g. (12.1%) of 3α-acetoxybisnor-17(20)-cholen-22-al, m.p. 140–148°, λ_{max}^{alc} 254 mμ; λ_{max}^{Nujol} 1735 (acetate), 1655 (conj. ald.), 1620 cm.$^{-1}$ (conj. C=C). The resinous residue (3.06 g.) was a mixture containing much 3-hydroxy compound, probably resulting from hydrolysis of the 3-acetate, λ_{max}^{alc} 256 mμ.

D. Dehydrobromination with γ-Collidine.—A solution of 2.27 g. (5 mmoles) of 3α-acetoxy-20-bromobisnorcholan-22-al in 5 ml. of γ-collidine was heated 2 hours (N_2 atm.) on a steam-bath. The mixture was diluted with 25 ml. of ether and filtered. The yield of collidine hydrobromide was 0.82 g. (82%). The filtrate was diluted with 75 ml. of ether and was washed with two 25-ml. portions of ice-cold 10% hydrochloric acid, and two 25-ml. portions of water. The solution was dried, concentrated to 5 ml., diluted with 5 ml. of Skellysolve A, and refrigerated. The first crop of crystals (0.29 g.) was 3α-acetoxybisnor-17(20)-cholen-22-al, m.p. 130–137°, λ_{max}^{alc} 253.5 mμ. The gummy residue (1.35 g.) was a mixture of the desired $\Delta^{17(20)}$-aldehyde and a large amount of the saturated aldehyde, probably from reductive removal of bromine.

KALAMAZOO, MICHIGAN

[CONTRIBUTION FROM THE INSTITUTO DE QUÍMICA DE LA UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO]

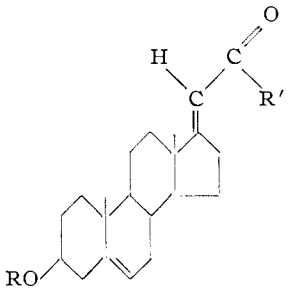
The Favorskii Rearrangement in the Pregnane Series. *cis–trans* Isomerism in Some 17,20-Dehydro Derivatives

BY J. ROMO AND A. ROMO DE VIVAR

RECEIVED SEPTEMBER 5, 1956

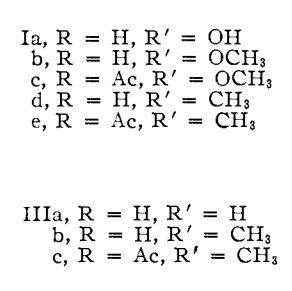
Treatment of 17α-bromo-21-iodo-Δ^5-pregnen-3β-ol-20-one acetate (II) with methanolic potassium hydroxide under the conditions of the Favorskii rearrangement yielded two isomeric acids, *cis*-$\Delta^{5,17(20)}$-pregnadien-3β-ol-21-oic acid (IIIa) and *trans*-$\Delta^{5,17(20)}$-pregnadien-3β-ol-21-oic acid (Ia), as well as the corresponding methyl esters IIIc and Ib. 20-Bromo-$\Delta^{5,17(20)}$-pregnadien-3β-ol-21-oic acid (Xa) was obtained from the 17α,21,21-tribromo-Δ^5-pregnen-3β-ol-20-one acetate which accompanies the iodinated ketone II as an impurity. The structure of Xa was proved definitely by zinc debromination. Various experiments with lithium aluminum hydride are described which afforded derivatives of the *cis* series. The *trans* configuration is assigned to various homologs of the pregnane series that were prepared by a new method.

Marker, *et al.*,[1] carried out a Favorskii rearrangement on the crude product obtained by treatment of 5,6,17α,21-tetrabromo-pregnan-3β-ol-20-one acetate with sodium iodide and obtained $\Delta^{5,17(20)}$-pregnadien-3β-ol-21-oic acid (Ia). Julian and Karpel[2] reported a quantitative yield of this acid using pure 17α-bromo-21-iodo-Δ^5-pregnen-3β-ol-20-one acetate (II) but gave no experimental data. Sondheimer, *et al.*,[3] also carried out the reaction with the halogenated derivative II and these authors obtained an 85% yield of crude acid with m.p. 215–222°. By repeated crystallization the m.p. rose to a constant value of 252–254°, and these authors[3] assumed that the low m.p. of the crude acid was due to the presence of the β,γ-unsaturated acid.



II

Ia, R = H, R′ = OH
b, R = H, R′ = OCH_3
c, R = Ac, R′ = OCH_3
d, R = H, R′ = CH_3
e, R = Ac, R′ = CH_3



IIIa, R = H, R′ = H
b, R = H, R′ = CH_3
c, R = Ac, R′ = CH_3

When we carried out the Favorskii reaction with the iodinated derivative II (m.p. 153–157° dec.) in methanolic potassium hydroxide, we obtained approximately 70% yield of an acidic fraction with m.p. 211–218°, which gave a positive Beilstein test and about 20% yield of a partially crystalline neutral fraction. By fractional crystallization of the crude acid we could isolate three acids: A, B and C. The acid A (m.p. 253–255°, λ_{max} 222 mμ, log ε 4.22) is identical with the one obtained previously,[1,3] Ia. The methyl ester prepared by treatment with diazomethane and the methyl ester acetate have physical constants in good agreement with those reported by Plattner and Schreck[4] for Ib and Ic.

These authors prepared the acid (Ia) (m.p. 249–250°) by Reformatzky reaction between bromo acetic ester and Δ^5-androstene-3β-ol-17-one acetate followed by dehydration.

The acid B ($C_{21}H_{30}O_3$, m.p. 265–267°, λ_{max} 224 mμ, log ε 4.10) is isomeric with A, since partial hydrogenation of its methyl ester acetate afforded the same unconjugated methyl ester IVa that Plattner and Schreck[4] obtained by selective hydrogenation of the methyl ester Ic.

As both acids have the ultraviolet absorption for α,β-unsaturated carboxylic acids, they must be *cis–trans* isomers.[5]

Examination of models[6] of the two isomers show very clearly that in the acid with the carboxyl

(1) R. E. Marker, H. M. Crooks, E. M. Jones and A. C. Shabica, THIS JOURNAL, **64**, 1276 (1942).

(2) P. L. Julian and W. J. Karpel, *ibid.*, **72**, 362 (1950).

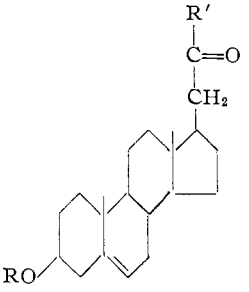
(3) F. Sondheimer, O. Mancera, M. Urquiza and G. Rosenkranz, *ibid.*, **77**, 4145 (1955).

(4) P. A. Plattner and W. Schreck, *Helv. Chim. Acta*, **22**, 1178 (1939).

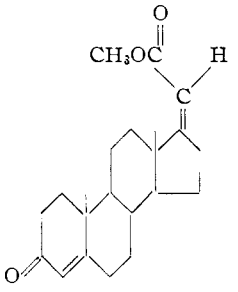
(5) The term *trans* is given to the isomer with the carboxyl group opposite to the angular methyl group, and the *cis* isomer has then the reverse configuration.

(6) Molecular models, made by Catalin Products, Ltd., Waltham Abbey, Essex, England.

group on the side of the side chain opposite to the ring system there is no distortion of the side chain due to steric hindrance, whereas with the carboxyl group on the same side as the ring system, the side chain is distorted and this distortion affects the co-



IVa, R = Ac, R′ = OCH_3
b, R = H, R′ = CH_3
c. R = Ac, R′ = CH_3

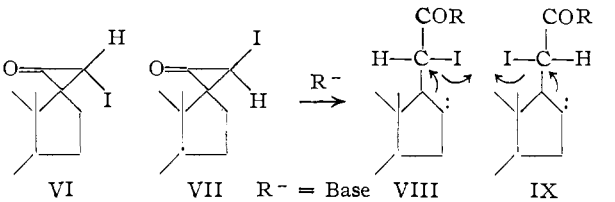


V

planarity between the double bond and the carboxyl group. Braude, *et al.*,[7] have pointed out that when this later situation occurs, there is an inhibition of resonance that reduces the intensity of absorption. The acid B_4 and the derived methyl ester, methyl ester acetate, all have a lower extinction coefficient than those derived from acid A and must therefore belong to the *cis* series and have structures IIIa, IIIb and IIIc, respectively. Other cases of *cis–trans* isomerism in steroids about the double bond in the 17,20-position are known. Marshall, *et al.*,[8] and Fieser and Huang-Minlon[9] have separated the *cis–trans* isomers of the enol acetates of 20-ketones, and recently the Upjohn workers[10] described some further *cis–trans* isomers. They assigned the configurations by oxidative experiments and also converted the *cis* into the *trans* isomer by means of sodium methoxide in anhydrous methanol. When we applied this method to our isomers we recovered our *trans* isomer Ib unchanged, whereas the *cis* IIIb was converted into the *trans* isomer Ib.

Direct crystallization of the neutral fractions gave the *trans*-methyl ester Ib, and the mother liquors on acetylation yielded the *cis*-methyl ester acetate IIIc. Loftfield[11] has pointed out that in most cases the Favorskii rearrangement involves the presence of a cyclopropanone intermediate and as the base can remove either of the two α-hydrogen atoms in the iodo ketone II, two cyclopropanone intermediates are possible, VI and VII. Further attack by base breaks the three-membered ring and gives the carbanions VIII and IX, and these, by elimination of iodide ion, produce the acids Ia and IIIa.

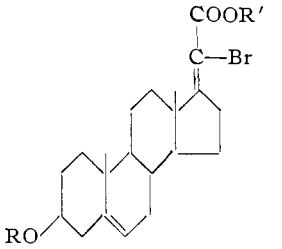
The acid C ($C_{21}H_{29}O_3Br$) (m.p. 275–278°, λ_{max} 248 mμ, log ϵ 3,80) is also a conjugated acid and must have the structure Xa since the ultraviolet maximum shows a bathochromic shift of *ca.* 24 mμ due to the bromine atom substituted on the double bond alpha to the carboxyl group.[12] This shift is observed also in the methyl ester Xb and in the acetate Xc.



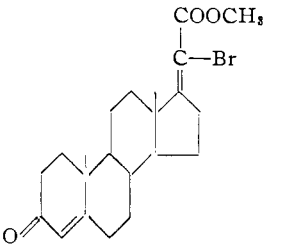
VI VII R⁻ = Base VIII IX

Wagner and Moore[13] prepared 20-bromo-$\Delta^{17(20)}$-pregnen-3β-ol-21-oic acid by rearrangement of the corresponding tribromo ketone with base. However, they did not report the ultraviolet spectrum.

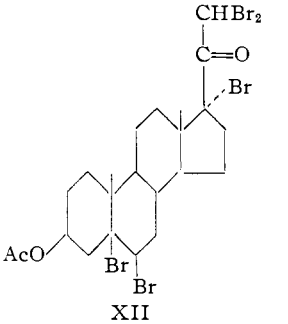
Zinc reduction of Xc afforded a mixture of the two methyl esters IIIc and Ic. Oppenauer oxidation of the methyl ester Xb afforded the Δ^4-3 keto derivative XI. Doubtless the acid Xa must be produced by action of the base on the tribrominated derivative XIII which occurs in small amounts as impurity in the iodo-ketone II. When the Favorskii reaction was carried out with a very pure specimen of ketone II, no brominated acid Xa was isolated.



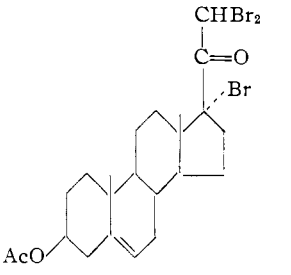
Xa, R = R′ = H
b, R = H, R′ = CH_3
c, R = Ac, R′ = CH_3



XI



XII



XIII

The same reaction on the tribrominated ketone XIII, gives a very pure acid Xa in 72% yield. This tribromo ketone XIII was prepared by pentabromination of a chloroform solution of Δ^5-pregnen-3β-ol-20-one acetate (if acetic acid is used, the 5,6,17α,21-tetrabromo derivative[2] is precipitated). The pentabromo derivative XII on further treatment with sodium iodide using the conditions reported by Julian[2] yielded XIII.

The lithium aluminum hydride reduction of the methyl ester IIIc afforded the *cis*-diol XIVa. This on oxidation with manganese dioxide[14] yielded the

(7) E. A. Braude, E. R. H. Jones, H. P. Koch, R. W. Richardson, F. Sondheimer and J. B. Toogood, *J. Chem. Soc.*, 1890 (1949).

(8) Ch. Marshall, T. H. Kritchevsky, S. Liebermann and T. F. Gallagher, THIS JOURNAL, **70**, 1837 (1948).

(9) L. F. Fieser and Huang-Minlon, *ibid.*, **71**, 1840 (1949).

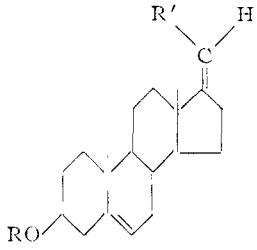
(10) J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze and R. W. Jackson, *ibid.*, **77**, 4436 (1955).

(11) R. B. Loftfield, *ibid.*, **73**, 4707 (1951).

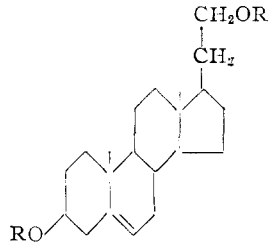
(12) A. L. Nussbaum, O. Mancera, R. Daniels, G. Rosenkranz and C. Djerassi, *ibid.*, **73**, 3263 (1951).

(13) R. B. Wagner and J. A. Moore, *ibid.*, **72**, 3655 (1950).

(14) F. Sondheimer, C. Amendolla and G. Rosenkranz, *ibid.*, **75**, 5930 (1953).

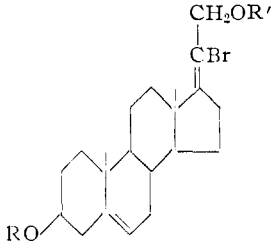


XIVa, R = H, R′ = CH_2OH
b, R = Ac, R′ = CH_2OAc
c, R = Ac, R′ = CH=O

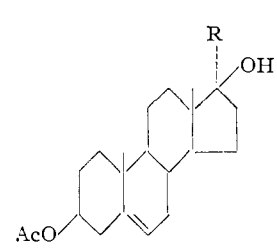


XVa, R = R′ = H
b, R = R′ = Ac

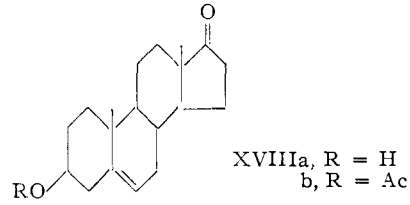
aldehyde, isolated as the acetate XIVc. The reduction with lithium aluminum hydride of the methyl esters IVa and Xc yielded the saturated diol XVa and the bromo diol XVIa.



XVIa, R = R′ = H
b, R = R′ = Ac



XVIIa, R = CH_2—C≡CH
b, R = CH_2—$COCH_3$



XVIIIa, R = H
b, R = Ac

By treatment of the chloride of the *trans*-acid Ia with methyl-zinc-iodide, Plattner and Schreck[15] prepared the α,β-unsaturated ketone Id. This ketone also must have the *trans* configuration. We have obtained this same ketone Id by dehydration with mineral acids of the acetonyl derivative XVIIb prepared, in very good yield, by hydration of the triple bond of 17α-propargyl-Δ^5-androstene-3β,17β-diol-3 acetate (XVIIa)[16,17] with mercuric chloride in presence of aniline.[18] It is interesting to note that the acetonyl derivative XVIIb suffers a reverse aldol condensation with alkalies, yielding Δ^5-androsten-3β-ol-17-one, and this proves that no gross rearrangement took place during the hydration of the triple bond.

In Table I are recorded optical rotation data of the *cis*, *trans* and brominated acids and their derivatives, as compared with the saturated analogs. It can be seen that in every case the *cis* and the brominated acids and their derivatives have the more positive rotation values than the saturated derivatives, whereas the *trans* isomers all have more negative rotations.

(15) P. A. Plattner and W. Schreck, *Helv. Chim. Acta*, **24**, 472 (1941).

(16) D. Magrath, V. Petrow and R. Royer, *J. Chem. Soc.*, 845 (1951).

(17) C. W. Greenhalgh, H. B. Henbest and E. R. H. Jones, *ibid.*, 1190 (1951).

(18) H. E. Stavely, THIS JOURNAL, **63**, 3127 (1941).

Acknowledgments.—We are indebted to Dr. George Rosenkranz of Syntex, S. A., for a generous gift of steroids. We wish to express our thanks to Mr. Héctor Macías for technical assistance.

Experimental[19]

Favorskii Rearrangement of 17α-Bromo-21-iodo-Δ^5-pregnen-3β-ol-20-one Acetate (II).—A solution of the iodo ketone[2] (60 g.) (m.p. 153–157° dec.) in methanol (2 l.) was mixed with 100 g. of potassium hydroxide dissolved in 100 ml. of water and refluxed for 2 hr., concentrated to one-half its volume, then diluted and acidified with concentrated hydrochloric acid. The precipitate was extracted with ethyl acetate and washed with water. The organic layer was extracted with 5% potassium hydroxide solution three times (the potassium salts were partially insoluble in water), the extracts were combined and made acid with hydrochloric acid, to precipitate the acidic fraction (23.85 g.). The ethyl acetate was washed with water, dried over anhydrous sodium sulfate and evaporated to dryness, yielding 7.2 g. of semicrystalline residue. The acidic fraction gave a positive Beilstein test and by repeated crystallization from methanol–ether, 4.22 g. of the *trans*-acid Ia with m.p. 240–245° was obtained. Further crystallization from methanol yielded prisms, m.p. 253–255°, $[\alpha]^{23}D$ −83.4° (ethanol), λ_{max} 222 mμ, log ϵ 4.22 (Marker, *et al.*[1], report m.p. 252–253°; Sondheimer, *et al.*,[3] give m.p. 252–254°, Plattner and Schreck[4] report m.p. 249–250°, $[\alpha]D$ −82° in dioxane), ν_{max} 1700, 1660 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.30; H, 9.57.

The methyl ester Ib was prepared by esterification, with diazomethane, following the directions of Plattner and Schreck.[4] In our hands the substance showed m.p. 188–190°, $[\alpha]^{23}D$ −83°, λ_{max} 222 mμ, log ϵ 4.24; ν_{max} 1700, 1660 cm.$^{-1}$ and free hydroxyl band. (Plattner and Schreck[4] report m.p. 188–189°, $[\alpha]D$ −73° in dioxane, λ_{max} 222 mμ, log ϵ 4.22.)

The methyl ester acetate Ic showed m.p. 159°, $[\alpha]^{23}D$ −87°, λ_{max} 222 mμ, log ϵ 4.23; ν_{max} 1730, 1700, 1660 cm.$^{-1}$ (Plattner and Schreck[4] reported m.p. 159°, $[\alpha]D$ −69° in chloroform, λ_{max} 222 mμ, log ϵ 4.22).

By crystallization of the mother liquors of the *trans*-acid Ia from methanol, there was obtained 1.53 g. of the *cis*-acid IIIa, m.p. 255–260°, further crystallization from methanol yielded glistening plates, m.p. 265–267° (mixed m.p. with equal amount of the *trans*-acid Ia gave m.p. 218–222°), $[\alpha]^{23}D$ −36.7° in ethanol, λ_{max} 224 mμ, log ϵ 4.04; ν_{max} 1700, 1660 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.51; H, 9.25.

***cis*-$\Delta^{5,17(20)}$-Pregnadien-3β-ol-21-oic Acid Methyl Ester (IIIc).**—The *cis*-acid (2 g.) was dissolved in 150 ml. of methanol, and an ethereal solution of diazomethane (prepared with 7 g. of N-nitrosomethylurea) was added; the mixture was left overnight at room temperature, then washed with water, dried and evaporated. The residue was crystallized from acetone–hexane yielding 1.51 g., m.p. 160–163° (the substance frequently separates from the solution as a jelly). The analytical sample was obtained as needles, m.p. 169–171° (from acetone–hexane) (mixed m.p. with the *trans*-ester Ib gives large depression), $[\alpha]^{23}D$ −48°, λ_{max} 224 mμ, log ϵ 4.09; ν_{max} 1700, 1660 cm.$^{-1}$ and free hydroxyl group.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.48; H, 9.37.

The acetate (acetic anhydride–pyridine, 1 hr. on the steam-bath) after crystallization from acetone–hexane showed m.p. 165–167° (on admixture with the acetate Ic gives depression), $[\alpha]^{23}D$ −47°, λ_{max} 224–226 mμ, log ϵ 4.10[20]; ν_{max} 1730, 1700, 1660 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.58; H, 8.87. Found: C, 74.37; H, 8.98.

(19) Melting points are uncorrected. Rotations were determined in chloroform and ultraviolet absorption spectra in 95% ethanol solution. The infrared spectra were measured on a Perkin-Elmer double beam spectrophotometer with sodium chloride prisms using Nujol suspensions. The microanalyses were performed by Dr. Franz Pascher, Bonn, Germany.

(20) It is interesting to note a small bathochromic shift in the *cis* series.

TABLE I

MOLECULAR ROTATIONS OF SOME PREGNENOIC ACIDS AND DERIVATIVES[a]

	$[\alpha]_D$	MD
20-Bromo-$\Delta^{5,17}$-pregnadien-3β-ol-21-oic acid (Xa)	−32.7° (ethanol)	−133.7°
cis-$\Delta^{5,17(20)}$-Pregnadien-3β-ol-21-oic acid (IIIa)	−36.7 (ethanol)	−121
Δ^5-Pregnen-3β-ol-21-oic acid	−56.4 (dioxane)	−186.5
trans-$\Delta^{5,17(20)}$-Pregnadien-3β-ol-21-oic acid (Ia)	−83.4 (ethanol)	−275.2
20-Bromo-$\Delta^{5,17(20)}$-pregnadien-3β-ol-21-oic acid, methyl ester (Xb)	−41	−173.4
cis-$\Delta^{5,17(20)}$-Pregnadien-3β-ol-21-oic acid, methyl ester (IIIb)	−48	−165.8
Δ^5-Pregnen-3β-ol-21-oic acid, methyl ester	−63.5[b] (dioxane)	−219.7
trans-$\Delta^{5,17(20)}$-Pregnadien-3β-ol-21-oic acid, methyl ester (Ib)	−83	−285.5
20-Bromo-$\Delta^{5,17(20)}$-pregnadien-3β-ol-21-oic acid, methyl ester acetate (Xc)	−49	−227.85
cis-$\Delta^{5,17(20)}$-Pregnadien-3β-ol-21-oic acid methyl ester acetate (IIIc)	−47	−181.4
Δ^5-Pregnen-3β-ol-21-oic acid methyl ester acetate (IVa)	−67	−260
trans-$\Delta^{5,17(20)}$-Pregnadien-3β-ol-21-oic acid methyl ester acetate (Ic)	−82	−316.5
20-Bromo-$\Delta^{4,17(20)}$-pregnadien-3-one-21-oic acid methyl ester (XI)	+102	+429.4
cis-$\Delta^{4,17(20)}$-Pregnadien-3-one-21-oic acid, methyl ester (V)	+140	+478.8
Δ^4-Pregnen-3 one-21-oic acid, methyl ester	+84[b] (dioxane)	+289
trans-$\Delta^{4,17(20)}$-Pregnadien-3-one-21-oic acid, methyl ester	+74	+253.7
21-Methyl-Δ^5-pregnen-3β-ol-21-one (IVc)	−46	−151.8
21-Methyl-$\Delta^{5,17(20)}$-pregnadien-3β-ol-21-one (Id)	−70	−229.6
21-Methyl-Δ^5-pregnen-3β-ol-21-one acetate (IVb)	−50	−186
21-Methyl-$\Delta^{5,17(20)}$-pregnadien-3β-ol-21-one acetate (Ie)	−65	−240.5
21-Methyl-Δ^4-pregnene-3,21-dione	+95	+328
21-Methyl-$\Delta^{4,17(20)}$-pregnadiene-3,21-dione	+90	+293.4

[a] Rotations were determined in chloroform solution unless otherwise indicated. [b] These rotations were taken from the paper of Plattner and Schreck.[4]

The mother liquors of the *cis*-acid IIIa by slow crystallization from methanol gave crystals of the brominated acid Xa which on repeated crystallization from methanol yielded large needles (560 mg.), m.p. 269–270° dec. The analytical sample was obtained by recrystallization from methanol, m.p. 274–276°, with progressive decomposition, $[\alpha]^{23}D$ −32.7° (ethanol), λ_{max} 248 mμ, log ε 3.80; ν_{max} 1700, 1680 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{21}H_{29}O_3Br$: C, 61.61; H, 7.14; Br, 19.52. Found: C, 60.92; H, 7.47; Br, 20.00.

20-Bromo-$\Delta^{5,17(20)}$-pregnadien-3β-ol-21-oic-acid Methyl Ester (Xb).—The bromo-acid Xa (1 g.) was esterified in 50 ml. of methanol with 150 ml. of an ethereal solution of diazomethane (prepared from 7 g. of N nitrosomethylurea). Crystallization from acetone–methanol furnished needles (780 mg.), m.p. 149–151° methanol); the analytical sample showed m.p. 156° (the substance very frequently melts in the 130–140° range, resolidifies and melts again), $[\alpha]^{23}D$ −41°; λ_{max} 222–224, 250 mμ, log ε 3.72, 3.85; ν_{max} 1700, 1680 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{22}H_{31}O_3Br$: C, 62.41; H, 7.38; Br, 18.90. Found: C, 61.82; H, 7.44; Br, 18.37.

The acetate (prepared with acetic anhydride in pyridine on the steam-bath) showed m.p. 192–193° (small prisms from chloroform–ether), $[\alpha]^{23}D$ −49°; λ_{max} 222–224, 248 mμ, log ε 3.78, 3.84; ν_{max} 1730, 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{33}O_4Br$: C, 61.93; H, 7.14; Br, 17.17. Found: C, 61.89; H, 7.00; Br, 17.38.

The last mother liquors of the acidic fractions (18.8 g.) were dissolved in 200 ml. of methanol, 1 l. of an ethereal solution of diazomethane (prepared from 40 g. of N-nitrosomethylurea) was added and the solution worked up as before. Crystallization from ether–hexane afforded the *trans*-methyl ester Ib (2.4 g.), m.p. 184–186°. One recrystallization from acetone–hexane raised the m.p. to 189–191° (mixed m.p. with an authentic specimen gave no depression), $[\alpha]^{23}D$ −85°.

Acetylation of the mother liquors (with acetic anhydride and pyridine on the steam-bath) yielded 15.5 g. of crude product. It was chromatographed on 340 g. of neutral alumina. The first fractions were eluted with hexane furnishing 1.77 g. of the *cis*-methyl ester acetate IIIc, $[\alpha]^{23}D$ −48°. The second fractions afforded 1.19 g. of the brominated acetate Xc, m.p. 185–187°, $[\alpha]^{23}D$ −52°.

From the neutral fraction there was isolated 1.15 g. of the *trans*-ester Ib, m.p. 188–190°; acetylation of the mother liquors yielded 800 mg. of the *cis*-acetate IIIc, m.p. 163–165°, and 3 g. of a mixture of the *cis*- and *trans*-acetates with a constant m.p. of 116–117°.

Isomerization of the *cis*-Methyl Ester IIIb to the *trans*-Ib.—The *cis*-ester IIIb (175 mg.) was dissolved in a methanolic solution of sodium methoxide prepared from sodium (1 g.) in methanol (50 ml.) and refluxed 3 hr. The solution was then diluted with water, acidified with hydrochloric acid and extracted with ether. The ethereal extract was washed with water and concentrated. On addition of hexane the *trans* isomer Ib crystallized (102 mg.), m.p. 184–187°, $[\alpha]^{23}D$ −88° (it was identified with an authentic specimen by mixed m.p. and infrared comparison).

A very pure sample of iodo ketone II was prepared by crystallization of the 5,6,17,21-tetrabromo-Δ^5-pregnen-3β-ol-20-one-acetate from chloroform–methanol and chloroform–ether (m.p. 177–178°) and treatment with sodium iodide under the conditions described by Julian and Karpel.[2] The alkaline rearrangement (5 g.) afforded 90 mg. of the *trans*-acid Ia, m.p. 249–250°, 80 mg. of the *cis*-acid IIIa, m.p. 259–262°; esterification with diazomethane furnished the *trans*-ester (200 mg.), m.p. 184–186°. Acetylation yielded 325 mg. of the *cis*-acetate IIIc, m.p. 162–164°, and 160 mg. of the *trans*-acetate, m.p. 148–151°. No brominated derivatives were isolated.

Selective Hydrogenation of $\Delta^{5,17(20)}$-Pregnadien-3β-ol-21-oic Acid Methyl Ester Acetate (IIIc).—A solution of 900 mg. of IIIc in 70 ml. of ethyl acetate and 30 ml. of acetic acid was hydrogenated with 100 mg. of prehydrogenated Adams catalyst until 1 mole of hydrogen was absorbed. The catalyst was filtered and the solution was washed with water, diluted sodium carbonate and water again. The dried solution was evaporated. Crystallization of the residue from acetone–methanol afforded needles (815 mg.), m.p. 127–130°. The analytical sample showed m.p. 131–132° (from acetone–methanol), $[\alpha]^{23}D$ −67°, ν_{max} 1730 cm.$^{-1}$ (Plattner and Schreck report m.p. 128–129°, $[\alpha]D$ +57° in dioxane).

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.19; H, 9.50.

Hydrogenation of the *trans* isomer in the same way afforded 760 mg., m.p. 128–130°, $[\alpha]^{23}D$ −69°, which was identical with the above substance by mixture m.p. and infrared comparison.

***cis*-$\Delta^{4,17(20)}$-Pregnadien-3-one-21-oic Acid Methyl Ester (V).**—The free ester IIIb (300 mg.) was dissolved in a mixture of 40 ml. of toluene and 10 ml. of cyclohexanone. Ten ml. was distilled to eliminate moisture, and a solution of 300 mg. of aluminum isopropoxide in 8 ml. of toluene was added

and the mixture refluxed for 1 hr. Water was then added and the volatile components were removed by steam distillation and the residue was extracted with ether. The dried extract was evaporated and the residue dissolved in hexane and chromatographed on 10 g. of alumina. The fractions eluted with hexane crystallized, affording brilliant plates (160 mg.), m.p. 136–137°. The analytical sample showed m.p. 139–140° (from hexane), $[\alpha]^{23}D$ +140°, λ_{max} 236–238 mμ, log ε 4.38; ν_{max} 1700, 1660 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.02; H, 8.84.

5,6,17α,21,21-Pentabromopregnan-3β-ol-20-one Acetate (XII).—To a solution of Δ^5-pregnen-3β-ol-20-one acetate (20 g.) in 300 ml. of chloroform 8.93 g. of bromine in 40 ml. of acetic acid was added rapidly. Decolorization took place immediately. A few drops of hydrobromic acid in acetic acid was added, followed by a solution of 26.67 g. of bromine in 70 ml. of acetic acid. After 2 hr. at room temperature, the solution was washed thoroughly with water, dried and concentrated *in vacuo*. On addition of methanol 34.5 g. of pentabromo derivative, m.p. 200–203° dec., crystallized. The analytical sample showed m.p. 203–205° (brilliant plates from chloroform–methanol), $[\alpha]^{23}D$ −61°.

Anal. Calcd. for $C_{23}H_{31}O_3Br$: C, 36.56; H, 4.13; Br, 52.94. Found: C, 36.35; H, 4.07; Br, 53.50.

17α,21,21-Tribromo-Δ^5-pregnen-3β-ol-20-one Acetate (XIII).—The pentabromo derivative XII (13 g.) was dissolved in a mixture of 250 ml. of benzene and 250 ml. of absolute ethanol, 30 g. of sodium iodide was added, and the mixture was left 24 hr. at room temperature. The dark red solution was washed with water, dilute sodium bisulfite and water. The dried solution was concentrated *in vacuo*, and the product crystallized from methanol as small prisms (6.8 g.), m.p. 180–182°. The analytical sample showed m.p. 185–187° (from chloroform–methanol), $[\alpha]^{23}D$ −70° (Julian and Karpel[7] report m.p. 190°).

Anal. Calcd. for $C_{23}H_{31}O_3Br_3$: C, 46.38; H, 5.24; Br, 40.30. Found: C, 46.09; H, 5.37; Br, 40.86.

Favorskii Rearrangement of 17α,21,21-Tribromo-Δ^5-pregnen-3β-ol-20-one Acetate (XIII).—To a suspension of 4 g. of the tribromo derivative XIII in 150 ml. of methanol, 4 g. of potassium hydroxide in 30 ml. of water is added; the mixture was refluxed 2 hr. Initially the tribromo derivative went into solution, but after 45 minutes a precipitate of the potassium salt began to appear. The suspension was diluted with water and acidified. The precipitate was collected and washed thoroughly with water, and it was the nearly pure bromo acid Xa (2 g., 72%), m.p. 270–274° dec. One crystallization from methanol raised the m.p. to 274–276°, $[\alpha]^{23}D$ −34°, λ_{max} 246–248 mμ, log ε 3.81. It was identical by mixture m.p. and infrared comparison with the acid obtained before.

Zinc Dust Debromination of 20-Bromo-$\Delta^{5,17(20)}$-pregnadien-3β-ol-20-one Acetate (Xc).—To a solution of the acetate Xc (700 mg.) in 40 ml. of ethanol (heating is necessary to dissolve the substance) 10 g. of zinc dust was added and refluxed 9 hr. The zinc was filtered and the solvent evaporated, the residue crystallized from ether, yielding 30 mg. of the *trans*-acetate Ic, m.p. 154–156°, $[\alpha]^{23}D$ −79°, and the mother liquors were chromatographed on 20 g. of neutral alumina. The first fractious eluted with hexane, on recrystallization, furnished 110 mg. of the *cis*-acetate IIIc, m.p. 163–166°, $[\alpha]^{23}D$ −47°; the second fractions afforded 190 mg. more of the *trans*-acetate Ic, m.p. 153–155°. (Both products were identified with the above *cis*- and *trans*-diacetates through mixed m.p. and infrared comparison.)

20-Bromo-$\Delta^{4,17(20)}$-pregnadien-3-one-21-oic Acid Methyl Ester (XI).—The methyl ester Xb (500 mg.) was dissolved in a mixture of 70 ml. of toluene and 20 ml. of cyclohexanone, 20 ml. was distilled off and 400 mg. of aluminum isopropoxide in 15 ml. of toluene was added and the reaction carried out as above. Crystallization from acetone–methanol furnished needles (330 mg.), m.p. 205–207°, further crystallization from acetone–methanol raised the m.p. to 207–208°, $[\alpha]^{23}D$ +87°, λ_{max} 244 mμ, log ε 4.37, ν_{max} 1700, 1660 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{29}O_3Br$: C, 62.70; H, 6.93; Br, 18.96. Found: C, 62.90; H, 6.92; Br, 19.27.

***cis*-$\Delta^{5,17(20)}$-Pregnadien-3β,21-diol (XIVa).**—A solution of the *cis*-methyl ester IIIb (500 mg.) in 20 ml. of anhydrous tetrahydrofuran was added slowly to a slurry of 300 mg. of lithium aluminum hydride in 80 ml. of ether; the mixture was refluxed 15 min. The excess of lithium aluminum hydride was destroyed with a few drops of ethanol, and the mixture was diluted with water and made acid with hydrochloric acid. The precipitate was extracted with ethyl acetate, the organic layer was washed with water and the dried solution evaporated. Crystallization of the residue from acetone–ether afforded brilliant plates (320 mg.), m.p. 196–202°. The analytical sample showed m.p. 211–213° (from acetone–ether), $[\alpha]^{23}D$ −76.8°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.66; H, 10.05.

The diacetate showed m.p. 128–129° (from methanol), $[\alpha]^{23}D$ −61°.

Anal. Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.52; H, 9.14.

***cis*-$\Delta^{5,17(20)}$-Pregnadien-3β-ol-21-al-acetate (XIVc).**—The *cis*-diol XIVa (1 g.) in 150 ml. of chloroform was shaken 8 hr. with 10 g. of manganese dioxide[21]; the residue after removal of the dioxide and the solvent was acetylated with acetic anhydride and pyridine overnight at room temperature. Crystallization from ether–hexane furnished needles (250 mg.), m.p. 158–160°; further crystallization raised the m.p. to 178–180° (needles from ether–hexane), $[\alpha]^{23}D$ −106°, λ_{max} 244 mμ, log ε 4.25; ν_{max} 1730, 1700, 1660 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.65; H, 9.17.

Δ^5-Pregnen-3β,21-diol (XVa).—The methyl ester acetate (1 g.) was reduced in the same conditions as the previous example. Crystallization from ethyl acetate–ether yielded 680 mg., m.p. 203–205°. The analytical sample showed m.p. 205–207° (plates from methanol), $[\alpha]^{23}D$ −63°.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.13; H, 10.88.

The diacetate XVb showed m.p. 116–117° (needles from acetone–methanol), $[\alpha]^{23}D$ −51.7°.

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 74.92; H, 9.80.

20-Bromo-$\Delta^{5,17(20)}$-pregnadien-3β,21-diol (XVIa).—The brominated methyl ester Xb (700 mg.) was reduced with lithium aluminum hydride in the same way described before. Crystallization from methanol furnished needles (500 mg.), m.p. 242–243°, $[\alpha]^{23}D$ −51°.

Anal. Calcd. for $C_{21}H_{31}O_2Br$: C, 63.79; H, 7.90; Br, 20.20. Found: C, 63.61; H, 7.72; Br, 20.33.

The diacetate XVIb showed m.p. 135–136° (plates from methanol), $[\alpha]^{23}D$ −31°. *Anal.* Calcd. for $C_{25}H_{35}O_4Br$: C, 62.62; H, 7.35; Br, 16.67. Found: C, 62.51; H, 7.50; Br, 16.78.

The 17α-Acetonyl-Δ^5-androstene-3β,17β-diol 3-Acetate (XVIIb).—A solution of 3 g. of mercuric chloride in 15 ml. of water and 1.5 ml. of aniline were added to 17α-propargyl-Δ^5-androstene-3β,17β-diol-3-acetate (XVIIa)[22] (1.5 g.), dissolved in 90 ml. of benzene and 90 ml. of ethanol. The mixture was refluxed 3 hr. (after a few minutes a precipitate began to form). It was then diluted with water and ether was added. The organic layer was washed with water several times, then with diluted sodium carbonate, dilute hydrochloric acid and water. The dried extract was evaporated and the residue crystallized from acetone. There was obtained 1.12 g. of brilliant plates, m.p. 190–192°; further crystallization from acetone–ether raised the m.p. to 195–197°, $[\alpha]^{23}D$ −71°; ν_{max} 1718, 1700 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.37; H, 9.37.

Mineral Acid Treatment of the Ketone XVIIa.—To a solution of 660 mg. of the ketone XVIIa in 60 ml. of methanol, 1

(21) Prepared according to the method of O. Mancera, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.*, 2189 (1953).

(22) This product was prepared using approximately the same conditions and in similar yield as reported by Greenhalgh, Henbest and Jones[17] but tetrahydrofuran was used instead of dioxane as solvent in the Reformatzky. In our hands the propargyl derivative showed m.p. 148–150°, $[\alpha]^{23}$ −83°; these authors reported m.p. 147–148°, $[\alpha]^{20}D$ −81° in $CHCl_3$. Magrath, Petrow and Royer[16] report m.p. 149°.

ml. of concentrated hydrochloric acid was added and refluxed 1 hr.; after dilution with water the precipitate was filtered. Crystallization from acetone–ether furnished prisms (500 mg.), m.p. 165–168°. The analytical sample showed m.p. 171–173° (from acetone–ether), $[\alpha]^{23}D$ −70°, λ_{max} 242 mμ, log ε 4.25, ν_{max} 1680 cm.$^{-1}$ and free hydroxyl band. (Plattner and Schreck[15] report m.p. 168–169°, $[\alpha]D$ −65° in dioxane.)

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 80.44; H, 9.82. Found: C, 80.43; H, 9.38.

The acetate showed m.p. 191–193° (needles from chloroform–methanol), $[\alpha]^{23}D$ −65°, λ_{max} 242 mμ, log ε 4.22 (Plattner and Schreck[15] report m.p. 189–190°, $[\alpha]D$ −63°, λ_{max} 240 mμ, log ε 4.25).

21-Methyl-Δ^5-pregnen-3β-ol-21-one Acetate (IVc).—A solution of the acetate Ie (1 g.) in 125 ml. of ethyl acetate was hydrogenated with 100 mg. of 5% palladium-on-charcoal until 1 mole of hydrogen was absorbed. The catalyst was filtered and the solution evaporated. Crystallization from ethyl acetate–methanol afforded long needles (780 mg.), m.p. 156–158°, $[\alpha]^{23}D$ −50° (Plattner and Schreck[15] report m.p. 156–157°, $[\alpha]D$ −49° in dioxane).

Anal. Calcd. for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74. Found: C, 77.49; H, 9.53.

Alkaline Treatment of the Ketone XVIIb.—To a solution of the ketone XVIIb (1 g.) in 50 ml. of methanol, 1 g. of potassium carbonate in 10 ml. of water was added and refluxed 1 hr. The solution was diluted with water and extracted with ether, the organic layer was washed with water and concentrated. On addition of hexane there crystallized 625 mg. of prisms, m.p. 147–148°. A second crop (200 mg.) was obtained, m.p. 143–145°, $[\alpha]^{23}D$ −3°, ν_{max} 1736 cm.$^{-1}$ and free hydroxyl band (this material proved to be identical with Δ^5-androstene-3β-ol-17-one by mixed m.p. determination and infrared comparison).

The acetate showed m.p. 169–171° (from ether–hexane), $[\alpha]^{23}D$ −1.3° (identical with Δ^5-androstene-3β-ol-17-one acetate by mixed m.p. and infrared comparison).

MEXICO, D.F.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF G. D. SEARLE AND CO.]

17-Alkyl-19-nortestosterones

BY FRANK B. COLTON, LEONARD N. NYSTED, BYRON RIEGEL AND ALBERT L RAYMOND

RECEIVED OCTOBER 8, 1956

A series of 17-alkyl-19-nortestosterone derivatives was prepared for evaluation as anabolic and androgenic agents. Of the compounds studied, 17-ethyl-19-nortestosterone appears to be of greatest interest from a biological point of view.

A concerted effort has been made in our laboratory directed toward finding a substance with an anabolic potency of the order of testosterone but with a lower androgenic activity. To this end, a series of 17-alkyl-19-nortestosterone (17α-alkyl-17-hydroxy-4-estren-3-one) derivatives was prepared and biologically evaluated.

19-Nortestosterone was first synthesized by Birch[1] and was reported[2] to possess about 20% of the androgenic activity of testosterone. Hershberger and co-workers recently reported[3] that the substance I was a potent anabolic agent having a very favorable anabolic to androgenic ratio. This work has since been confirmed by Stafford and co-workers[4] as well as in our laboratories.[5] Djerassi and co-workers[6] have prepared 17-methyl-19-nortestosterone and stated that this substance was at least as potent an androgen as 17-methyltestosterone in the chick comb test but only weakly active in rats in so far as the increase in seminal vesicle weight was concerned. No mention was made of its anabolic activity.

Recent publications[7] disclosed the preparation of several 11-oxygenated derivatives of 17-methyltestosterone possessing very marked activity as oral anabolic and androgenic agents. The most active compound in this series, 17-methyl-9α-fluoro-11-oxotestosterone, is reported to possess 22 and 8.5 times the oral anabolic and androgenic activity, respectively, of 17-methyltestosterone.

The 19-nortestosterone derivatives included in this study and their physical constants are recorded in Table I.

TABLE I

17-ALKYL-19-NORTESTOSTERONE DERIVATIVES

	M.p., °C.	$[\alpha]D$ ($CHCl_3$)
19-Nortestosterone	123–124	55°
17-Methyl-19-nortestosterone[6]	156–158	31
17-Ethyl-19-nortestosterone[5]	136–139	25
17-Propyl-19-nortestosterone[8]	122–123	21
17-Butyl-19-nortestosterone[8]	126–127	
17-Octyl-19-nortestosterone[8]	120–122	
17-Vinyl-19-nortestosterone[9]	169–171	25, 36 (C_2H_5OH)
17-Allyl-19-nortestosterone[8]	93–95	
17-Ethynyl-19-nortestosterone[6]	202–204	−22

The anabolic potency of the substances studied was determined by the levator ani method of Eisenberg and Gordan and the androgenic properties were ascertained by the increase in weight of the seminal vesicle and the ventral prostate.[10]

Of the compounds studied, 17-ethyl-19-nortestosterone (I)[8,11] appeared to be the most applicable for clinical use because of its high anabolic po-

(1) A. J. Birch, *J. Chem. Soc.*, 367 (1950); A. J. Birch and S. M. Mukherji, *Nature*, **163**, 766 (1949); *J. Chem. Soc.*, 253 (1949).

(2) A. J. Birch, *Annual Reports on the Progress of Chemistry for 1950*, The Chemical Society, London, 1951, p. 210.

(3) L. G. Hershberger, E. G. Shipley and L. K. Meyer, *Proc. Soc. Exp. Biol. and Med.*, **83**, 175 (1953).

(4) R. O. Stafford, B. J. Bowman and K. J. Olson, *ibid.*, **86**, 322 (1954).

(5) Private communication from our biology staff.

(6) C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **76**, 4092 (1954).

(7) M. E. Herr, J. A. Hogg and R. H. Levin, *ibid.*, **78**, 500 (1956); S. C. Lyster, G. H. Lund and R. O. Stafford, *Endrocrinology*, **58**, 781 (1956).

(8) F. B. Colton, U. S. Patent 2,721,871 (1955).

(9) A. Sandoval, L. Miramontes, G. Rosenkranz, C. Djerassi and F. Sondheimer, THIS JOURNAL, **75**, 4117 (1953); F. B. Colton, U. S. Patents 2,655,518 (1953), 2,704,768 (1955).

(10) F. J. Saunders and V. A. Drill, *Endocrinology*, **58**, 567 (1956); (10a) V. A. Drill and F. J. Saunders, "Hormones and the Aging Process," Academic Press Inc., New York, N. Y., 1956, pp. 99–113.

(11) G. D. Searle and Co. has recently introduced this material under the trade name of Nilevar.