methylene chloride–hexane afforded 3α,9α-oxido-5β-pregnane-20β-ol-11-one (XVIa) (190 mg.), m.p. 203–206°, raised by crystallizations from methylene dichloride–hexane to 208–209°, $[\alpha]D$ +71°; λ_{max}^{KBr} 3650, 1705 and 1000 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.40. Found: C, 75.59; H, 9.50; O, 14.63.

Further elution with benzene–ether (70:30, 1 l.) and one crystallization from acetone–hexane gave 5β-pregnane-3α,20β-diol-11-one 20-acetate (XIVc) (170 mg.), m.p. 191–201°, raised by crystallizations from acetone–hexane to 228–229°, $[\alpha]D$ +58°; λ_{max}^{KBr} 3550, 1730, 1695 and 1235 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64; O, 17.00. Found: C, 73.37; H, 9.48; O, 17.14.

Room temperature acetylation of 3α,9α-oxido-5β-pregnane-20β-ol-11-one (XVIa) with acetic anhydride and pyridine afforded the 20β-acetate XVIb, m.p. 174–176° from aqueous methanol, $[\alpha]D$ +92°; λ_{max}^{KBr} 1725, 1700, 1245 and 1000 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15; O, 17.09. Found: C, 74.05; H, 9.28; O, 16.80.

3α,9α-Oxido-5β-pregnane-11,20-dione (XVIII).—A solution of 3α,9α-oxido-5β-pregnane-20β-ol-11-one (XVIa) (75 mg.) in acetone (5 cc.) at 0° was treated with an excess of 8 *N* chromic acid[7] for 2–3 minutes. Addition of water, isolation with ether and crystallization from aqueous methanol gave 3α,9α-oxido-5β-pregnane-11,20-dione (XVIII) (41 mg.), m.p. 120–122°, raised by two further crystallizations from aqueous methanol to 125–127°, $[\alpha]D$ +164°, λ_{max}^{KBr} 1700 and 995 cm.$^{-1}$; lit.[17] m.p. 126–127°, $[\alpha]D$ +167°.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15; O, 15.53. Found: C, 76.15; H, 8.99; O, 15.37.

Lead Tetraacetate Treatment of 5β-Pregnane-3α,11β,20β-triol (XIIIa).—Lead tetraacetate (20 g.) was added to a suspension of 5β-pregnane-3α,11β,20β-triol (XIIIa) (10 g.) in benzene (300 cc.) and heated under reflux for 18 hr. The reaction mixture was cooled and filtered and the residue was washed well with benzene. The combined benzene solutions were washed with water, dried (Na_2SO_4) and the solvent removed *in vacuo* to afford a residue, fraction A (6.1 g.). The benzene-insoluble solids were dissolved in methanol (75 cc.). Addition of ice-water to this solution and filtration afforded 5β-pregnane-3α,20β-diol-11-one (XIVa) (2.4 g.), m.p. 233–235°, $[\alpha]D$ +36° (EtOH); the m.p. was undepressed upon admixture with an authentic sample and the infrared spectra were identical.

Fraction A was then adsorbed from benzene onto alumina (400 g.). Elution with benzene–ether (70:30, 750 cc.) and one crystallization from methylene dichloride–hexane afforded 3α,9α-oxido-5β-pregnane-20β-ol-11-one (XVIa) (270 mg.), m.p. 203–205°, undepressed on admixture with the sample obtained previously (XIVa→XVIa); the infrared spectra were identical.

Further elution with benzene–ether (50:50, 750 cc.) and one crystallization from methylene dichloride–hexane gave a product (320 mg.), m.p. 167–185°. Further chromatography of this product over alumina furnished 5β-pregnane-3α,20β-diol-11-one 3-acetate (XVII) (200 mg.), m.p. 198–200°, raised by crystallizations from methylene dichloride–hexane to 207–208°, $[\alpha]D$ +67°; λ_{max}^{KBr} 3400, 1730, 1685 and 1245 cm.$^{-1}$; lit.[12] m.p. 205–206°, $[\alpha]D$ +66° (acetone).

Oxidation of XVII with 8 *N* chromic acid at 0° smoothly led to 5β-pregnane-3α-ol-11,20-dione acetate (XIa), m.p. 128–130°, $[\alpha]D$ +133°. The m.p. was undepressed upon admixture with an authentic sample of XIa and the infrared spectra were identical.

5β-Pregnane-20β-ol-3α-tetrahydropyranyl Ether-11-one (XIVd).—*p*-Toluenesulfonic acid monohydrate (600 mg.) was added to a solution of 5β-pregnane-3α-ol-11,20-dione (XIb) (15 g.) in dry benzene (300 cc.) containing dihydropyran (30 cc.). After 20 hours at room temperature the solution was washed with sodium carbonate solution and water. Removal of the solvent after drying (Na_2SO_4) afforded an oil which was adsorbed from benzene–hexane (70:30) onto alumina (400 g.). Elution with benzene–hexane (50:50) afforded 5β-pregnane-3α-tetrahydropyranyl ether 11,20-dione (XIc) (7.6 g.) as an oil which could not be obtained crystalline, $[\alpha]D$ +47°, $\lambda_{max}^{CHCl_3}$ 1710 cm.$^{-1}$.

Sodium borohydride (2.0 g.) was added to a solution of XIc (4.7 g.) in methanol (150 cc.) and kept at 20° for 1 hour. Addition of water and isolation with ethyl acetate afforded a product which was adsorbed from benzene onto alumina (150 g.). Elution with benzene–ether (50:50; 1200 cc.) and one crystallization from hexane afforded 5β-pregnane-20β-ol-3α-tetrahydropyranyl ether-11-one (XIVd) (1.5 g.), m.p. 147–155°, raised by several crystallizations from hexane to 160–162°, $[\alpha]D$ +5°; λ_{max}^{KBr} 3400, 1685 and 1025 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11; O, 15.29. Found: C, 74.38; H, 10.03; O, 15.11.

5β-Pregnane-20β-ol-3α-tetrahydropyranyl Ether-11-one Acetate (XIVe).—Acetic anhydride (0.5 cc.) was added to a solution of the 20β-alcohol XIVd (190 mg.) in pyridine (3.0 cc.). After 18 hours at room temperature addition of ice-water and filtration afforded the acetate XIVe (200 mg.), m.p. 145–150°, raised by crystallizations to 155–157°; λ_{max}^{KBr} 1730, 1700 and 1240 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{44}O_5$: C, 73.00; H, 9.63; O, 20.15. Found: C, 72.81; H, 9.40; O, 19.73.

5β-Pregnane-3α,20β-diol-11-one 20-Acetate (XIVc).—Hydrochloric acid (0.05 cc., 2 *N*) was added to a solution of the tetrahydropyranyl ether (100 mg.) in acetic acid (3.0 cc.). After 5 hours at room temperature, addition of ice-water, isolation of the product with methylene dichloride, followed by one crystallization from acetone–hexane afforded 5β-pregnane-3α,20β-diol-11-one 20-acetate (XIVc) (35 mg.), m.p. 222–226°, raised by one further crystallization from acetone–hexane to 227–229°, $[\alpha]D$ +60°. The m.p. was undepressed with the product isolated from the action of lead tetraacetate on XIVa and the infrared spectra were identical in every respect.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS, THE STATE UNIVERSITY, NEW BRUNSWICK, N. J.]

The Synthesis of Desoxyequilenin. The Stereochemistry of the C/D Ring Junction of Some Steroid Intermediates

BY RODERICK A. BARNES AND RICHARD MILLER[1]

RECEIVED JANUARY 13, 1960

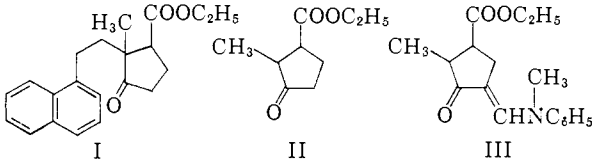
2-Methyl-2-β(1′-naphthyl)-ethylcyclopentanone-3-carboxylic acid has been prepared and cyclized to yield 14,15-dehydroequilenane-17-β-carboxylic acid. The catalytic hydrogenation of the double bond of this latter substance produced *trans-d,l*-equilenane-17-β-carboxylic acid in good yield. The stereochemistry of the reduction product was determined by degradation to *trans-d,l*-3-desoxyequilenin.

A projected plan for the synthesis of 18-oxygenated- and 19-norsteroids involved the preparation of substances having a 14,15-double bond. The purpose of the work reported here was to explore some aspects of the basic synthetic scheme and particularly to investigate the stereochemistry of the products from the reduction of the double bond. The desoxyequilenin series was chosen for

(1) Abstracted from a thesis presented by R. Miller to the Graduate School for the Ph.D. degree, November, 1956.

study since substances from both the *d,l-cis* and *d,l-trans* series have been characterized by Bachmann and Wilds.[2]

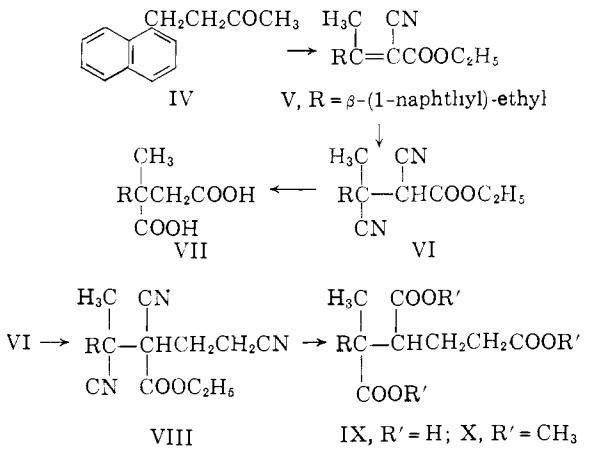
It was initially planned to prepare ketoester I by alkylation of the enolate ion from II or III with β-(1-naphthyl)-ethyl bromide. Unfortunately the major reaction path with both II and III was the



I II III

elimination of hydrogen bromide from β-(1-naphthyl)-ethyl bromide rather than displacement of the bromide ion.

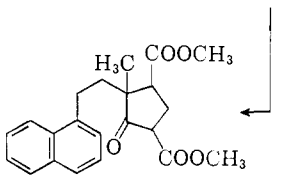
A more lengthy preparation of I started from methyl β-(1-naphthyl)-ethyl ketone (IV). The



IV V, R = β-(1-naphthyl)-ethyl

VII VI

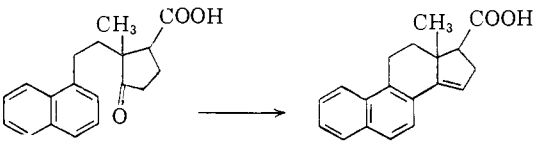
VI → VIII → IX, R′ = H; X, R′ = CH₃



XI

condensation of IV with ethyl cyanoacetate produced V having a broad melting range, apparently a mixture of geometric isomers. Repeated crystallization permitted isolation of a pure form, but this was not necessary, since good yields of VI resulted even from crude V. Compound VI was obtained only as an oil, but its hydrolysis in excellent yield to a crystalline dibasic acid VII demonstrated that it had been formed. Compounds VIII to XI also failed to crystallize and with the exception of X, could not be distilled, without decomposition, even under high vacuum. The failure to obtain these substances in crystalline form may have been due to the presence of mixtures of diastereoisomers. Finally, hydrolysis of XI produced a crystalline acid XII whose properties indicated it to have the desired structure.

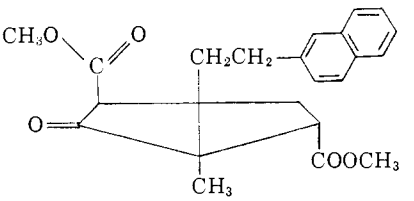
(2) (a) W. E. Bachmann and A. L. Wilds, THIS JOURNAL, **62**, 2084 (1940); and (b) A. L. Wilds, L. W. Beck and T. L. Johnson, *ibid.*, **68**, 2161 (1946).



XII XIII

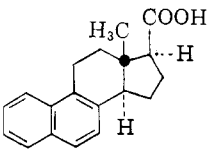
The cyclization of XII occurred more readily than had been anticipated. The first attempts to isolate XII were complicated by the fact that in the hydrochloric-acetic acid mixture, used for the hydrolysis of the ester groups of XI, appreciable conversion to XIII had also occurred.

It was believed likely that in the Dieckmann reaction used for the preparation of XI, equilibration to the most stable isomer would take place. Inspection of models suggests that in isomer XIV with the methyl and adjacent carbethoxyl group on the same side, there would be least interference between the substituent groups on the five-membered ring. The configurational relation of



XIV

the methyl and carboxyl groups should be maintained in compound XIII and should tend to direct the hydrogenation of this substance. The formation of new carbon-hydrogen bonds from the side opposite to the methyl and carboxyl group would yield a saturated acid with the stereochemistry represented by XV. By analogy with



XV

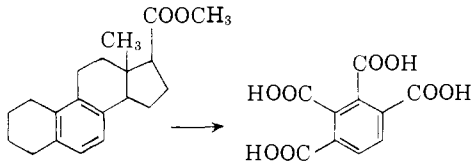
results obtained with a related molecule,[3] a first attempt was made to reduce the methyl ester of acid XIII with Raney nickel catalyst. No dihydro product could be isolated by partial hydrogenation, and if the reaction proceeded to completion, a hexahydro derivative of XIII resulted. From previous work on the reduction of equilenin[4] it seemed most likely that ring A had been reduced to yield XVI. This was confirmed by nitric acid oxidation of XVI to prehnitic acid (XVII).

The reduction of XIII with a palladium catalyst afforded the desired acid XV in good yield. There was no evidence for the formation of an isomer of XV. Although Johnson and co-workers had obtained both isomers in the reduction of 14,15-dehydroequilenin methyl ether,[5] there is con-

(3) S. M. Hirshfield, Ph.D. thesis, Rutgers, The State University, June, 1954.

(4) R. E. Marker and E. Rohrmann, THIS JOURNAL, **61**, 3314 (1939); V. Pralog and J. Führer, *Helv. Chim. Acta*, **28**, 583 (1945).

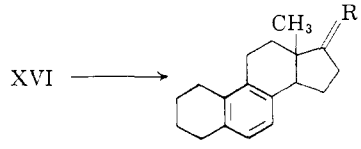
(5) W. S. Johnson, J. W. Petersen and C. D. Gutsche, THIS JOURNAL, **67**, 2278 (1945).



XVI XVII

siderable evidence that a variety of β-orientated substituents at position 17 will direct the hydrogenation so that a *trans* C/D ring junction results.[6]

To prove that XV did, indeed, have the desired stereochemistry it was necessary to convert it to a known substance. The 17-ketone was the most obvious reference compound, but the degradation to this substance proved to be rather difficult. Preliminary experiments were carried out using the more highly saturated ester XVI. The Barbier-Wieland degradation could be carried only as

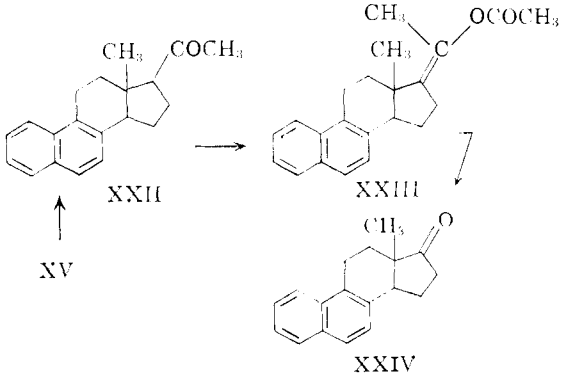


XVIII, R = $=C(C_6H_5)_2$; XX, R = $=CH_2$

XIX, R = $\begin{matrix}-H\\-CH_2OH\end{matrix}$; XXI, R = $=O$

far as olefin XVIII. Ozonolysis of the sterically hindered double bond of XVIII could not be effected without also producing extensive further transformations. The preparation of the less hindered olefin XX proceeded from alcohol XIX *via* the tosylate or iodide. However, the elimination reactions with these latter compounds were complicated and the major products were olefins isomeric with XX. The small amount of XX which was obtained reacted with ozone to yield a few milligrams of ketone XXI having the properties described previously by Bachmann and Morin.[7]

In a more successful degradation, acid XV was transformed first to methyl ketone XXII. The



enol acetate XXIII of this ketone was ozonized to yield *d,l-trans*-desoxyequilenin whose properties agreed with the reported values[2b] and whose infrared spectrum was identical with an authentic sample.[8]

Experimental[9]

Ethyl 2-Methylcyclopentanone-3-carboxylate (II).—The procedure of Haworth and Perkin[10] for the cyclization of ethyl 1,3,4-pentanetricarboxylate was followed (97% yield). Saponification of the cyclization product with hydrochloric acid produced 2-methylcyclopentanone-3-carboxylic acid, m.p. 85–91° (85%). Esterification of this acid with azeotropic removal of water yielded II (94.5%), b.p. 63–64°-(0.08 mm.) (reported[10] 130–135°(20 mm.), $n^{26}D$ 1.4456.

Attempted Alkylation of II.—The potassium enolate of II (prepared from potassium *t*-butoxide) in *t*-butyl alcohol was refluxed for 42 hours, under nitrogen, with one equivalent of β-(1-naphthyl)-ethyl bromide. Processing of the reaction mixture yielded some recovered starting materials, considerable polymerized 1-vinylnaphthalene and a rather small amount of an unidentified oil. Hydrolysis of the oil followed by chromatography on silica gel failed to yield any crystalline fractions; the expected acid XII was later shown to be a crystalline substance.

2-Methyl-5-methylanilinomethylenecyclopentanone-3-carboxylic Acid.—Dry sodium ethoxide, prepared from sodium (24.3 g.), was suspended in benzene (700 ml.) and then ethyl formate (140 ml.) was added. The suspension was stirred in an ice-bath while II (59.8 g.) was added during 90 minutes. The reaction mixture was allowed to stand overnight at room temperature and then decomposed by addition of 10% hydrochloric acid at 0°. The product was extracted with ether, the ether solution was washed with water, dried, and concentrated. The residual hydroxymethylene derivative of II and its derivatives were sensitive to oxidation, as expected. Also the carbethoxyl group was rather sensitive toward hydrolysis. An attempt to separate the hydroxymethylene compound from unreacted II by extraction into cold 2% potassium hydroxide resulted in almost complete hydrolysis of the carbethoxyl group. A sample of this substance, **ethyl 2-methyl-5-hydroxymethylenecyclopentanone-3-carboxylate**, was evaporatively distilled; a center cut distilled at 61°(0.1 mm.), $n^{26}D$ 1.4949. This fraction was believed to be pure, but it was difficult to avoid all air oxidation in handling prior to analysis.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 59.53; H, 7.37.

A solution of this substance (70.3 g.) and N-methylaniline (76.3 ml.) in absolute alcohol (300 ml.) was allowed to stand for a day. Additional N-methylaniline (30 ml.) was added and the reaction mixture allowed to stand for 3 more days. The ethanol and excess N-methylaniline were removed *in vacuo* and the residue evaporatively distilled at 167°(0.1 mm.). Redistillation of a center fraction yielded a sample of III, ethyl 2-methyl-5-methylanilinomethylenecyclopentanone-3-carboxylate, with $n^{26}D$ 1.5977.

Anal. Calcd. for $C_{17}H_{21}O_3$: C, 71.06; H, 7.37. Found: C, 70.11; H, 7.33.

A portion of III was hydrolyzed by heating for 3 minutes on the steam-bath with a solution of potassium hydroxide in ethanol. Acidification of the cold solution produced a yellow solid which could be recrystallized from absolute ethanol, m.p. 201–203.5° dec.

Anal. Calcd. for $C_{15}H_{17}O_3N$: C, 69.48; H, 6.61. Found: C, 69.34; H, 6.69.

This same substance resulted directly from the reaction of N-methylaniline with a sample of the hydroxymethylene derivative of II which had been "purified" by extracting into aqueous base.

(6) (a) P. A. Plattner, L. Ruzicka, H. Heusser and E. Angliker, *Helv. Chim. Acta*, **30**, 395 (1947); D. K. Banerjee, S. Chatterjee, C. N. Pilllai and M. V. Bhatt, THIS JOURNAL, **78**, 3769 (1956); (b) O. R. Rodig, N. A. Nelson, E. M. Gross, M. Harnik and A. L. Wilds, Abstracts 131st Meeting, American Chemical Society, p. 32-O.

(7) W. E. Bachmann and R. D. Morin, THIS JOURNAL, **66**, 553 (1944).

(8) The authors wish to thank Professor A. L. Wilds for his kindness in determining the infrared spectrum of our sample and comparing it with his sample; see ref. 2b.

(9) Microanalyses are by W. Manser, Zurich, Switzerland, and G. Robertson, Florham Park, N. J. Melting points were determined using the Kofler hot-stage. Infrared spectra were determined using the Perkin–Elmer model 21 spectrophotometer. Ultraviolet spectra were determined in alcohol solution using a Cary recording spectrophotometer.

(10) W. N. Haworth and W. H. Perkin, *J. Chem. Soc.*, **93**, 573 (1908).

Attempted Alkylation of III.—The enolate of III was prepared using potassium *t*-butoxide in *t*-butyl alcohol, sodium hydride in xylene and sodamide in benzene. However as with the enolate of II, treatment with β-(1-naphthyl)-ethyl bromide produced, in addition to polymer, only very small amounts of uncharacterizable oils.

Methyl β-(1-Naphthyl)-ethyl Ketone (IV).—Ethyl acetoacetate (314.5 g.) was alkylated with 1-chloromethylnaphthalene (213.5 g.) using the procedure employed by Newman and Bye[11] for an analogous halide. The crude alkylation product was hydrolyzed by stirring with a solution of sodium hydroxide (277 g.) in water (2 liters) at room temperature for 17 hours. Ketone IV was extracted from the hydrolysis solution with ether. The ether solution was washed with water, dried and concentrated. The residue was distilled to yield 183 g. (77%) of IV which boiled mostly at 101°(0.07 mm.). The semicarbazone melted at 175–176° (reported[12] m.p. 176–177°).

Ethyl 2-Cyano-3-methyl-5-(1′-naphthyl)-2-pentenoate (V).—The procedure of Cope[13] was followed using ketone IV (214.7 g.), ethyl cyanoacetate (122.8 g.), glacial acetic acid (49.5 ml.), ammonium acetate (17.2 g.) and benzene (500 ml.). The crude product was heated at 0.3 mm. in a bath at 140° to remove starting materials. The residue was dissolved in ether (650 ml.) and seeded with crystals of a by-product of unknown constitution (from a previous run). The solution was allowed to stand overnight and then filtered to remove 5.3 g. of the by-product which melted at 200–218°. Most of the ether was distilled from the filtrate and the concentrate seeded with crystals of V from a previous run. There was obtained 106 g. (33%) of V which melted at 82–95°. Trituration of the concentrated filtrate with ethanol yielded an additional 100 g. (32%) of product which melted at 79–96°. A pure substance was obtained by recrystallizing twice from ethanol, twice from ether and twice more from ethanol using decolorizing charcoal. The sample of V prepared in this way melted at 99–100°, $\lambda_{max}^{CHCl_3}$ 4.52 (nitrile) and 5.80 μ (ester).

Anal. Calcd. for $C_{19}H_{19}O_2N$: C, 77.79; H, 6.53. Found: C, 77.78; H, 6.58.

3-Methyl-3-carboxyl-5-(1′-naphthyl)-pentanoic Acid (VII).—A suspension of V (105.6 g.) in 50% ethanol was treated with sodium cyanide (35.2 g.). As the solution was rapidly stirred at room temperature, there was spontaneous evolution of heat and compound V dissolved in about 20 minutes to give a clear solution. The reaction mixture was diluted with ice-water (1 liter) and acidified with hydrochloric acid (55 ml., concd.). The product was extracted with hydrochloric acid (55 ml., concd.). The product was extracted with ether, the ether was removed and the residual viscous oil warmed to constant weight *in vacuo*. There was obtained 113.5 g. (98%) of crude VI, **ethyl 2,3-dicyano-3-methyl-5-(1′-naphthyl)-pentanoate**, $\lambda_{max}^{CHCl_3}$ 4.49 (nitrile) and 5.75 μ (ester).

A portion of VI (3.3 g.) was dissolved in warm acetic acid (5 ml.) and hydrobromic acid (5 ml., 48%) was added. The solution was refluxed for 42 hours and the bulk of the solvents were distilled *in vacuo*. The residue was treated with water and the product extracted with ether. The ether layer was extracted five times with 15-ml. portions of sodium carbonate solution (15%). Acidification of the alkaline solution precipitated a gummy material which could be crystallized by trituration with hexane to yield 2.5 g. (95%) of acid VII which melted at 138–141°. The analytical sample prepared by recrystallization from acetone–hexane melted at 140–142.5°.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.28; H, 6.35.

The neutral equivalent for the product, m.p. 138–141°, was 147 (calculated value 143).

Methyl 4,5-Dicarbomethoxyl-5-methyl-7-(1′-naphthyl)-heptanoate (X).—A solution of compound VI (113.5 g.) and freshly distilled acrylonitrile (58 g.) in *t*-butyl alcohol (635 ml.) was treated with a solution of Triton B (15.8 g., 40% aqueous solution) and water (3.2 ml.) in *t*-butyl alcohol (560 ml.). The solution was heated for 40 hours at 50 ± 3°. The reaction mixture was neutralized with 10% hydrochloric acid and the solvent distilled *in vacuo*. The residual oil was dissolved in benzene, the benzene solution washed with water, dried and concentrated to yield 134.8 g. (theory 132.2 g.) of **VIII, 4-carbethoxyl-4,5-dicyano-5-methyl-7-(1′-naphthyl)-heptanonitrile**, as a heavy oil which could not be distilled, even at high vacuum, without decomposition.

The hydrolysis of VIII (36 g.) was carried out exactly as for compound VII. The crude acid **IX, 4,5-dicarboxyl-5-methyl-7-(1′-naphthyl)-heptanoic acid**, was obtained as a pale yellow foam (31.2 g., 90%) when an ether solution was concentrated and the residue warmed *in vacuo* for 36 hours to remove all solvents. This product would not crystallize after chromatography on silica gel or by trituration with a variety of solvents; $\lambda_{max}^{CHCl_3}$ 2.55–3.68 (OH and CH), 5.77–5.88 μ (carboxyl).

A cold solution of acid IX (115.3 g.) in ether (400 ml.) was treated with a cold solution of diazomethane in ether (prepared from 100 g. of nitrosomethylurea). The excess diazomethane was destroyed with a little acetic acid and the solvents were removed. The residual oil was evaporatively distilled in a Hickmann still at 238–240°(0.02 mm.) to yield 105.8 g. (82%) of triester X. A sample was redistilled at 180–181°(0.02 mm.), $\lambda_{max}^{CHCl_3}$ 5.62 and 5.74–5.81 μ (ester).

Anal. Calcd. for $C_{23}H_{26}O_6$: C, 68.98; H, 7.05, sapon. equiv., 133.5, Found: C, 67.69; 68.46; H, 6.86, 6.60, sapon. equiv., 140.

2-Methyl-2-β-(1′-naphthyl)-ethylcyclopentanone-3-carboxylic Acid (XII).—Dry sodium methoxide prepared from sodium (6.7 g.) and methanol was suspended in benzene (200 ml.) and ester X (105.8 g.) in benzene (860 ml.) was added. The reaction mixture was stirred and refluxed for 6 hours in a nitrogen atmosphere. The cold reaction mixture was treated successively with acetic acid (25 ml.), ice-water (400 ml.) and 2 *N* hydrochloric acid (20 ml.). The product was extracted with ether, the ether extract washed with sodium bicarbonate solution and concentrated. The residue was a pale yellow oil (104 g., theory 97.5 g.) which could not be crystallized.

The Dieckmann reaction was also conducted using sodium sand (3.54 g.) in xylene. From X (40.9 g.) there was obtained 39 g. of crude product, about one-third of which was soluble in sodium bicarbonate solution. Although the yield appeared to be lower by this procedure, the subsequent hydrolysis experiments indicated that about the same yield of cyclized ketoester **XI, methyl 2-methyl-2-β-(1′-naphthyl)-ethylcyclopentanone-3,5-dicarboxylate**, resulted from either procedure.

A portion (1.24 g.) of crude XI was refluxed for 3 days with a mixture of hydrochloric acid (2 ml.), acetic acid (5 ml.) and water (18 ml.). The solvents were distilled under reduced pressure and the residue was treated with water and ether. The ether layer was extracted with 5% sodium carbonate solution and the alkaline extract acidified. The crude acid was extracted with ether and the ether solution was dried and concentrated. The residual oil crystallized when triturated with a little ether to yield 267 mg. (26%) of acid XII which melted at 166–171°. From the filtrate a second crop of crystals (264 mg., 26%) could be isolated, m.p. 147–166°. The analytical sample prepared by recrystallization from methanol melted at 167–171°; λ_{max}^{Nujol} 5.75, 5.85 and 6.09 μ.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.01; H, 6.80.

An attempt to hydrolyze crude XI (104 g.) by boiling for 47 hours with hydrochloric acid (115 ml., concd.) and water (1 liter) was only partly successful. A neutral fraction (30 g.), an unknown acid (19 g.) and acid XII (5 g.) were isolated. The unknown acid had a neutral equivalent of *ca.* 350 and melted at 179–182° after recrystallization from methanol. The analysis (C, 70.08; H, 6.19) indicated that it was not an isomer of the acid XII. The neutral fraction was further hydrolyzed with acetic acid and hydrochloric acids to yield a mixture of XII and XIII.

14,15-Dehydroequilenane-17-carboxylic Acid (XIII).—Acid XII was added to a mixture of acetic acid (90 ml.) and hydrochloric acid (110 ml., concd.) and the mixture refluxed for 3 days under nitrogen. The solution was concentrated to a small volume and the crystalline product filtered, washed with water and air-dried. This product, (4.29 g., theory 4.22 g.) was recrystallized from methanol to yield 3.34 g. (80%) of product which melted at 237–

(11) M. S. Newman and T. S. Bye, THIS JOURNAL, **74**, 905 (1952).
(12) F. Mayer and A. Sieglitz, *Ber.*, **55**, 1842 (1922).
(13) A. C. Cope, THIS JOURNAL, **59**, 2327 (1937).

240° dec. The filtrates contained some of ketoacid XII which could be recyclized. The analytical sample melted at 240–241° dec.

Anal. Calcd. for $C_{19}H_{18}O_2$: C, 81.99; H, 6.52. Found: C, 81.82; H, 6.47.

Acid XIII was also obtained directly from crude ester XI (20 g.). Heating for 12 hours with a mixture of acetic acid (598 ml.) and hydrochloric acid (295 ml.) and water (56 ml.) yielded 6.07 g. (37%) of a crystalline product which could be fractionally crystallized from methanol to yield *ca.* 150 mg. of pure XIII and 5.5 g. of acid XII.

Methyl 14,15-Dehydroequilenane-17-carboxylate.—A suspension of acid XIII (4.3 g.) in methanol (80 ml.) and ether (30 ml.) was treated with diazomethane (from 14 g. of nitrosomethylurea). The solution was concentrated and the ester recrystallized from methanol to yield 4.42 g. (98%) of ester which melted at 163–166°.

Anal. Calcd. for $C_{20}H_{20}O_2$: C, 82.16; H, 6.90. Found: C, 82.15; H, 6.93.

Equilenane-17-carboxylic Acid (XV).—Acid XIII was dissolved in acetic acid (150 ml.) and the solution stirred with palladium-on-charcoal (1 g., 10%) and hydrogen at atmospheric pressure and room temperature. The calculated volume of hydrogen was absorbed in 40 minutes. The catalyst was filtered and the solution concentrated under reduced pressure. There was obtained 880 mg. (88%) of product which melted at 235–237°. The analytical sample, prepared by recrystallization from methanol, melted at 236–238°.

Anal. Calcd. for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found: C, 80.90, 80.43; H, 7.53, 7.19.

The methyl ester of acid XV was prepared by treating a portion (513 mg.) suspended in methanol (6 ml.) with diazomethane in ether (from 2 g. of nitrosomethylurea). There was obtained 508 mg. (93%) of the methyl ester, m.p. 140–145°. The analytical sample melted at 143–145°.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.90; H, 7.64.

Methyl 1,2,3,4-Tetrahydroequilenane-17-carboxylate (XVI). A.—A solution of the methyl ester of acid XIII (1.5 g.) in methanol was shaken with hydrogen (45 p.s.i.) at 54° for 21 hours in the presence of Raney nickel catalyst (*ca.* 15 g.). The solution was filtered and concentrated to a small volume. There was obtained 1.32 g. (87%) of ester XVI which melted at 113–115°.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.28; H, 8.80.

B.—The methyl ester of acid XV (150 mg.) was hydrogenated as described in part A to yield 127 mg. (83%) of ester XVI which melted at 113–114.5°. The melting point of a mixture with the sample in part A was also 113–115°.

The hydrolysis of XVI was accomplished by boiling with glacial acetic acid (5 ml.) and hydrochloric acid (1 ml., concd.) for a few minutes and then adding water (1 ml.) and boiling for an hour. The mixture was chilled to yield 270 mg. (100%) of **1,2,3,4-tetrahydroqeuilenane-17-carboxylic acid** melting at 210–215° dec. A sample, recrystallized from methanol, melted at 216–218° dec. and even after drying at 100° appeared to retain methanol.

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Calcd. for $C_{19}H_{24}O_2 \cdot 1/4CH_3OH$: C, 79.07; H, 8.62. Found: C, 79.21; H, 8.97.

Basic hydrolysis produced this acid in less pure form, m.p. 202–209°, presumably because of epimerization during the reaction.

Nitric Acid Oxidation of XVI.—A sample of ester XVI (75 mg.) was sealed in a Carius tube with nitric acid (1 ml., concd.) and water (2 ml.). The mixture was heated at 190° for 12 hours. The contents of the tube were evaporated to dryness, the residue was washed with fuming nitric acid and dried. The acid was identified as prehnitic acid by conversion to its methyl ester with diazomethane. The crude ester was recrystallized from methanol to yield needles which melted at 130–130.5°, alone or when mixed with an authentic sample.[15]

(14) Kindly furnished by Professor L. I. Smith; see L. I. Smith and E. J. Carlson, THIS JOURNAL, **61**, 288 (1939).

Diphenyl-1,2,3,4-tetrahydro-17-equilenylcarbinol.—A solution of ester XVI (800 mg.) in ether (12 ml.) was added to phenylmagnesium bromide prepared from magnesium (1.06 g.), bromobenzene (6.86 g.) and ether (35 ml.). The reaction mixture was refluxed for 3 hours and then allowed to stand overnight. The ether was distilled, benzene was added and the refluxing was continued for 10 hours. The reaction mixture was treated with dilute hydrochloric acid and the product removed by ether extraction. Evaporation of the ether and crystallization of the residue from ethanol furnished 790 mg. (70%) of carbinol which melted at 216–218°.

Anal. Calcd. for $C_{31}H_{34}O$: C, 88.10; H, 8.11. Found: C, 88.25; H, 8.05.

17-Diphenylmethylene-1,2,3,4-tetrahydroequilenane (XVIII).—The diphenylcarbinol from the previous experiment was heated on the steam-bath for 3 hours with a mixture of acetic anhydride (60 ml.) and acetyl chloride (30 ml.). The solvents were removed *in vacuo* and the product recrystallized from ethanol with the aid of decolorizing charcoal. There was obtained 447 mg. (77%) of olefin XVIII which melted at 149–153°. The analytical sample melted at 150–161°.

Anal. Calcd. for $C_{31}H_{32}$: C, 92.03; H, 7.97. Found: C, 91.96; H, 8.03.

Ozonolysis of XVIII yielded some benzophenone but none of the desired ketone.

The reaction of olefin XVIII with formic acid and hydrogen peroxide yielded a new substance, m.p. 205–211°. This product had no absorption bands in the hydroxyl region and is believed to be mainly the epoxide of XVIII although it was not obtained in pure form.

Anal. Calcd. for $C_{31}H_{32}O$: C, 88.53; H, 7.67. Found: C, 87.07; H, 7.78.

Tosylate of 17-Hydroxymethyl-1,2,3,4-tetrahydroequilenane.—A solution of ester XVI (550 mg.) was added during 10 minutes to a suspension of lithium aluminum hydride (300 mg.) in ether (35 ml.). The reaction mixture was stirred and refluxed for 6 hours. The excess hydride was destroyed by adding ethyl acetate and saturated sodium sulfate solution. The ether layer was separated and concentrated to yield a colorless oil. This carbinol, **17-hydroxymethyl-1,2,3,4-tetrahydroequilenane (XIX)**, failed to crystallize even after purification by chromatography on alumina; yield 495 mg. (99%), $\lambda_{max}^{CHCl_3}$ 2.77 and 2.93 μ (hydroxyl).

Carbinol XIX (485 mg.) was dissolved in dry pyridine (5 ml.) and treated with a solution of *p*-toluenesulfonyl chloride (390 mg.) in dry pyridine (5 ml.). The solution was allowed to stand for 40 hours. Ice-water was added and the product extracted with ethyl acetate. The extracts were washed with 2 *N* hydrochloric acid, sodium bicarbonate solution and water. When the solution was concentrated to a small volume there was obtained 549 mg. (72%) of tosylate, m.p. 156–159°. Recrystallization from ethyl acetate did not change the melting point.

Anal. Calcd. for $C_{26}H_{32}O_3S$: C, 73.55; H, 7.59. Found: C, 73.56; H, 7.54.

17-Methylene-1,2,3,4-tetrahydroequilenane (XX).—The tosylate (300 mg.) from the previous experiment was dissolved in 2,4,6-collidine (15 ml.) and the solution refluxed for 3 days under nitrogen. The cold reaction mixture was treated with 2 *N* hydrochloric acid and the product extracted with ether. The ether extract was washed with water and sodium bicarbonate, dried and concentrated. The residual oil (99 mg.) was dissolved in petroleum ether and passed through a column of alumina to yield 65 mg. (36%) of crystalline material, m.p. 68–76°. The analytical sample was recrystallized from ethanol, m.p. 88–89.5°, $\lambda_{max}^{CHCl_3}$ 6.02 and 11.33 μ (methylene).

Anal. Calcd. for $C_{19}H_{24}$: C, 90.41; H, 9.59. Found: C, 90.27; H, 9.56.

1,2,3,4-Tetrahydro-17-equilenone (XXI).—Olefin XX (17 mg.) was dissolved in methylene chloride (6 ml.) and pyridine (2 drops) was added. Ozone (1 millimole/minute was passed into the solution at −78° for 1 minute. Zinc dust (100 mg.) and acetic acid (6 ml.) were added and the mixture allowed to come to room temperature. The solution was filtered, ether and water added, and the ether layer was evaporated. The residue was dissolved in 5% benzene in hexane and adsorbed on neutral alumina. A crystalline

fraction with m.p. 114–116° (reported[7] 114–115°) was eluted with benzene. This substance had a strong adsorption band at 5.75 μ. The semicarbazone melted at 273–274° (reported[7] 274–275°).

1,2,3,4-Tetrahydro-17-equilenyl Methyl Ketone.—Acid XVI (879 mg.) was converted to the acid chloride by refluxing with thionyl chloride (18 ml.) for 90 minutes and then removing the excess reagent *in vacuo*. The acid chloride was purified by sublimation at 133°(0.01 mm.), m.p. 120–131°. This compound (858 mg.) was added to a solution of dimethylcadmium in benzene prepared from cadmium chloride (526 mg.), magnesium (140 mg.) and methyl iodide (1.15 g.).[15] The reaction mixture was refluxed for 2.25 hours and then ice, dilute hydrochloric acid and ether were added. The ether layer was washed with water and sodium bicarbonate solution and then dried and concentrated to yield 926 mg. of crude product. This material was chromatographed on a column of Florisil (30 g.); elution with benzene–petroleum ether (1:2) removed six semi-solid fractions containing the desired ketone (773 mg.). Recrystallization from methanol yielded 424 mg. (53%) of product which melted at 110–115° and 160 mg. of less pure material, m.p. 85–110°. The analytical sample melted at 116.5–118°.

Anal. Calcd. for $C_{20}H_{26}O$: C, 85.06; H, 9.28. Found: C, 84.76; H, 9.12.

17-Equilenyl Methyl Ketone (XXII).—Acid XV (950 mg.) was converted to the acid chloride and this crude product allowed to react with dimethylcadmium (from 642 mg. of cadmium chloride) exactly as with the tetrahydro derivative of XXII. The crude product (1.246 g.) was chromatographed on Florisil (40 g.) to yield 490 mg. (52%) of XXII which melted at 160–166°. Recrystallization from methanol afforded a product (345 mg.) of analytical purity, m.p. 162–165°.

(15) J. Cason, *Chem. Revs.*, **40**, 15 (1947).

Anal. Calcd. for $C_{20}H_{22}O$: C, 86.29; H, 7.97. Found: C, 85.94; H, 7.99.

***d,l-trans*-3-Desoxyequilenin (XXIV).**—A solution of ketone XXII (345 mg.) in acetic anhydride (32 ml.) containing *p*-toluenesulfonic acid (80 mg.) was slowly distilled during 5.3 hours. The residual solution was concentrated *in vacuo* and then ice and sodium carbonate solution were added. The product was extracted with ether, the extract was dried and concentrated. The dark residue was dissolved in petroleum ether and passed through a column of alumina (4 g.) to yield 270 mg. (68%) of semi-solid enol acetate XXIII. Attempts to recrystallize a portion (29 mg.) of this substance from petroleum ether were not successful.

The enol acetate (240 mg.) was dissolved in ethyl acetate (100 ml.) and methanol (100 ml.) and cooled to −78°. A solution of ozone (1 millimole/min.) was passed through the solution for 1.5 minutes. The cold solution was shaken with hydrogen in the presence of pre-reduced palladium-on-calcium carbonate catalyst (1.1 g.) for 18 minutes. The solution was filtered and concentrated and the residue (245 mg.) was chromatographed on alumina. A crystalline fraction (41 mg., 22%) was eluted with 2% chloroform in benzene. This material melted at 170–177° but recrystallization from methanol–acetone furnished nearly pure XXIV (26 mg., 14%), m.p. 189–191.5° (evacuated capillary). Sublimation and an additional recrystallization from ethanol raised the melting point (190–191.5°) only slightly. The infrared spectrum was identical with that of an authentic sample.[8]

The semicarbazone melted at 256–257.5° (dec., cap.) after recrystallization from ethanol (reported[2b] 256.5–257.5°). The trinitrobenzene adduct, prepared in ethanol, melted at 153–154° (cap.) (reported[2b] 153–154°).

(16) W. E. Bachmann and A. S. Dreiding, THIS JOURNAL, **72**, 1323 (1950).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CLARK UNIVERSITY, WORCESTER, MASSS., FROM THE POSTGRADUATE MEDICAL SCHOOL OF LONDON, LONDON, ENG., AND FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY, SHREWSBURY, MASS.]

D-Homosteroids. IV.[1] 17β,17aβ-Dimethyl-17α-17aα-dihydroxy- and 17,17-Dimethyl-17a-keto-D-homosteroids[2]

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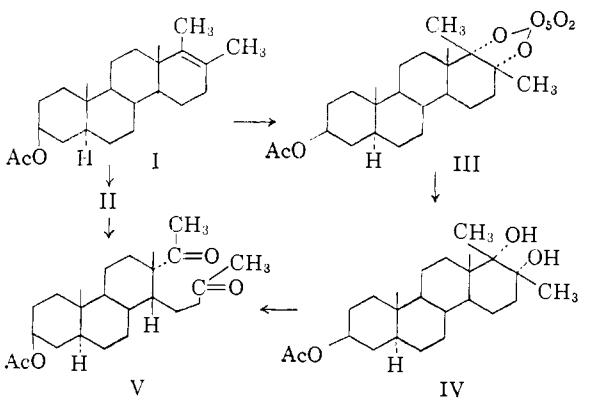
RECEIVED MARCH 1, 1960

Hydroxylation of 17,17a-dimethyl-D-homoandrost-17(17a)-en-3β-ol acetate with osmium tetroxide produced 17β,17aβ-dimethyl-D-homoandrostane-3β,17α,17aα-triol 3β-acetate. Chromic acid oxidation of this glycol produced 3β-acetoxy-17,17a-dimethyl-17,17a-secohomoandrostane-17,17a-dione. The glycol also underwent a pinacolic rearrangement to 3β-acetoxy-17,17-dimethyl-D-homoandrostan-17-one which is quite novel in that it required a boat conformation for ring D in the transition state. To explain the course of this rearrangement, mechanistic arguments are presented and supported by optical rotatory dispersion findings which indicate that ring D in the product also does not possess an ideal chair conformation.

It has been shown in a previous paper[1] that 17,-17a-dimethyl-D-homoandrost-17(17a)-en-3β-ol acetate (I) gave an ozonolysis product which was tentatively assigned the structure 3β-acetoxy-16-acetyl-17-methylandrostane-17-hydroperoxide (II). Compound II decomposed on heating to 3β-acetoxy-17,-17a-dimethyl-17,17a-secohomoandrostane-17,17a-dione (V).

It has now been found that treatment of I with osmium tetroxide in dioxane gave the crystalline osmic ester III of the 17α,17aα-glycol, which was



decomposed by hydrogen sulfide to 17β,17aβ-dimethyl-D-homoandrostane-3β,17α,17aα-triol 3β-

(1) Paper III, Milan Uskoković, Marcel Gut and R. I. Dorfman, THIS JOURNAL, **82**, 3668 (1960).

(2) Taken in part from a dissertation by Milan Uskoković in partial fulfillment of the requirements for the Ph.D. degree in Organic Chemistry, Clark University. Presented, in part, before the Division of Organic Chemistry, 136th National A.C.S. Meeting, Atlantic City, N. J., Sept., 1959, p. 82P. This investigation was supported, in part, by grants PSH-C-321 and PHS-CY-2193.