIVISION, AMERICAN CYANAMID CO.]

Steroidal Cyclic Ketals. XVI.[1] 16-Hydroxylated Steroids. II.[2] The Preparation of 16-Keto- and 16β-Hydroxyprogesterone

BY SEYMOUR BERNSTEIN, MILTON HELLER AND STEPHEN M. STOLAR

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Chromic acid–pyridine oxidation of Δ^5-pregnene-16α-ol-3,20-dione 3,20-bis-ethylene ketal (Ia) afforded the 16-one bis-ketal IIa. Mild acid hydrolysis of IIa gave Δ^4-pregnene-3,16,20-trione (IV), which was converted into the 20-enol acetate V (13% yield) on mild acetylation. Reduction of the 16-one bis-ketal IIa with lithium aluminum hydride resulted in the 16β-ol bis-ketal IIIa, which was hydrolyzed to Δ^4-pregnene-16β-ol-3,20-dione (VIa). Its acetate VIb also was prepared.

In a recent publication[2] from this Laboratory there was reported synthetic pathways to 16α-hydroxyprogesterone and related compounds *via* ethylene ketal intermediates. The latter have lent themselves to a number of interesting transformations which elaborate further the chemistry of the C-16 position. The results obtained form the basis of this paper.

Chromic acid–pyridine oxidation[3] of Δ^5-pregnene-16α-ol-3,20-dione 3,20-bis-ethylene ketal (Ia)[2] afforded in 80% yield the 16-one bis-ketal IIa, which displayed in the infrared spectrum the expected 5-membered ring carbonyl absorption at 1748 cm.$^{-1}$. The oxime IIb of the 16-one bis-ketal IIa also was prepared and characterized. It was noted that the infrared absorption spectrum of the oxime IIb showed an abnormally weak absorption band in the C=N region at 1670 cm.$^{-1}$.

Mild acid hydrolysis of the 16-one bis-ketal IIa gave Δ^4-pregnene-3,16,20-trione (IV) in fairly good yield. It appeared to exist mainly in an enol form as shown by its complex infrared absorption spectrum (see Experimental) and by its ultraviolet absorption spectrum with bands at 240 and 285 mμ.[4] The expected bathochromic effect of the ultraviolet absorption band in basic solution was observed with a shift of the higher absorption band (285 mμ) to 308 mμ. No shift of the absorption band was noticed on dilution.[5] It was not possible to determine from the above physical data in which direction (or both) enolization might have taken place. Acetylation under mild conditions, however, furnished one of the two possible enol acetates after purification by several crystallizations (perhaps necessary for the separation of both enol acetates). This new compound had an ultraviolet absorption band at 242 mμ (ε 26,400) (the ultraviolet absorption spectrum in basic solution reverted to that of the free enol). Since the bands of the two chromophores combined in the ultraviolet, no information could be obtained from that source as to the direction of enolization. Its infrared absorption spectrum, however, clearly indicated the probable structure. The spectrum in the carbonyl and double bond regions was complex and had bands at 1755, 1725, 1679, 1652 and 1625 cm.$^{-1}$. The band at 1755 cm.$^{-1}$ could best be assigned to the enol acetate grouping,[6] so that the band at 1725 cm.$^{-1}$ must be the result of the conjugated ketone, $\Delta^{17(20)}$-16-one (the Δ^4-3-ketone was, of course, shown by the band at 1679 cm.$^{-1}$). Therefore, the enol acetate was assigned the structure

(1) Paper XV, W. S. Allen, S. Bernstein, M. Heller and R. Littell, THIS JOURNAL, **77**, 4784 (1955).

(2) Paper I, S. Bernstein, M. Heller and S. M. Stolar, *ibid.*, **76**, 5674 (1954).

(3) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *ibid.*, **75**, 422 (1953).

(4) The value 285 mμ disagrees with that of 277 mμ recorded for the same chromophore system by H. H. Inhoffen, F. Blomeyer and K. Brückner, *Ber.*, **87**, 593 (1954).

(5) L. Dorfman, *Chem. Revs.*, **53**, 47 (1953).

(6) R. N. Jones, P. Humphries, F. Herling and K. Dobriner, THIS JOURNAL, **74**, 2820 (1952).