19-Norsteroids of Unnatural Configuration from Ergosterol

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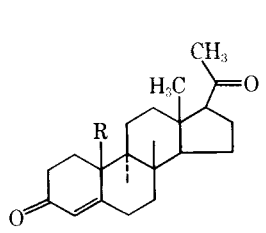
Abstract □ A new method for the preparation of a 19-norsteroid of unnatural configuration from ergosterol has been described. This method led to the preparation of 5α,8α,9α,10α-19-norpregnan-3,20-dione which possesses unnatural configuration at positions 8 and 10. The following reaction sequence was utilized to prepare this steroid. Ergosterol was photo-oxidized to give bisergostatrienol that was pyrolyzed to yield neoergosterol whose side chain was cleaved by ozonolysis to yield 3β-hydroxy-19-norpregna-5,7,9(10)-20α-aldehyde. This aldehyde, for the first time obtained in a crystalline state, was degraded *via* ozonolysis of the 3β-hydroxy-20-morpholino-methylene-19-norpregna-5,7,9(10)-triene derivative to give 3β-hydroxy-19-norpregna-5,7,9(10)-triene-20-one. The latter was reduced to the corresponding diol with Ru/carbon, and its Ring B in turn successfully hydrogenated in cyclohexane with Rh/alumina as the catalyst. The diol was oxidized to the diketone with the Jones reagent. Although some of the above transformations previously have been recorded, this report describes marked improvements in the techniques and yields of most of the intermediates.

Keyphrases □ 19-Norsteroids, unnatural configuration—synthesis □ Ergosterol—19-norsteroid synthesis □ IR spectrophotometry—structure □ NMR spectroscopy—identity □ Polarimetry—identity □ Optical rotatory dispersion—identity

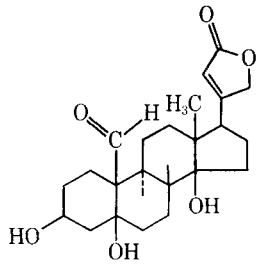
It is well established that progesterone (I), the naturally occurring progestin, possesses a wide range of biological activities together with other metabolic effects when administered parenterally (1). *Via* the oral route, however, it is essentially inactive. Ehrenstein's multistep transformation of strophanthidin (II) (2) to yield 14β,17α-19-norprogesterone (III) gave an opportunity to study the biological activity of a 19-norsteroid (3). It also gave an opportunity to study structure–activity relationships in the progestins that had certain unnatural configurations. In the case of progesterone (I), it has been shown that inversion of configuration at C-17 (from β to α), or at C-14 (from α to β), or at both centers destroys the biological activity, while inverting the configuration at C-8 (from β to α) only reduces it (4). However, activity is retained by inversion of the configuration at C-10 to 10α-progesterone;[1] also, double inversion at both C-9 and C-10 gives retroprogesterone (9β,10α-progesterone) whose progestational activities are more potent than progesterone (5).

In the case of 19-norprogesterone (IV), which is orally active, inversion at either C-17, C-14, or C-8 provides progestational agents of high order of activity (2,4,6).

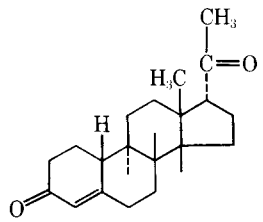
It is evident that progestational activity has been retained in progestins that have an unnatural configuration at C-8 or C-10. Also, loss of the C-19 methyl group exerts a favorable biological effect which is great enough to overcome the unfavorable changes in 14β,17α-progesterone (inactive). Thus, 14β,17α-19-norprogesterone (III) is 8 times as active as progesterone (I) (7). Therefore, the preparation and testing of progestins and 19-norprogestins that have other multiple unnatural configurational centers are of considerable interest. One of these is 8α,10α-19-norprogesterone (V).



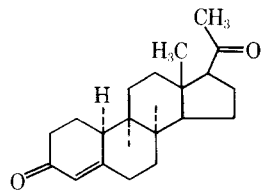
I, R = CH_3
IV, R = H



II



III



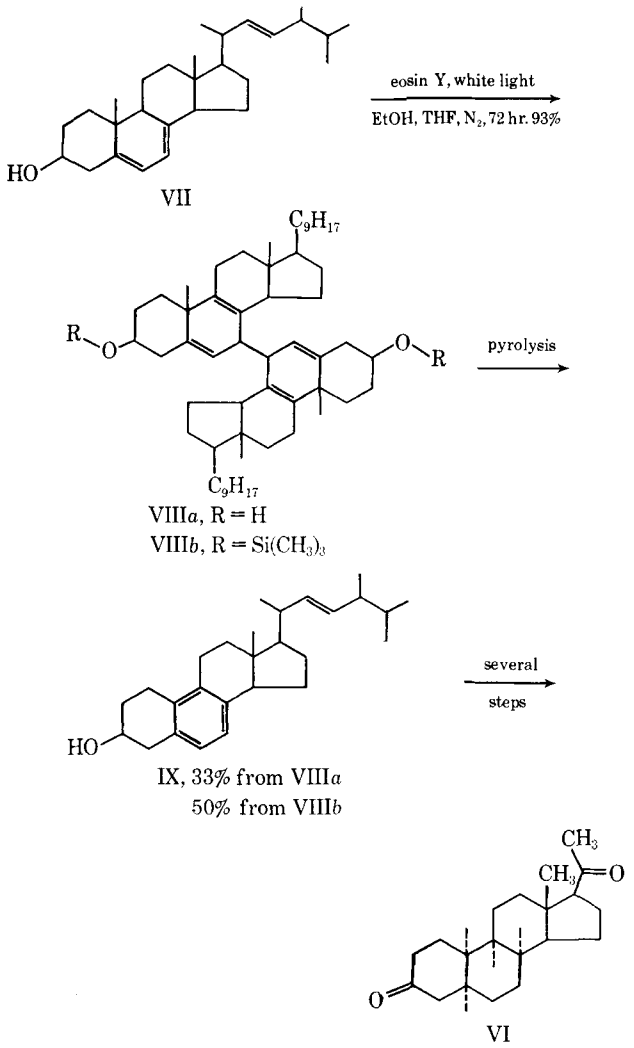
V

A key intermediate for the preparation of this isomer of 19-norprogesterone is the 5α,8α,9α,10α-19-norpregnan-3,20-dione (VI). This article describes the transformation of ergosterol (VII), *via* neoergosterol (IX)—a Ring B aromatic sterol (8), to the key intermediate (VI) possessing the unnatural configuration at C-8 and C-10[2] (Scheme I).

Ergosterol (VII) was chosen as the most suitable starting sterol because the presence of a double bond in the side chain would permit its degradation by suitable techniques to the C-17 methyl ketone found in the pregnane series. Also the presence of the diene system in Ring B enables one to prepare 19-nor Ring B aromatic steroids *via* a previously known method (8). This route of partial synthesis was preferred over a totally synthetic one because, generally, the former would lead to a pure *d*-enantiomer which is twice as active biologically as the racemic (*dl*-) form expected from the latter (9).

[1] Cited as footnote 5 in *J. Amer. Chem. Soc.*, **88**, 4538(1966) by M. Uskokovic *et al.* that in Belgian Patent 634,693 (1964), Ciba, 10α-progesterone was reported to be a progestational agent.

[2] The transformation of 5α,8α,9α,10α-19-norpregnan-3,20-dione (VI) to 8α,10α-19-norprogesterone (V), with the biological results, will be the subject of a forthcoming communication.



Scheme I

DISCUSSION

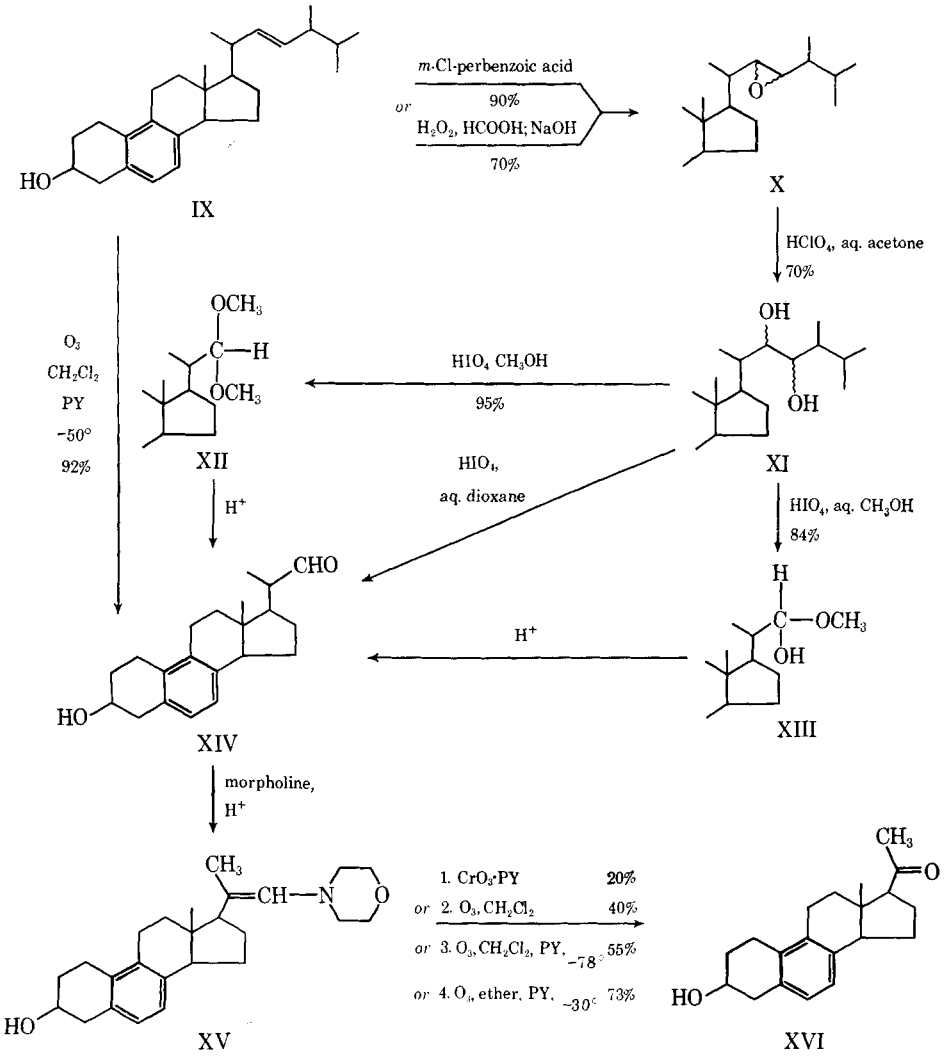
Preparation of Neoergosterol—Ergosterol (VII) (Scheme I) was photo-oxidized with white light in the presence of eosin Y as a sensitizer by a modification of the method of Mosettig and Scheer (8). The time of exposure to the light was increased from 48 to 72 hr., and also a more diluted solution was used to effect better exposure of ergosterol and eosin to the light. This was necessary because as bisergostatrienol (VIII*a*) was formed, it produced a dense white flocculent precipitate. In this way, bisergostatrienol (VIII*a*) was obtained in an average yield of 90–96%. Decomposing bisergostatrienol by refluxing in diethylene glycol monoethyl ether (Carbitol) afforded neoergosterol (IX) in 33% yield. Realizing that such a low yield for the second step in the synthesis might mitigate its practical aspects, it was decided to investigate possible variations in this step to increase the yield of neoergosterol. It was reported that pyrolysis of the acetates of these biscompounds affords the Ring B aromatic sterol acetates in 50% yield (8). However, the preparation of the acetate of bisergostatrienol requires large volumes of pyridine (1/180) and a reaction period of 1 week (10), which gave 80% yield. Because protection of the alcohol group had a certain advantage in the pyrolysis step, another method to protect this group, such as the trimethylsilylation method, was sought. Bisergostatrienol (VIII*a*) was silylated with bis-(trimethylsilyl)-acetamide (11) by refluxing in benzene under anhydrous conditions. The corresponding bis-(trimethylsilyl)-ether derivative (VIII*b*) was obtained in 95% yield. Decomposition of this silyl ether derivative by refluxing in diethylene glycol diethyl ether (Diethyl Carbitol) and by treating the reaction mixture with water and a small amount of *p*-toluenesulfonic acid, to cleave the silyl ether, afforded neoergosterol (IX) in 50% yield.

Degradation of the Side Chain of Neoergosterol—Prior to these studies, neoergosterol (IX) was subjected to ozonolysis conditions in carbon tetrachloride, or to the action of osmium tetroxide followed by periodate cleavage in methanol and acid hydrolysis of the resulting acetal (12). The aldehyde (XIV) obtained in both cases was an oil characterized as the 2,4-dinitrophenylhydrazone. Other investigators (13) ozonized neoergosterol in a mixture of chloroform and acetic acid and purified the crude product by separation of the aldehyde (XIV) with sodium bisulfite. However, no physical data for this aldehyde were reported. Because both ozone and osmium tetroxide cleavage methods did not lead to the separation of a characterizable aldehyde, a different method was sought. Neoergosterol (IX) (Scheme II) was treated with *m*-chloroperbenzoic acid in a mixture of chloroform and benzene at room temperature. The epoxides (X) (mixture of two possible isomers) were obtained by direct crystallization in 90% yield. Opening of the epoxide was accomplished by perchloric acid at the reflux temperature of aqueous acetone. The triols (XI) (two erythro isomers) were obtained in 70% yield. Fieser (14) reacted cholesterol with formic acid and hydrogen peroxide where 3β,5α,6β-cholestatriol was obtained in 91% yield. This method was applied on neoergosterol hoping to obtain the triol (XI) in an overall yield higher than in the route *via* epoxide formation and perchloric acid cleavage. However, the epoxide (X) was obtained instead, in about 70% yield. Furthermore, the epoxide (X) proved very resistant to cleavage with hot formic acid. Cleavage of the triol (XI) with periodic acid (15) in methanol afforded the dimethyl acetal (XII) in 95% yield, identical with that previously prepared (12). This indicated that the erythro diol structure underwent the periodate cleavage as readily as the *threo* isomer. Cleavage with periodic acid in aqueous methanol gave the hemiacetal (XIII) as a crystalline compound in high yields. A similar hemiacetal of a C-22 steroidal aldehyde has been reported to be formed under comparable conditions (16). Acetic acid hydrolysis of either the acetal (XII) or the hemiacetal (XIII) in aqueous dioxane gave the aldehyde (XIV) but as a semisolid material. All attempts to induce it to crystallize were unsuccessful; however, it exhibited one spot on TLC using different solvent systems. It showed the characteristic bands for aldehydes in the infrared and gave the reported (12) 2,4-dinitrophenylhydrazone. Cleavage of the triol (XI) with periodic acid in aqueous dioxane gave the aldehyde (XIV), again as an oil possessing the same properties as the one prepared by hydrolysis of the acetals.

These unsuccessful trials in obtaining the aldehyde (XIV) in a pure form prompted a reinvestigation of the ozonolysis of neoergosterol (IX). Slomp (17) has found that methylene chloride is a superior solvent for ozonolysis studies, and that the presence of pyridine, on a mole for mole basis, favors the selective ozonolysis of isolated double bonds over the conjugated ones. It also was reported (18) that a 2% KI solution could be used to determine accurately the cessation of the consumption of ozone by the double bond of isosafrol. A distinct yellow color appears in the KI solution after the reaction of ozone with the double bond has occurred and before ozone attacks the benzene ring. These conditions were applied to the ozonolysis of neoergosterol (IX) which was conducted in methylene chloride at −50° using one equivalent of pyridine. The pure crystalline aldehyde (XIV) was isolated in 92% yield. It was found that both the rate of passing ozone through the reaction and the rate of stirring affect the detection of a correct endpoint in the KI solution. Details are included in the experimental part.

Treatment of the aldehyde (XIV) with morpholine in the presence of a catalytic amount of *p*-toluenesulfonic acid at the reflux temperature of benzene afforded the enamine (XV). Molecular sieve also was used to absorb the water formed during the reaction.

Oxidation of the enamine (XV) with chromic acid in pyridine by the method of Elks (13) afforded, after chromatographic purification and Girard's separation, the C-20 keto compound (XVI) in 20% yield. Such a low yield, together with the successful result of the ozonolysis of neoergosterol (IX), prompted an investigation of the ozonolysis of this enamine. Ozonolysis of the enamine (XV) in methylene chloride at −78° afforded the ketone (XVI), after Girard's separation, in about 40% yield. When pyridine was present, on a mole for mole basis, the ketone (XVI) was obtained in 55% yield. The uptake of ozone was only half of that when pyridine was absent. Greenwood and Rubinstein (19) have found that ether had



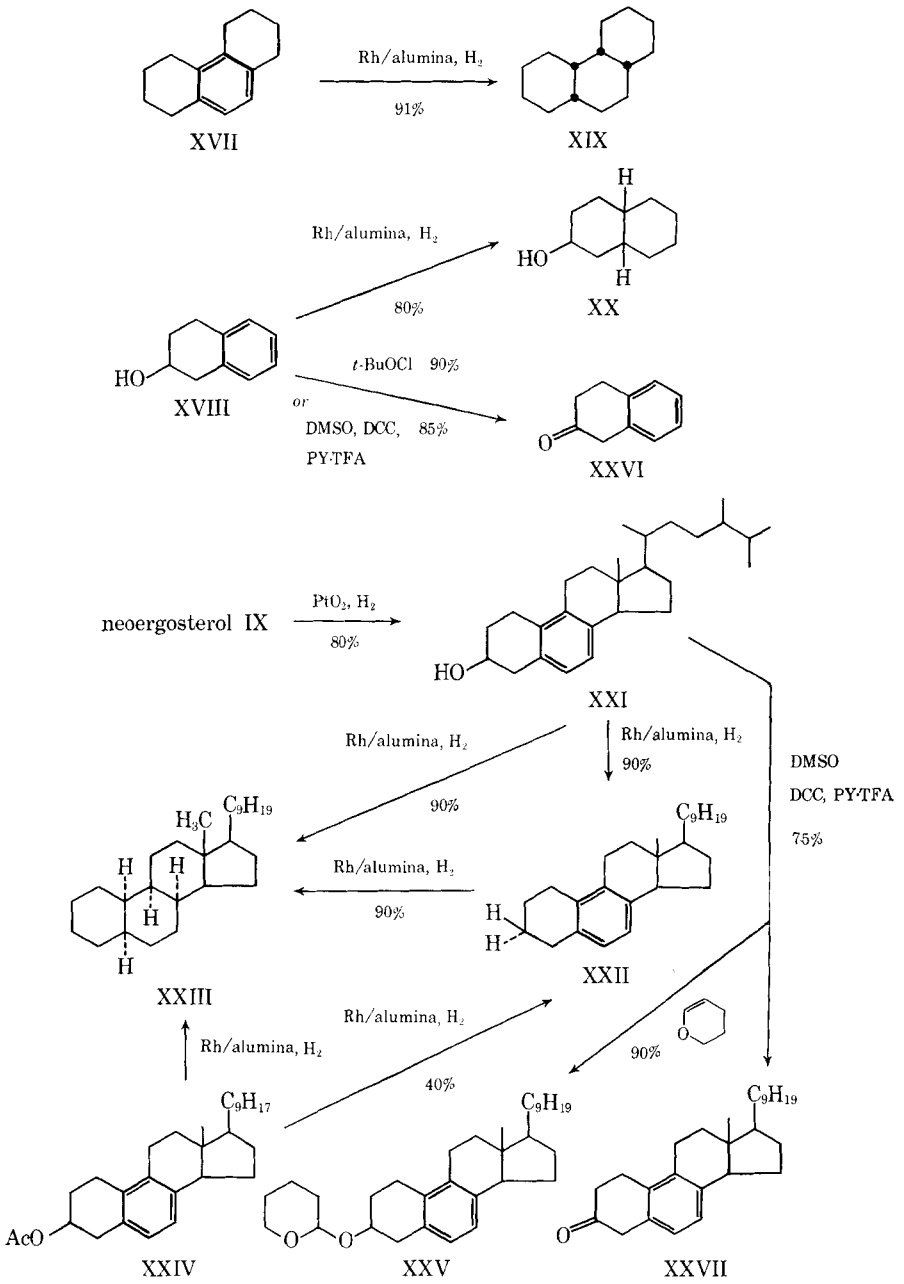
Scheme II

some advantages over methylene chloride in increasing the yields of aldehydes and ozonides, while minimizing the formation of other side reactions, during ozonolysis of certain alkenes. Also, raising the temperature of the reaction had a similar effect. Therefore, the enamine (XV) was ozonized in ether at $-30°$ in the presence of 1 mole of pyridine. The ketone (XVI) was obtained in 73% yield after the usual Girard's separation process.

Hydrogenation Studies—For the conversion of the ketone (XVI) to the key intermediate 5α,8α,9α,10α-19-norpregnan-3,20-dione (VI), the aromatic Ring B must be reduced by suitable methods. The assignment of the α-configuration at positions 5, 8, 9, and 10 as a result of catalytic reduction methods arises from the fact that the β-side of the molecule of the Ring B aromatic steroids is considerably hindered by the C-18 angular methyl group. This will require that the catalyst approaches the molecule from the less hindered side, the α-side. This is further supported by the report of Farkas and Rapala (20) who found that hydrogenation of equilenin and neoergosterol over ruthenium afforded 40% yield of 5α,8α,9α,10α-estrane-3β,17β-diol and 19-nor-24-methyl-5α,8α,9α,10α-cholestan-3β-ol in 10% yield, respectively. This denotes that such hydrogenations are from the α-side.

Two model compounds (Scheme III), 1,2,3,4,5,6,7,8-octahydrophenanthrene (XVII) and 1,2,3,4-tetrahydro-β-naphthol (XVIII), were selected for catalytic hydrogenation studies. Both are related in structure to the ketone (XVI) in that the former possesses the carbon skeleton of Rings A, B, and C and the latter contains Rings A and B. It is reasonable to assume that conditions needed to hydrogenate these two compounds should be of value in designing experiments to reduce dihydroneoergosterol (XXI) and then the ketone (XVI) with a minimum of undesirable side reactions. Hydrogenation of the octahydrophenanthrene (XVII) in ethanol containing 1% acetic acid over Rh/alumina at room temperature and 60 p.s.i. proceeded smoothly to provide the *cis*-syn-*cis*-perhydrophenanthrene (XIX) in excellent yields. The reduction of this compound was previously reported to occur only at 240° and 200 atmospheric pressures over Raney Ni (21). Reduction of 1,2,3,4-tetrahydro-β-naphthol (XVIII) in the same solvent system and under the same conditions afforded *cis,cis*-2-decalol in about 80% yield. Dihydroneoergosterol (XXI) was obtained in 80% yield by hydrogenating neoergosterol (IX) over Adam's catalyst. When dihydroneoergosterol (XXI) was subjected to the hydrogenation conditions used for the octahydrophenanthrene (XVII), the hydrocarbon (XXII) was obtained in about 90% yield, indicating complete hydrogenolysis of the hydroxyl group. Even when a hydrogen pressure of 250 p.s.i. was applied, reduction of this hydrocarbon went very slowly. However, when the amount of catalyst was increased to 10 times that needed to reduce an equimolar amount of octahydrophenanthrene (XVII), reduction went at the usual rate at room temperature and 60 p.s.i. The hydrocarbon (XXIII) was obtained in about 90% yield. The successful hydrogenation of the aromatic B Ring without hydrogenolysis of the hydroxyl group at C-3 is of prime importance to prepare ultimately the key intermediate (VI). Different forms of the oxygen function were prepared in order to prevent hydrogenolysis during the reduction reaction. Hydrogenation of neoergosteryl acetate (XXIV) afforded, as a final product, the hydrocarbon (XXIII), with the aromatic compound (XXII) as the intermediate product of hydrogenation.

Dihydroneoergosterol (XXI) was treated with dihydropyran according to the method of Petersen and Gisvold (22) where the tetrahydropyranyl ether (XXV) was obtained. Hydrogenation of

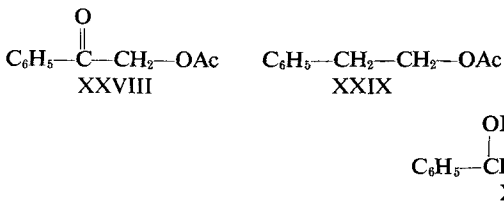


Scheme III

this derivative did not proceed under the previously employed conditions. Even when the amount of catalyst was increased to twice that needed to reduce neoergosteryl acetate and the reaction mixture shaken for 2 days, the tetrahydropyranyl ether derivative (XXV) was recovered unchanged. Because the effectiveness of rhodium in hydrogenating ketones is not conclusive (23), it was thought that hydrogenating dihydroneoergosterone (XXVII) might proceed by reducing the aromatic ring with the preservation of the oxygen function at C-3. To prepare dihydroneoergosterone (XXVII) with a minimum of by-products, preliminary studies were performed on 1,2,3,4-tetrahydro-β-naphthol (XVIII). Oxidation with *t*-butyl hypochlorite (24) afforded the ketone (XXVI) in 90% yield. Oxidation with dimethyl sulfoxide by the method of Pfitzner and Moffatt (25) afforded the ketone (XXVI) in 85% yield. The DMSO method proved more fruitful than *tert*-butyl hypochlorite in oxidizing dihydroneoergosterol, and the ketone (XXVII) was obtained, after purification through Girard's separation, in 75% yield. Hydrogenation of this ketone at room temperature and under ordinary pressures over Rh/alumina proved very difficult, and practically no noticeable absorption of hydrogen occurred during a period of 32 hr. The ketone was recovered from the reaction, *via* the use of Girard's reagent, in 50% yield. No other substances could be separated from the nonketonic fraction.

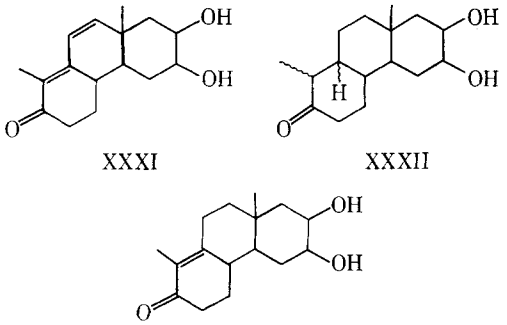
In a study of the factors affecting hydrogenation and those favoring hydrogenation over hydrogenolysis, Nishimura (26) reported the usefulness of the catalyst rhodium oxide–platinum oxide (7:3) in hydrogenations where hydrogenolysis is to be avoided. The catalyst consists of rhodium oxide and platinum oxide in a 7:3 ratio by weights of the metals. When this catalyst was employed in the hydrogenation of 1,2,3,4-tetrahydro-β-naphthol (XVIII), dihydroneoergosterol (XXI), neoergosteryl acetate (XXIV), the tetrahydropyranyl ether of dihydroneoergosterol (XXV), and the ketone (XXVII), results similar to those with Rh/alumina reductions were obtained. Nishimura also reported that the hydrogenolysis reaction is acid-catalyzed. Therefore, the amount of acetic acid (1%) used in the hydrogenation of dihydroneoergosterol (XXI) was decreased gradually in an attempt to favor hydrogenation over hydrogenolysis. At a concentration of 0.1%, neither hydrogenation nor hydrogenolysis occurred. With a gradual increase in the amount of acid, very slow absorption of hydrogen occurred which was due chiefly to hydrogenolysis. This was found to be the case with either Rh/alumina or Rh–Pt oxides (7:3) as the catalyst.

These unsuccessful results prompted the investigation of other factors, such as the solvent effect, influencing the extents of hydrogenation and hydrogenolysis reactions. Kindler and Blaas (27) hydrogenated benzoylcarbinyl acetate (XXVIII) over palladium in different solvents. They found that by using an oxygenated solvent such as methanol, dioxane, ethyl acetate, or acetic acid, 2 moles of hydrogen were absorbed and XXIX was obtained in 70–80% yield. However, when a nonoxygenated solvent such as cyclohexane, benzene, or toluene was used, reduction ceased after absorption of 1 mole of hydrogen and XXX was the main product formed. A similar effect was also found in the hydrogena-



XXVIII XXIX XXX

tion of 4-chloro- or 4-bromo-2-allylphenol (28). Reduction of the double bond in oxygenated solvents results in appreciable loss of the halogen; while if benzene or cyclohexane is used, elimination of the halogen does not occur. Woodward *et al.*, in their total synthesis of the steroids (29), obtained the glycol (XXXI) as one of the intermediates. Hydrogenation of this glycol, or its acetate or the acetonide, over supported Pd in alcohol or ethyl acetate did not cease with the absorption of 1 mole of hydrogen. But, if the reduction was arbitrarily stopped at that point, mixtures of the starting material product of reduction of the disubstituted double bond (XXXIII), and products of reduction of both double bonds (XXXII) were

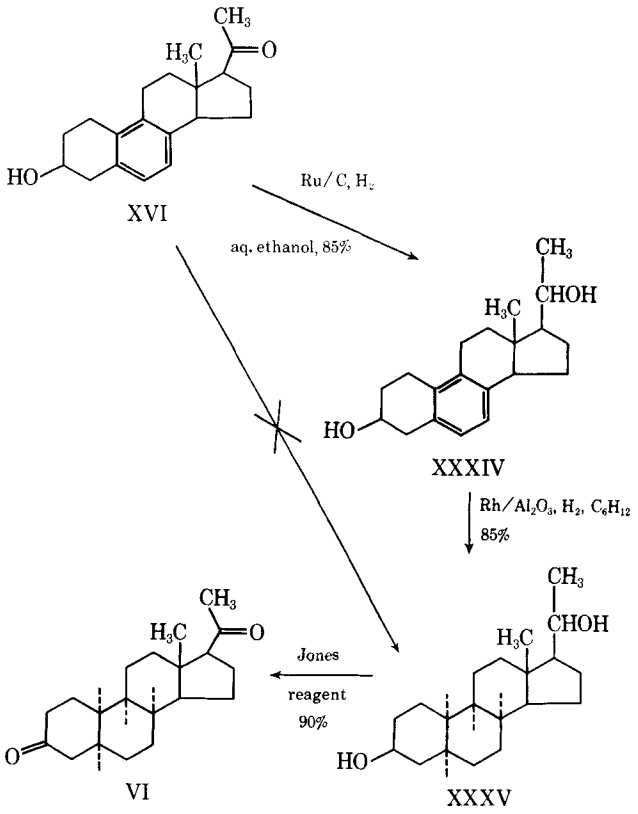


XXXI XXXII

XXXIII

obtained. When the hydrogenation of XXXI was allowed to proceed to completion, 2 moles of hydrogen were absorbed, giving a complicated mixture of stereoisomeric saturated keto compounds (XXXII). They found that by changing the solvent to benzene, hydrogenation of XXXI, or its diacetate or the acetonide, stopped completely after absorption of 1 mole of hydrogen to furnish the corresponding monounsaturated compound (XXXIII) in excellent yields. Therefore, cyclohexane was chosen as the solvent for the reduction of Ring B of the aromatic ketone (XVI).

Hydrogenation of the ketone (XVI) over Rh/alumina in cyclohexane did not proceed even at 1400 p.s.i. hydrogen pressure and the ketone was recovered unchanged (Scheme IV). This ketone was hydrogenated in 65% ethanol at room temperature and 60 p.s.i. over Ru/carbon where 1 mole of hydrogen was absorbed in 2 days. The diols (XXXIV) (mixture of 20α- and 20β-) were obtained in 85% yield. When the reduction was conducted in the same way except under 1200 p.s.i., 10 hr. was enough to afford the diols in the same yield. Hydrogenation of this aromatic diol over Rh/alumina in cyclohexane at room temperature and 1400 p.s.i. for 12 hr. afforded the aliphatic diol (XXXV) in 85% yield. The crude reaction product gave a negative tetranitromethane test, indicating the absence of a double bond (30). The IR spectrum of the diol (XXXV) showed the presence of strong OH and C—O stretching vibrations, absence of the phenyl C=C stretching, and the out of plane aromatic C—H bending. NMR spectrum of the crude reaction product showed no aromatic or olefin protons and also the absence of allylic protons at 1.85–2.20 δ. By integration it showed the presence of a multiplet of two protons centering at 3.67 δ corresponding to



XVI XXXIV VI XXXV

Scheme IV

the two protons at C-3 and C-20. By deuterium exchange there was a decrease of two protons in the total value of the integration. This indicates that the hydrogenation of the benzene ring of the aromatic diol (XXXIV) in cyclohexane did not cause hydrogenolysis of the C-3 hydroxyl group.

Oxidation of the diol (XXXV) with Jones reagent (31) in acetone afforded the diketone 5α,8α,9α,10α-19-norpregnan-3,20-dione (VI) in 90% yield.

Since this compound contains two carbonyl groups not interacting with each other, its rotatory dispersion curve should be the summation of the RD curves of the two separate carbonyl groups (32). However, the specific rotation at the peak (313 mμ) is +2566° (a value of about +3300° was expected). This order of rotation could be accounted for through the contribution of the 17β-methyl ketone alone, which would indicate that no contribution, or a weak positive Cotton effect, is provided by the 3-keto group. A careful examination of a conformational model of VI in its octant projection would indicate that a positive contribution can be attributed to C-6. Carbon atoms 7 and 8 lying in the horizontal B plane of the octant rule (32) will make no substantial contribution. Carbon atoms 13, 14, 15, 16, 17, and 18 will appear in the lower-left octant and hence will make a negative contribution. These carbon atoms, being more distant from the keto group than C-6 is, will have a smaller influence. Therefore, a resultant weak positive Cotton effect might be obtained for the C-3 keto group, which in turn might explain the RD curve of the diketone (VI).

EXPERIMENTAL

All melting points were determined in capillary tubes in a Thomas-Hoover melting point apparatus and are uncorrected. Optical rotations were obtained using a Perkin-Elmer 114 polarimeter, with a 1-dm. cell at 22°. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. IR spectra (KBr pellets) were determined on a Perkin-Elmer 237B grating IR spectrophotometer. NMR spectra[3] were recorded on a

[3] The authors are grateful to Daniel A. Koechel and Thomas N. Riley for preparing the NMR spectra and the ORD curves, respectively.

Varian Associates A-60D spectrometer using concentrations of about 10% and tetramethylsilane as the internal reference standard. ORD curves were determined with a Cary recording spectropolarimeter model 60, using a 1-cm. cell at 25°. Hydrogenations at ordinary pressures were done in a Parr low-pressure hydrogenation apparatus (Parr Instrument Co., Moline, Ill.). Hydrogenations at high pressures were carried out in an autoclave (Autoclave Engineers Inc., Erie, Pa.), and the hydrogenation mixture was stirred magnetically at 500–600 r.p.m. Supported rhodium or ruthenium catalysts (5%) were purchased from Engelhard Industries, Inc., Newark, N. J.

Bisergostatrienol (VIII*a*)—The photo-oxidation apparatus consisted of four horizontally fixed, 32-w. white circular fluorescent lamps, with a minimum space between lamps, and enclosed with a reflecting shield of highly polished white interior. The reaction vessel, usually a suitably sized round-bottom flask fitted with a reflux condenser and an efficient stirrer, was placed in the center of the circle of lamps. Fifty grams of Eosin Y[4] was dissolved in 1500 ml. of ethanol. To this solution, 3.84 ml. of concentrated sulfuric acid (sp. gr. 1.84) was added slowly and with stirring to liberate the free acid. The solution was filtered from the formed sodium sulfate. After bubbling nitrogen through the solution for 30 min., 750 ml. of tetrahydrofuran (THF) (previously passed through activated alumina column to decompose the peroxides) and 50 g. of ergosterol[5] were added in the dark. The mixture was stirred and irradiated with the white light for 72 hr. under a nitrogen atmosphere. During the reaction time, bisergostatrienol precipitated as dense fine white needles. The mixture was diluted with 4.3 l. of ethanol and the THF was allowed to evaporate spontaneously under the hood overnight. The fine needles were filtered, washed with ethanol and with ether, and dried in a vacuum desiccator. A yield of 45.5 g. (93%) of bisergostatrienol (VIII*a*), m.p. 201–203° with decomposition [reported (33) 202–203°], was obtained. The yields of several such reactions averaged 90–96%.

Neoergosterol (IX)—A mixture of bisergostatrienol (VIII*a*) (5.0 g.) and diethylene glycol monoethyl ether (Carbitol) (250 ml.) was refluxed for 5 min. in a nitrogen atmosphere. The solution was rapidly cooled to approximately 100° and then added to a mixture of water and crushed ice (250 g.) while stirring. The mixture was kept at −15° for 1 day and filtered while cold; the residue was washed with cold water, dissolved in hot methanol (60 ml.), and allowed to cool slowly. The fine needles of neoergosterol were collected and recrystallized from methanol (60 ml.). The yield was 1.65 g. (33%), m.p. 151–153° [reported (33) 151–152°]; $[\alpha]_D$ −10° (c 1.0). The IR spectrum showed characteristic peaks at 3330 cm.$^{-1}$ (OH); 3055, 3030 cm.$^{-1}$ (aromatic C—H); 1485, 810 cm.$^{-1}$ (aromatic ring); and 970 cm.$^{-1}$ (*trans* C=C).

Acetylation of Bisergostatrienol—A solution of bisergostatrienol (VIII*a*) (1 g.) in pyridine (180 ml.) was mixed with acetic anhydride (15 ml.). After a week the solution was poured into cold water (400 ml.); the separated crystals were collected and washed with dilute acetic acid and with water. After two recrystallizations from benzene–alcohol and drying over P_2O_5 *in vacuo*, colorless fine needles, 830 mg., 80%, m.p. 203–205°, were obtained [reported (10) m.p. 205.5–206°].

Pyrolysis of the Diacetate of the Biscompound; Preparation of Neoergosteryl Acetate (XXIV)—The diacetate of the biscompound (500 mg.) was pyrolyzed by the method described for the biscompound using 40 ml. of diethylene glycol monoethyl ether as the solvent. The yield of neoergosteryl acetate (XXIV) after two recrystallizations from methanol was 250 mg. (50%), m.p. 121–123° [reported (10) 123.5–124°]. The IR spectrum (KBr pellet) showed the absence of the OH group, presence of the ester carbony group band (1735 cm.$^{-1}$), presence of acetate ester characteristic band (1240 cm.$^{-1}$), and also the bands of the aromatic ring and *trans* double bond were present.

Bis(trimethylsilyl)ether of Bisergostatrienol (VIII*b*)—Bisergostatrienol (VIII*a*) (2 g.; 0.0025 mole) was suspended in anhydrous benzene (100 ml.), and bis(trimethylsilyl)-acetamide (Aldrich Chem. Co., Milwaukee, Wis.) (11) (1.12 g.; 0.0055 mole) was added. The stirred mixture was refluxed gently for 3 hr. under atmosphere of dry nitrogen. The solution was allowed to cool to room temperature. The solvent was removed *in vacuo*, and to the residue dry acetone (60 ml.) was added. After cooling at 5° for 1 hr., the material that precipitated was collected and dried *in vacuo* for 24 hr. at room temperature. The yield was 2.2 g. (95%), m.p. 190–192°. The IR spectrum showed the absence of OH absorbance and the presence of the following characteristic bands (34): 1250, 840, 750 cm.$^{-1}$ [$Si(CH_3)_3$]; 1090–1075 cm.$^{-1}$ (Si—O—C).

Anal.—Calcd. for $C_{89}H_{102}O_2Si_2$: C, 79.58; H, 10.99; Si, 6.00. Found: C, 79.13; H, 10.84; Si, 6.26.

Pyrolysis of the Bis(trimethylsilyl)ether of the Biscompound (VIII*b*)—A mixture of bisergostatrienol bis(trimethylsilyl)ether (VIII*b*) (1 g.) and diethylene glycol diethyl ether (Diethyl Carbitol) (50 ml.) was refluxed for 5 min. in a nitrogen atmosphere. The solution was cooled rapidly to approximately 100° and added to a stirred mixture of water and crushed ice (50 g.) containing a few crystals of *p*-toluenesulfonic acid. The mixture was worked up in the same way as mentioned under pyrolysis in diethylene glycol monoethyl ether. The yield of neoergosterol (IX) was 490 mg. (50%), m.p. 151–153°.

Neoergosterol-22,23-epoxide (X)—*A. With* m-*Chloroperbenzoic Acid*—Neoergosterol (IX) (2 g.; 0.0052 mole) was dissolved in dry olefin-free benzene (20 ml.) and chloroform (10 ml.). To this solution was added slowly a cold solution of *m*-chloroperbenzoic acid (FMC Corp., New York, N. Y.) (1 g.; 0.0058 mole) in benzene (15 ml.) and chloroform (10 ml.) and the solution was kept in the dark for 9 hr. at 25°. The solution was diluted with ether (200 ml.), washed with a 10% sodium sulfite solution, sodium bicarbonate solution, and with water until the washings were neutral. The organic solvents were dried over anhydrous sodium sulfate and distilled under reduced pressure. To the solid glassy residue was added 88% methanol (20 ml.) after which a white dense flocculent precipitate was obtained upon trituration. The precipitate was collected, dried *in vacuo* for 48 hr. at 30°. The yield was 1.8 g. (90%), m.p. 105–109° (the wide range is possibly due to the presence of a mixture of the two stereoisomeric epoxides); $[\alpha]_D$ −13.5° (c 1.0). The IR spectrum showed the absence of the 970 cm.$^{-1}$ band (*trans* C=C) and the presence of a new band at 909 cm.$^{-1}$ (so-called "11-μ band") characteristic of epoxide rings (35).

Anal.—Calcd. for $C_{27}H_{40}O_2$: C, 81.76; H, 10.17. Found: C, 81.48; H, 10.30.

B. With Formic Acid and Hydrogen Peroxide—A suspension of neoergosterol (1 g.) in 88% formic acid (20 ml.) was heated at 80° with stirring for 20 min. during which a clear solution was obtained. When the solution came to room temperature, it was treated with 30% hydrogen peroxide solution (3 ml.) and 88% formic acid (10 ml.). The mixture was stirred in the dark at room temperature for 24 hr. The mixture was treated with boiling water (100 ml.), stirred, and kept at 80° for 1 hr., then cooled to room temperature. The oil that separated was collected, dissolved in methanol (50 ml.), and treated with 1 ml. of 25% sodium hydroxide solution and warmed on a steam bath for 15 min. The solution was cooled to room temperature, acidified with dilute HCl, diluted with water (200 ml.), and extracted with ether. The ether extract was washed with water until the washings were neutral, dried, and the ether removed *in vacuo*. The glassy residue was crystallized from 88% methanol. The yield was 710 mg. (70%), m.p. 112–115° (possibly a different ratio of the two isomeric epoxides was obtained). Mixed melting point with the epoxide prepared by the *m*-chloroperbenzoic acid method gave a m.p. of 110–113°. The IR spectrum was identical to that prepared by *m*-chloroperbenzoic acid.

Anal.—Calcd. for $C_{27}H_{40}O_2$: C, 81.76; H, 10.17. Found: C, 81.95; H, 10.44.

Erythro-22,23-dihydroxy-22,23-dihydroneoergosterol (XI)—To a solution of neoergosterol epoxide (1 g.) in acetone (40 ml.) was added a solution of 2.5 ml. of 70% $HClO_4$ in 10 ml. water. The solution was refluxed in a nitrogen atmosphere for 3 hr. The solution was diluted with water and extracted with ethyl acetate. The ethyl acetate extract was washed with water until the washings were neutral, dried, and evaporated *in vacuo*. The residue was crystallized from ether when 700 mg. (70%) of colorless crystals were obtained, m.p. 173–175°, that gave a positive periodate–benzidine test (36), indicative of the presence of vicinal diol structure. One of the two erythro isomers was obtained after two recrystallizations from ether–petroleum ether. It was dried *in vacuo* at 70° for 5 hr.; m.p. 206–208°, $[\alpha]_D$ +29° (c 1.0). The IR spectrum showed the absence of the epoxide band and the presence of strong hydroxyl absorbance at 3375 cm.$^{-1}$

[4] Color index 45380, National Aniline Division, Allied Chemical & Dye Corp., New York, N. Y.
[5] Melting point 161–163°; Aldrich Chem. Co., Milwaukee, Wis.

Anal.—Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 77.99; H, 9.93.

3β-Hydroxy-19-norpregna-5,7,9(10)-triene-20α-aldehyde Dimethyl Acetal (XII)—A solution of the triol (XI) (1 g.) in methanol (40 ml.) was treated with a solution of periodic acid (0.6 g.) in methanol (7 ml.). The solution was stirred in the dark for 18 hr., neutralized with 1*N* NaOH solution, and filtered. The residue on the filter was washed with methanol. The filtrate and washings were concentrated *in vacuo* to a volume of 20 ml., cooled, and 850 mg. (95%) of white crystals of the dimethyl acetal (XII) were obtained; m.p. 177–179°, lit. (12) 178.6–180.9°.

3β-Hydroxy-19-norpregna-5,7,9(10)-triene-20α-aldehyde Methyl Hemiacetal (XIII)—A solution of the triol (XI) (1 g.) in methanol (50 ml.) was treated with a solution of periodic acid (0.6 g.) in water (9 ml.). The solution was stirred in the dark for 18 hr. after which time the precipitate that formed was collected and dried *in vacuo*. The yield was 750 mg. (84%); m.p. 142–143°. The IR spectrum showed the absence of a carbonyl absorbance, presence of strong hydroxyl absorbance at 3380 cm.$^{-1}$ and at 3430 cm.$^{-1}$. It also showed several sharp peaks at 2820, 1145, 1100, and 1075 cm.$^{-1}$, characteristic of ethers (35).

Anal.—Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.47; H, 9.48.

3β-Hydroxy-19-norpregna-5,7,9(10)-triene-20α-aldehyde (XIV)—*A. From the Triol (XI)*—A solution of the triol (XI) (1 g.) in peroxide-free dioxane (45 ml.) was treated with a solution of periodic acid (0.6 g.) in water (10 ml.). The solution was stirred in the dark for 24 hr. after which time it was diluted with ethyl acetate (200 ml.) and ether (100 ml.) The solution was washed with water till neutral, dried over anhydrous sodium sulfate, and the organic solvents evaporated *in vacuo* at a temperature less than 40°. The glassy pale yellowish mass that remained was dried *in vacuo* over P_2O_5 for 24 hr. when 620 mg. (82%) was obtained. It was very soluble in the organic solvents and failed to crystallize from most of them. With ether–petroleum ether as solvent for crystallization, an oil was always obtained, $[\alpha]_D$ −17° (c 1.0). The IR spectrum showed the characteristic bands of the aldehyde group at 2700 cm.$^{-1}$ (H of CHO) and at 1725 cm.$^{-1}$ (C=O).

B. By Hydrolysis of the Acetal (XII) or the Hemiacetal (XIII)—A solution of the acetal (XII) or the hemiacetal (XIII) (500 mg.) in dioxane (20 ml.) was refluxed in a nitrogen atmosphere with a solution of acetic acid (2 ml.) in water (10 ml.) for 5 min. The solution was allowed to cool to room temperature, mixed with ether and ethyl acetate (100 ml. each), and the organic layer washed with water until it was free of acid. The solution was dried over anhydrous sodium sulfate and concentrated to dryness *in vacuo*. The glassy mass that remained was dried *in vacuo* over P_2O_5 for 24 hr. when 420 mg. was obtained. This material was identical to that prepared in Method A in every respect. The 2,4-dinitrophenylhydrazone of this aldehyde melted at 230–231° after one recrystallization from ethyl acetate–methanol, reported (12) 230–232°.

C. By Ozonolysis of Neoergosterol (IX)—A solution of neoergosterol (IX) (5 g.; 0.013 mole) in methylene chloride (400 ml.) and pyridine (1.1 ml.; 0.014 mole) in a tubular reactor equipped with a magnetic stirrer, a gas inlet, and an outlet leading to a $CaSO_4$ drying tube which in turn led to a 2% KI solution, was cooled to −50° in a dry ice–acetone bath. A stream of ozone-rich dry oxygen (5.40% w/w; 7.77 mg. O_3/100 ml.) (generated by a Welsbach model T-23 ozonator) was passed at a rate of 0.0026 cu. m./min. (0.03 cu. ft./min.) into the stirred solution, and the outcoming gases from the reaction were bubbled through the KI solution. After 15 min. a yellow color was obtained in the KI solution, indicating that about 95% of attack on the double bond had occurred. After an additional 45 sec., the flow of ozone was stopped (1.65 mole equivalents of ozone) and zinc dust (6 g.) and glacial acetic acid (27 ml.) were added. The mixture was allowed to stir at 0–10° for 1 hr. and finally for 5 min. at 35°. The bright-yellow mixture was filtered and washed with two 150 ml. portions of water. It then was cooled by the addition of crushed ice (100 g.) and washed with two 20-ml. portions of cold 10% sodium carbonate, 15 ml. of cold 10% sodium hydroxide, and five 150-ml. portions of cold water, all aqueous washings being back-washed with 20 ml. of methylene chloride. The combined methylene chloride solutions were dried over anhydrous sodium sulfate and the solvent removed under reduced pressure at a temperature less than 40° when a white crystalline residue was obtained. This solid material was dried *in vacuo* over P_2O_5 for 24 hr. when 3.8 g. (92%), m.p. 132–134°, was obtained; $[\alpha]_D$ −20° (c 1.0.). The IR spectrum showed the following characteristic bands: 3515, 3400 cm.$^{-1}$ (OH); 3040, 3010 cm.$^{-1}$ (aromatic C—H); 2700, 2680 (H of CHO); 1725 cm.$^{-1}$ (C=O); 1480, 810 cm.$^{-1}$ (aromatic ring), beside the other aliphatic C—H and C—O stretching vibrations. The NMR spectrum showed the following characteristic peaks: singlet at 0.63 δ (C-18 CH_3); doublet centering at 1.20 δ J = 7 c.p.s. (C-21 CH_3); singlet at 6.83 δ (2 aromatic protons); and a doublet centering at 9.60 δ J = 2.9 c.p.s. (H of CHO). A portion of this material was washed on a funnel with ethyl acetate, anhydrous ether, dried *in vacuo* for 24 hr., m.p. 136–138°; $[\alpha]_D$ −21° (c 1.0).

Anal.—Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.54; H, 9.13. The 2,4-dinitrophenylhydrazone of this aldehyde did not depress the melting point when present in a mixture with that prepared from the aldehyde of the periodate reactions. The following observations are significant:

1. During the ozonolysis, if the rate of passing O_3 was increased [0.0035 cu. m./min. (0.04 cu. ft./min.)], an earlier end-point might show in the KI solution and neoergosterol will be separated along with the aldehyde.

2. Also if the rate of stirring is too fast, O_3 will be forced to saturate the solution, and further attack the benzene ring and an incorrect end-point will be obtained. An average rate of stirring of 200–250 r.p.m. with either a magnetic or a mechanical stirrer should be maintained during the ozonolysis.

3. If temperatures colder than −50° are used, the intermediate ozonide will precipitate along with some neoergosterol, causing an incomplete reaction.

3β-Hydroxy-20-morpholino-methylene-19-norpregna-5,7,9(10)-triene (XV)—A solution of the aldehyde (XIV) (3 g.) in anhydrous benzene (80 ml.) was distilled under nitrogen atmosphere until 20 ml. of distillate was collected (to remove the traces of moisture). To the benzene solution was added 2 ml. of dry morpholine and 12 mg. of *p*-toluenesulfonic acid. This solution was refluxed, while stirred magnetically, under dry nitrogen atmosphere for 4 hr. in the presence of 7 g. of conditioned (by heating at 320° for 5 hr.) Linde 4A molecular sieve 0.160-cm. (0.063-in.) pellets in a continuous-extraction apparatus placed between the condenser and the reaction flask. This assembly permits the condensed vapors of water and benzene to pass through the molecular sieve, so that water will be adsorbed, before it returns to the reaction flask. The solution was cooled, benzene and excess morpholine distilled *in vacuo*, and the pale brown glassy residue dried *in vacuo* over P_2O_5 for 24 hr. The yield was 3.64 g. (99%). The IR spectrum of this enamine showed the absence of carbonyl absorbance and the presence of the enamine double bond absorption frequency at 1645 cm.$^{-1}$ (37).

3β-Hydroxy-19-norpregna-5,7,9(10)-triene-20-one (XVI)—*A. By Oxidizing the Enamine (XV) with CrO_3·PY*—Finely powdered chromic acid (1.65 g.) was added, over a period of 15 min., to stirred anhydrous pyridine (25 ml.) at 0° under nitrogen. A solution of the enamine (XV) (2 g.) in pyridine (25 ml.) was added over 5 min. The mixture was stirred for 4 hr. at 0° and then was allowed to stand overnight at room temperature. Benzene (200 ml.) was added and the mixture was filtered through a column of alumina (25 g.) and the column was eluted with benzene. Evaporation of the eluate *in vacuo* yielded 1 g. of a semisolid material. The ketone (XVI) was separated from this material through the formation of Girard "T" derivative as follows: this semisolid material was dissolved in absolute ethanol (10 ml.), glacial acetic acid (1 ml.), and 1 g. of Girard T reagent was added. The mixture was refluxed under dry nitrogen atmosphere for 1 hr. The solution then was added to sodium bicarbonate (1.26 g.) in water (40 ml.) and the resulting colloidal solution was extracted twice with ether. The clear aqueous layer was acidified to pH 1 with hydrochloric acid and extracted with ether. The ether extract was washed with water until it was free of acid, dried over anhydrous sodium sulfate, and the solvent removed *in vacuo*. The residue was crystallized twice from ether when 0.31 g. (20%) of white rosettes was obtained: m.p. 150–151°, $[\alpha]_D$ +57° (c 1.0 in $CHCl_3$); lit. (13) m.p. 151–152°, $[\alpha]_D$ +58° (c 0.9 in $CHCl_3$). The IR spectrum showed the following characteristic bands: 3340 cm.$^{-1}$ (OH); 3040, 3015 cm.$^{-1}$ (aromatic C—H); 1700 cm.$^{-1}$ (C=O); 1420, 1355 cm.$^{-1}$ (CH_3—C(=O)—); 1480, 810 cm.$^{-1}$ (aromatic ring), beside the other aliphatic C—H and C—O stretching vibrations. The NMR spectrum (in CCl_4) showed the following peaks: singlet at 0.51 δ (C-18 CH_3); singlet at 2.11 δ (C-21 CH_3);

multiplet centering at 3.95 δ (H of C-3); and a singlet at 6.73 δ (2 aromatic protons).

B. By Ozonolysis of the Enamine (XV)—Using methylene chloride, a solution of the enamine (XV) (2 g.; 0.0052 mole) in dry methylene chloride (200 ml.) was put in the same tubular reactor with the same outfit used for ozonizing neoergosterol. A stream of ozone-rich dry oxygen (5.40% w/w) was passed at a rate of 0.0026 cu. m./min. (0.03 cu. ft./min.) into the stirred solution at −78°. After 17 min. a yellow color was obtained in the KI solution, indicating about 95% attack on the double bond had occurred. Ozone was stopped after 30 sec. more (4.6 mole equivalents of ozone were absorbed); zinc dust (3 g.) and glacial acetic acid (14 ml.) were added. The solution was worked up and processed for the neutral fraction as previously described under the ozonolysis of neoergosterol. The semisolid material (1.4 g.), that was obtained after distilling the methylene chloride, was purified through Girard T separation procedure as previously described. The residue that remained, after distilling the ether extract of the ketonic fraction, was crystallized twice from ether when 0.62 g. (40%) of white rosettes was obtained; m.p. 151–152°, mixed melting point with the ketone (XVI) prepared by $CrO_3 \cdot PY$ method showed no depression.

Using methylene chloride with pyridine, the above mentioned experiment was conducted in the same way except that pyridine (0.44 ml., 0.0056 mole) was added to the enamine solution before the ozonolysis. A yellow color appeared in the KI solution after passing ozone through the solution for 10 min. The flow of ozone was stopped after 30 sec. more (2.7 mole equivalents of ozone were absorbed). The yield of the ketone (XVI), after Girard T separation and two crystallizations from ether, was 0.85 g. (55%), m.p. 150–151°. The IR spectrum was identical to that prepared by $CrO_3 \cdot PY$ oxidation method and to that prepared by the previously mentioned ozonolysis method.

Using ether, the previous experiment was conducted in the same way except that anhydrous ether (300 ml.) was used as the solvent instead of methylene chloride, and the temperature of the reaction during ozonolysis was adjusted at −30°. The yellow color appeared in the KI solution after 10.8 min. and the flow of ozone was stopped after 30 sec. more (2.9 mole equivalents of ozone were absorbed). The yield of the ketone (XVI), after evaporating the ether extract from Girard T separation under reduced pressure and drying the residue *in vacuo* over P_2O_5 for 24 hr., was 1.28 g., m.p. 142–144°. One recrystallization from ether afforded 1.13 g. (73%), m.p. 151–152°. The IR spectrum was identical to that prepared by the previous methods.

Model Procedure for Hydrogenation—The described amount of catalyst was soaked with a few milliliters of the solvent.[6] The compound to be hydrogenated was dissolved in the rest of the solvent, mixed with the presoaked catalyst, and the mixture was hydrogenated under the conditions described. After the time used to effect reduction had elapsed, the solution was filtered from the catalyst and diluted with ether (four times the amount of solvent used), washed with 5% sodium bicarbonate solution, water, and then dried over anhydrous sodium sulfate. The organic solvents were distilled under reduced pressure and the products in each case separated as described below.

Perhydrophenanthrene (XIX)—A mixture of 1,2,3,4,5,6,7,8-octahydrophenanthrene (Aldrich Chem. Co., Milwaukee, Wis.) (XVII) (930 mg.; 0.005 mole), ethanol (50 ml.) containing 1% glacial acetic acid, and 5% Rh/alumina (400 mg.) was hydrogenated at room temperature and 60 p.s.i. initial pressure for 9 hr. The hydrogen uptake was 0.016 mole. The crude product was distilled at 87–89°/2 mm. when 870 mg. (91%) of colorless oil, n_D^{20} 1.5010 was obtained; lit. (38) b.p. 109–111°/4 mm. The IR spectrum (liquid film) showed the absence of the aromatic bands (3050, 3025, 3000 cm.$^{-1}$, and 1480, 800 cm.$^{-1}$) and the presence of the aliphatic C—H stretching frequencies at 2890, 2835 cm.$^{-1}$, and C—H bending frequency at 1440 cm.$^{-1}$.

***cis,cis*-2-Decalol (XX)**—A mixture of 1,2,3,4-tetrahydro-β-naphthol (XVIII) (K & K Laboratories, Inc., Plainview, N. Y.) (740 mg.; 0.005 mole), ethanol (50 ml.) containing 1% glacial acetic acid, and 5% Rh/alumina (200 mg.) was hydrogenated at room temperature and 60 p.s.i. initial pressure for 5.5 hr. The hydrogen uptake was 0.015 mole. The crude product was crystallized twice from petroleum ether when 615 mg. (80%), m.p. 102–104°, lit. (39) m.p. 105°, of XX was obtained. The IR spectrum showed the absence of the aromatic bands (3040, 3000 cm.$^{-1}$ and 1485, 735 cm.$^{-1}$) that were present in XVIII and the presence of the following characteristic bands: 3300 cm.$^{-1}$ (OH); 1050, 1026 cm.$^{-1}$ (C—O), and the other aliphatic C—H bands.

3β-Hydroxy-19-norergosta-5,7,9(10)-triene; Dihydroneoergosterol (XXI)—A solution of neoergosterol (IX) (5 g.) in ethyl acetate (135 ml.) containing perchloric acid [0.05 ml. of a solution prepared from 70% perchloric acid (10 ml.) and ethyl acetate (90 ml.)] was hydrogenated at room temperature and atmospheric pressure over PtO_2 (100 mg.) for 0.5 hr. The solution was filtered from the catalyst, washed with water till neutral, dried over anhydrous sodium sulfate, and the solvent removed *in vacuo*. The residue was crystallized from methanol when 4.01 g. (80%) of XXI was obtained; m.p. 145–147°, lit. (40) m.p. 146–148°. The IR spectrum showed the absence of the *trans* double bond band at 970 cm.$^{-1}$.

19-Norergosta-5,7,9(10)-triene (XXII)—A mixture of dihydroneoergosterol (XXI) (1.14 g.; 0.003 mole), ethanol (50 ml.) containing 1% glacial acetic acid, and 5% Rh/alumina (500 mg.) was hydrogenated at room temperature and 60 p.s.i. for 7 hr. The crude product was crystallized from methanol when 0.99 g. (90%), m.p. 66–67°, lit. (40) 67–68°, of XXII was obtained. The IR spectrum showed the absence of OH and C—O absorbance and the presence of the aromatic characteristic bands at 3040, 3010, 1485, and 810 cm.$^{-1}$. When the pressure in the above experiment was raised to 250 p.s.i., absorption of H_2 was very slow, and when the reaction was worked up as usual the product (XXII) was isolated in 75% yield (820 mg.).

5α,8α,9α,10α-19-Norergostane (XXIII)—A mixture of 19-norergosta-5,7,9(10)-triene (XXII) (1.1 g.; 0.003 mole) of dihydroneoergosterol (XXI) (1.14 g.; 0.003 mole), ethanol (50 ml.) containing 1% glacial acetic acid, and 5% Rh/alumina (2.4 g.) was hydrogenated at room temperature and 60 p.s.i. initial pressure for 12 hr. The hydrogen uptake was 0.009 mole, 0.012 mole in case of dihydroneoergosterol. The crude product, 0.99 g. (90%), was a heavy colorless oil that showed no OH bands or aromatic bands in the IR, and it only showed the usual aliphatic C—H absorbances at 2930, 2900, 2840, 1465, 1445, 1380, 1375, and 1365 cm.$^{-1}$ This compound was not investigated further.

Hydrogenation of Neoergosteryl Acetate (XXIV)—A mixture of neoergosteryl acetate (XXIV) (420 mg.; 0.001 mole), ethanol (25 ml.) containing 1% glacial acetic acid, and 5% Rh/alumina (800 mg.) was hydrogenated at room temperature and 60 p.s.i. for 12 hr. The hydrogen uptake was 0.005 mole. The crude product, 330 mg. (90%), was a colorless oil that had an IR spectrum similar to that of XXIII prepared from dihydroneoergosterol (XXI). When the experiment was conducted in the same way except for only 3 hr., 19-norergosta-5,7,9(10)-triene (XXII) was isolated from the crude product by crystallization from methanol in 40% yield (150 mg.), m.p. 65–67°. The IR spectrum was similar to that of the product previously prepared.

3β-2′-Tetrahydropyranyloxy-19-norergosta-5,7,9(10)-triene (XXV)—Dihydroneoergosterol (XXI) (500 mg.) was dissolved in chloroform (3 ml.) and dihydropyran (200 mg.) (previously dried over KOH, distilled from KOH, and then distilled from sodium). As one drop of a solution containing one drop of phosphorus oxychloride in 5 ml. of ethyl acetate was added, the solution became warm. This solution was warmed to 50° for 20 min., cooled to room temperature, and diluted with ether (100 ml.). The solution was washed with sodium bicarbonate solution, water, dried over sodium sulfate, and solvents removed *in vacuo*. The residue was dried *in vacuo* over P_2O_5 for 24 hr. and then crystallized from methanol. The yield was 540 mg. (90%) of colorless needles, m.p. 125–127°, $[\alpha]_D$ +13.5° (c 1.0). The IR spectrum showed the absence of OH absorbance and the presence of the following characteristic sharp bands: 1195, 1130, 1115, 1070, 1050, and 1025 cm.$^{-1}$ (C—O—C—O—C and C—O vibrations) (35). Additional aromatic and aliphatic C—H bands also were present.

Anal.—Calcd. for $C_{32}H_{50}O_2$: C, 82.35; H, 10.80. Found: C, 82.35; H, 10.94.

Attempted Hydrogenation of the Tetrahydropyranyl Derivative of Dihydroneoergosterol (XXV)—A mixture of the tetrahydropyranyl ether derivative (XXV) (200 mg.), absolute ethanol (40 ml.) containing 1% glacial acetic acid, and 5% Rh/alumina (400 mg.; and in another similar experiment 800 mg.) was shaken in a Parr hydrogenator at room temperature and under 60 p.s.i. H_2 pressure

[6] All the solvents used were boiled for 5 min. to drive off all the dissolved O_2 and then were allowed to cool in an atmosphere of N_2.

for 2 days. After the usual workup of the reaction, the crude product was crystallized from methanol when 180 mg. of white needles, m.p. 124–126°, that had an IR spectrum similar to that of XXV, were obtained.

3,4-Dihydro-2(1-*H*)-naphthalenone (XXVI)—*A. With tert-Butyl Hypochlorite*—A solution of 1,2,3,4-tetrahydro-β-naphthol (XVIII) (595 mg.; 0.004 mole) in carbon tetrachloride (2 ml.) and pyridine (0.32 ml.; 0.004 mole) was cooled to −5°. From a capillary, *tert*-butyl hypochlorite (0.47 ml.; 0.004 mole) was added and the temperature was allowed to stay at 0° for 15 min. The PY·HCl that precipitated was filtered and washed with cold CCl_4 (2 ml.). The filtrate and washings were evaporated at reduced pressure under N_2. A pale yellow liquid remained, 525 mg. (90%), which yielded a semicarbazone (crystallized from ethanol), m.p. 192–194°, lit. (41) m.p. 193–194°. The IR spectrum (liquid film) showed the absence of OH bands, the presence of strong and sharp carbonyl band at 1720 $cm.^{-1}$ together with the other aliphatic and aromatic C—H bands. The NMR spectrum showed the following characteristic peaks: multiplet centering at 2.60 δ (2 protons at C-3), multiplet centering at 3.05 δ (2 protons at C-4), a singlet at 3.61 δ (2 protons at C-1), and a multiplet centering at 7.24 δ (4 aromatic protons).

B. With DMSO—1,2,3,4-Tetrahydro-β-naphthol (XVIII) (595 mg.; 0.004 mole) was dissolved in anhydrous dimethyl sulfoxide (6 ml.) and benzene (6 ml.) containing pyridine (0.32 ml.; 0.004 mole) and trifluoroacetic acid (0.16 ml.; 0.002 mole). After the addition of dicyclohexylcarbodiimide (2.48 g.; 0.012 mole) the reaction mixture was stirred magnetically, under anhydrous conditions, at room temperature for 18 hr. when a fine white precipitate of dicyclohexylurea was being formed throughout the reaction. The mixture was diluted with ether (100 ml.) followed by the dropwise addition of a solution of oxalic acid (1.08 g.; 0.012 mole) in methanol (10 ml.) and the solution was stirred till gas evolution had ceased (0.5 hr.). The solution was cooled, filtered from the urea derivative (m.p. 234°), washed with 5% sodium bicarbonate and twice with water, dried over anhydrous sodium sulfate, and the solvents removed under reduced pressure. The yellow oil that remained was distilled at 117–118°/2 mm. under N_2. The yield was 495 mg. (85%), its semicarbazone had a m.p. 193–194° which did not depress the melting point of the semicarbazone of the material prepared by *tert*-butyl hypochlorite. The IR and NMR spectra were also identical with the material prepared by *tert*-butyl hypochloride.

19-Norergosta-5,7,9(10)-triene-3-one (XXVII)—Dihydroneoergosterol (XXI) (1.52 g.; 0.004 mole) was treated as under DMSO oxidation of 1,2,3,4-tetrahydro-β-naphthol (XVIII). The duration, workup of the reaction, was exactly the same as that previously described. The crude residue left after evaporating the solvents under reduced pressure was subjected to Girard's separation procedure as mentioned before under the ketone (XVI) except that a nitrogen atmosphere always was used. The residue that remained after distilling the ether extract of the ketonic fraction was crystallized from methanol. The yield was 1.13 g. (75%) of white needles, m.p. 90–91°, reported (40) m.p. 91–92°. The IR spectrum showed the absence of OH absorbance, presence of carbonyl band at 1720 $cm.^{-1}$ and the other aliphatic and aromatic C—H bands.

Attempted Reduction of the Ketone (XXVII)—A mixture of the ketone (XXVII) (380 mg.; 0.001 mole), ethanol (40 ml.) containing 1% glacial acetic acid, and 5% Rh/alumina (750 mg.) was hydrogenated at room temperature and 60 p.s.i. initial pressure for 32 hr. when no noticeable absorption of H_2 occurred. After the usual workup of the reaction mixture, the residue (340 mg.) was subjected to Girard's separation where the ketonic fraction gave 190 mg. (50%) of the ketone (XXVII) identified by its melting point and IR spectrum. Distillation of the ether extract of the nonketonic fraction of Girard's separation did not afford any residue.

Rhodium–Platinum (7:3) Oxides—A mixture of rhodium trichloride trihydrate (769 mg.), chloroplatinic acid (345 mg.), and sodium nitrate (20 g.) was heated slowly until a temperature of 300° was reached in 30 min. The mixture started to melt and the red fumes of the oxides of nitrogen evolved. After the evolution of the gases had subsided (temperature about 400°), the temperature was raised and kept at 460–480° for about 10 min. After cooling, the solid mass was rinsed with distilled water. The solid was collected, washed with 100 ml. of 0.5% aqueous sodium nitrate, and then dried over calcium chloride for 48 hr. The yield was 525 mg. (80%) of fine brown powder.

General Procedure for Reduction over Rh–Pt (7:3) Oxides—The solvent, to be used in the hydrogenation, was boiled for 5 min. to drive off all the dissolved O_2, then allowed to cool in an atmosphere of N_2. The amount of glacial acetic acid was added to make a 1% solution. The catalyst was suspended in few milliliters of this solvent and reduced to the metals by hydrogenation at room temperature and 20 p.s.i. for 0.5 hr. The substance to be reduced was dissolved in the rest of the solvent and then was added to the reduced catalyst and the hydrogenation conducted under the prescribed conditions. The mixture then was filtered, diluted with ether (*ca.* 3 times as the amount of solvent used), washed with sodium bicarbonate solution, water, and dried over anhydrous sodium sulfate. The solvents were removed *in vacuo* and the product was worked up as the conditions warrented.

***cis,cis*-2-Decalol (XX)**—A mixture of 1,2,3,4-tetrahydro-β-naphthol (XVIII) (370 mg.; 0.0025 mole), ethanol (25 ml.), and the catalyst (25 mg.) was hydrogenated at room temperature and 60 p.s.i. The hydrogen uptake was 0.0075 mole in 70 min. The crude product crystallized after the removal of the ether, m.p. 85–89°, one recrystallization from petroleum ether afforded 345 mg. (90%), m.p. 103–104°. The IR spectrum was identical with that of the product prepared from the reduction with Rh/alumina.

Hydrogenation of Dihydroneoergosterol (XXI)—A mixture of dihydroneoergosterol (XXI) (380 mg.; 0.001 mole), ethanol (30 ml.), and the catalyst (50 mg.) was hydrogenated at room temperature and 60 p.s.i. for 24 hr. The crude product was an oil whose IR was similar to that of XXIII. When the above experiment was conducted in the same way and the hydrogenation was stopped after 6 hr., 19-norergosta-5,7,9(10)-triene (XXII) was isolated from the crude product by crystallization from methanol. The yield was 160 mg. (50%), m.p. 65–67°.

Hydrogenation of Neoergosteryl Acetate (XXIV)—The previous two experiments were repeated in the same way except using neoergosteryl acetate (XXIV) (420 mg., 0.001 mole) instead of dihydroneoergosterol. From the first experiment the same oily material was separated, and from the second experiment 19-norergosta-5,7,9(10)-triene (XXII) was obtained in a similar manner.

Attempted Hydrogenation of the Tetrahydropyranyl Derivative of Dihydroneoergosterol (XXV)—A mixture of the tetrahydropyranyl ether derivative (XXV) (200 mg.), absolute ethanol (40 ml.) containing 1% glacial acetic acid (the boiling step was omitted), and the catalyst (40 mg.) was shaken under 60 p.s.i. H_2 pressure and at room temperature for 1 day. Standard manipulation afforded 185 mg. of the ether (XXV) identified by its melting point and IR spectrum.

Attempted Hydrogenation of the Ketone (XXVII)—A mixture of the ketone (XXVII) (250 mg.), ethanol (30 ml.), and the catalyst (40 mg.) was shaken under 60 p.s.i. H_2 and at room temperature for 1 day. Standard manipulation afforded 200 mg. which upon Girard's separation process gave 110 mg. (45%) of the ketone (XXVII), m.p. 89–91°. Nothing could be obtained from the nonketonic fraction after the use of the Girard reagent.

Effect of Acid—A series of experiments was conducted using in each a mixture of dihydroneoergosterol (XXI) (200 mg.), ethanol (30 ml.), and the catalyst (30 mg.) or Rh/alumina (400 mg.). Glacial acetic acid in 0.1, 0.2, 0.3, 0.4, or 0.5% concentration was used. The mixtures were hydrogenated at room temperature and 60 p.s.i. for 8 hr. After the usual workup, the experiments with 0.1% and 0.2% acetic acid concentrations yielded dihydroneoergosterol (XXI). The experiments with higher acid concentrations (they had a slow absorption of H_2) afforded 19-norergosta-5,7,9(10)-triene (XXII) in 40–60% yields, identified by its melting point and IR spectrum.

3β,20β-Dihydroxy-19-norpregna-5,7,9(10)-triene (XXXIV)—A mixture of 3β-hydroxy-19-norpregna-5,7,9(10)-triene-20-one (XVI) (894 mg.; 0.003 mole), ethanol 65% (80 ml.) (without acetic acid), and 5% Ru/carbon (1.0 g.) was hydrogenated at room temperature at 60 p.s.i. for 2 days. The hydrogen uptake was 0.003 mole. The crude solid (870 mg.) that was obtained after evaporating the organic solvents was crystallized from ether when 760 mg. (85%) of colorless rosettes of the 20α- and 20β-diols were obtained, m.p. 169–171°. One hundred milligrams of this mixture was recrystallized twice from methylene chloride to yield 20 mg. (of the 20β-isomer), m.p. 209–210°, $[\alpha]_D$ −23° (c 1.0). The IR spectrum showed the absence of carbonyl band, presence of the following characteristic bands: 3330, 3295 $cm.^{-1}$ (OH); 3040, 3000 $cm.^{-1}$ (aromatic C—H); 1485, 810 $cm.^{-1}$ (aromatic ring); and 1140, 1115, 1080, 1040, and 1020 $cm.^{-1}$ (C—O), beside the aliphatic C—H vibrations.

Anal.—Calcd. for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39. Found: C, 79.66; H, 9.45. When this experiment was conducted in the same way, except at 1200 p.s.i. for 10 hr., the same product was separated and the same yield of the diols (XXXIV) was obtained.

3β-20β-Dihydroxy-5α,8α,9α,10α-19-norpregnanediol (XXXV)—3β-20β-(& 20α-)Dihydroxy-19-norpregna-5,7,9(10)-triene (XXXIV), m.p. 169–171° (600 mg.; 0.002 mole), finely powdered, was dissolved in cyclohexane (600 ml.) (previously boiled then cooled under N_2) with the aid of few drops of ethyl acetate. This solution was hydrogenated at room temperature and 1400 p.s.i. over 5% Rh/alumina (1.2 g.) for 12 hr. The catalyst was filtered from the solution which was distilled under reduced pressure and the solid residue (600 mg.) was recrystallized from ether. The yield was 515 mg. (85%), m.p. 185–188°. One hundred milligrams of this mixture was recrystallized twice from methylene chloride when 25 mg. (of the 20β-isomer) dried for 24 hr. *in vacuo* at 60°, m.p. 230–232°, was obtained, $[\alpha]_D$ −6.5° (c 0.5). The IR spectrum showed the absence of the aromatic bands and the presence of the following characteristic bands: 3300, 3200 cm.$^{-1}$ (OH); 1140, 1095, 1065–1055, 1040, and 1010 cm.$^{-1}$ (C—O); and the other aliphatic C—H bands. The NMR spectrum (of the crude reaction product) did not show any peaks in the aromatic, olefinic, or the allylic (1.85–2.20 δ) regions. Also the crude reaction product gave a negative tetranitromethane test (30). Mass spectral molecular ion at *m/e* 306.

Anal.—Calcd. for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.38; H, 10.92.

5α,8α,9α,10α-19-Norpregnan-3,20-dione (VI)—3β-20β-(& 20α-)-Dihydroxy-5α,8α,9α,10α-19-norpregnanediol (XXXV), m.p. 185–188° (306 mg.; 0.001 mole), was dissolved in acetone (40 ml.) previously distilled from potassium permanganate. The solution was cooled to 10° and 0.28 ml. of Jones reagent (31) was added rapidly while stirring the solution under N_2. After 4 min. the solution was diluted with ether (150 ml.) and washed with water, dried over anhydrous sodium sulfate, and the ether evaporated *in vacuo*. The semisolid residue that remained (298 mg.) was dried *in vacuo* over P_2O_5 for 2 days when colorless fine needles were formed. This residue was recrystallized from ether (10 ml.) when 270 mg. (90%), m.p. 159–161°, was obtained. Another recrystallization afforded 220 mg., dried *in vacuo* at room temperature for 48 hr., m.p. 163–164°, $[\alpha]_D$ + 32° (c 0.5). The IR spectrum showed the absence of OH bands, and the presence of the following characteristic bands: 1710–1700 cm.$^{-1}$ (C=O); 1427, 1420 cm.$^{-1}$ (CH_2 at C-2 and C-4; and 1355 cm.$^{-1}$ (CH_3—C(=O)—). The NMR spectrum showed the following peaks: 0.82 δ (C-18 CH_3), 2.15 δ (C-21 CH_3), and a multiplet centering at 2.25 δ (methylene protons at C-2, C-4, and C-17). The ORD (c 0.03 g./100 ml. $CHCl_3$), t = 27°, $[\alpha]_{600}$ +33°, $[\alpha]_{589}$ +33°, $[\alpha]_{400}$ +226.6°, $[\alpha]_{350}$ +566.6°, $[\alpha]_{320}$ +2162°, $[\alpha]_{315}$ +2450°, $[\alpha]_{313}$ +2566° (peak), $[\alpha]_{310}$ +2430°, $[\alpha]_{294}$ 0000°, $[\alpha]_{270}$ −3333°, $[\alpha]_{260}$ −3433° (trough), and $[\alpha]_{250}$ −3433°. The dispersion curve of this diketone is a "single, positive Cotton-effect curve."

Anal.—Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.30; H, 9.79.

REFERENCES

(1) O. Gisvold, in "Textbook of Organic Medicinal and Pharmaceutical Chemistry," C. O. Wilson, O. Gisvold, and R. F. Doerge, Eds., J. B. Lippincott, Philadelphia, Pa., 1966, p. 701.

(2) G. W. Barber and M. Ehrenstein, *Ann. Chem.*, **603,** 89(1957).

(3) C. Djerassi, *Science*, **151,** 1055(1966).

(4) T. Miyake and W. H. Rooks, II, in "Methods in Hormone Research," R. I. Dorfman, Ed., vol. V, 59(1966).

(5) E. H. Reerink, H. F. L. Scholer, P. Westerhof, A. Querido, A. A. H. Kassenaar, E. Diczfalusy, and K. C. Tillinger, *Nature (London)*, **186,** 168(1960).

(6) L. Velluz, J. Mathieu, and G. Nominé, *Tetrahedron Suppl.*, **8,** part II, 495(1966).

(7) M. Ehrenstein, G. W. Barber, and H. Hertz, *Endocrinology*, **60,** 681(1957).

(8) E. Mosettig and I. Scheer, *J. Org. Chem.*, **17,** 764(1952).

(9) R. A. Edgren, R. C. Jones, and D. L. Peterson, *Fert. Steril.*, **18,** 238(1967).

(10) T. Ando, *Bull. Chem. Soc. Jap.*, **13,** 371(1938).

(11) J. F. Klebe, H. Finkbeiner, and D. M. White, *J. Amer. Chem. Soc.*, **88,** 3390(1966).

(12) W. E. Bachmann, M. P. Cava, and A. S. Dreiding, *Helv. Chim. Acta*, **42,** 1790(1959).

(13) J. Elks, J. F. Oughton, and L. Stephenson, Brit. pat. 864,231, 1961.

(14) L. F. Fieser and S. Rajagopalan, *J. Amer. Chem. Soc.*, **71,** 3938(1949).

(15) J. M. Bobbitt, in "Advances in Carbohydrate Chemistry," vol. 11, Academic, New York, N. Y., 1956, p. 1.

(16) G. Slomp, Jr., Y. F. Shealy, J. L. Johnson, R. A. Donia, B. A. Johnson, R. P. Holysz, R. L. Pederson, A. O. Jensen, and A. C. Ott, *J. Amer. Chem. Soc.*, **77,** 1216(1955).

(17) G. Slomp, Jr., and J. L. Johnson, *ibid.*, **80,** 915(1958).

(18) A. Maggiolo and A. Tumolo, *J. Amer. Oil Chemists Soc.*, **38,** 279(1961).

(19) F. L. Greenwood and H. Rubinstein, *J. Org. Chem.*, **32,** 3369(1967).

(20) E. Farkas and R. T. Rapala, U. S. pat. 3,015,666, 1958.

(21) J. R. Durland and H. Adkins, *J. Amer. Chem. Soc.*, **59,** 135(1937); **60,** 1501(1938).

(22) R. V. Petersen and O. Gisvold, *J. Amer. Pharm. Ass., Sci. Ed.*, **45,** 572(1956).

(23) P. N. Rylander and D. R. Steele, *Engelhard Ind. Tech. Bull.*, **3,** 125(1963).

(24) L. F. Fieser and M. Fieser, in "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p. 90.

(25) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **85,** 3027(1963); **87,** 5661(1965); **87,** 5670(1965).

(26) S. Nishimura and H. Taguchi, *Bull. Chem. Soc. Jap.*, **36,** 353(1963).

(27) K. Kindler and L. Blaas, *Chem. Ber.*, **77B,** 585(1944).

(28) K. Kindler, H. Oelschlager, and P. Henrich, *ibid.*, **86,** 167(1953).

(29) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Amer. Chem. Soc.*, **74,** 4223(1952).

(30) "Elucidation of Structures by Physical and Chemical Methods," K. W. Bentley, Ed., Interscience, New York, N. Y., 1963, 34, 161–163.

(31) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21,** 1547(1956).

(32) C. Djerassi, in "Optical Rotatory Dispersion," McGraw-Hill, New York, N. Y., 1960, pp. 51, 71–72, 83, 178, 189.

(33) A. Windaus and P. Borgeaud, *Ann.*, **460,** 235(1928).

(34) L. J. Bellamy, in "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1954, p. 274.

(35) K. Nakanishi in "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1964, pp. 21, 36.

(36) J. A. Cifonelli and F. Smith, *Anal. Chem.*, **26,** 1132(1954).

(37) J. Szmuszkovicz, in "Advances in Organic Chemistry," vol. 4, Interscience, New York, N. Y., 1963, p. 1.

(38) R. P. Linstead, R. R. Whetstone, and P. Levine, *J. Amer. Chem. Soc.*, **64,** 2014(1942).

(39) W. Huckel, R. Mentzel, E. Brinkmann, and E. Kamenz, *Ann.*, **451,** 109(1927).

(40) E. L. McGinnis, G. D. Meakins, and D. J. Morris, *J. Chem. Soc.*, **1967,** 1238.

(41) G. Stork and E. L. Foreman, *J. Amer. Chem. Soc.*, **68,** 2172 (1946).

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