Experimental Section[10]

Dimedone Condensation Product (3) of Gitingensine.—The hydrochloride of gitingensine (**1a**)[1] (250 mg) was treated with 5% sodium bicarbonate solution. The free base was extracted with methylene chloride; the organic solution was washed, dried, filtered, and concentrated *in vacuo*. The dry material was dissolved in 100 ml of anhydrous benzene and 100 mg of dimedone was added. The reaction mixture was gently refluxed for 24 hr, water being eliminated with a Stark separation funnel. The solution was then evaporated to dryness under vacuum and the residue was separated on preparative thin layer chromatoplate on silica gel. The crude product obtained was dissolved in ether and a stream of dry hydrogen chloride was passed through the solution. The crystalline hydrochloride (185 mg) was purified by further crystallization from methylene chloride–acetone to afford the hydrochloride of (**3**), mp 245–260°. Mild base hydrolysis with sodium bicarbonate provided the dimedonyl condensation product (**3**) of gitingensine, exhibiting mp 252–253°; $[\alpha]_D$ + 59°; RD (*c* 0.058, methanol), $[\Phi]_{600}$ +285°, $[\Phi]_{350}$ +1706°, $[\Phi]_{302}$ +9344°, $[\Phi]_{290}$ ±0°, $[\Phi]_{274}$ −12059°, $[\Phi]_{244}$ −10239°, $[\Phi]_{208}$ −23038°; CD (*c* 0.058, ethanol), $[\theta]_{288}$ +13400, $[\theta]_{217}$ +7185; $\lambda_{max}^{dioxane}$ 293 mμ (log ε 4.52); $\nu_{max}^{CHCl_3}$ 3500, 1750, 1580, and 1520 cm^{-1}; nmr, 63.1 (*gem*-dimethyl), 66.1 (19-H), 78.5, 84.7 (21-H, doublet), 129.4 (allylic CH_2 and CH_2CO), ~210–230 (3 β-H), ~265–295 (NH and 20-H), 306 (vinylic H of dimedonyl group), ~324 cps (vinylic 6-H); mass spectrum, M^+ = 451.6, 421.6 (M − $2CH_3$), 311, 140. *Anal.* Calcd for $C_{29}H_{41}O_3N$ (mol wt 451.63): C, 77.12; H, 9.15; N, 3.10. Found: C, 76.66; H, 9.18; N, 3.53.

Dimedone Condensation Product (4b) of 3α-Amino-5α-pregnane.—A solution of 400 mg of 3α-amino-5α-pregnane,[11] 210 mg of dimedone, and 30 mg of *p*-toluenesulfonic acid in 100 ml of anhydrous benzene was heated under reflux for 24 hr, eliminating the water with a Stark separating funnel. After cooling, the benzene layer was washed with 5% sodium bicarbonate–water solution until neutral. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was chromatographed on alumina. Elution with benzene–chloroform (3:7) afforded 450 mg of compound, which was recrystallized in acetone, providing 40 mg of the 3β isomer (**4a**), mp 291–292° (see below).

The mother liquors of these crystals were dissolved in methylene chloride and a stream of dry hydrogen chloride was passed through the solution. The hydrochloride of **4b** which precipitated was crystallized from methanol and then treated with a 5% sodium bicarbonate solution. The free base was extracted with chloroform, washed with water, dried over sodium sulfate, filtered, and evaporated to dryness. The crystalline material was recrystallized from methanol–water to furnish the analytical sample of **4b**: mp 227–228°; $[\alpha]_D$ +44°; RD (*c* 0.004, dioxane), $[\Phi]_{600}$ +187°, $[\Phi]_{320}$ +788°, $[\Phi]_{300}$ +830°, $[\Phi]_{284}$ +3527°, $[\Phi]_{270}$ ±0°, $[\Phi]_{254}$ −2697°, $[\Phi]_{236}$ −3181°, $[\Phi]_{222}$ −4011°, $[\Phi]_{218}$ −2351°; $\lambda_{max}^{dioxane}$ 280 mμ (log ε 4.43); $\nu_{max}^{CHCl_3}$ 3500 and 1540 cm^{-1}; nmr, 34 (18-H), 49.6 (19-H), 64.6 (*gem*-dimethyl), ~132 (CH_2CO), ~222 (3β-H), 307.9 cps (vinylic H of dimedonyl group). *Anal.* Calcd for $C_{29}H_{47}ON$: C, 81.82; H, 11.13; O, 3.76; N, 3.29. Found: C, 81.70; H, 11.13; O, 3.76; N, 3.20.

Dimedone Condensation Product (4a) of 3β-Amino-5α-pregnane.—A solution containing 200 mg of 3β-amino-5α-pregnane,[12] 100 mg of dimedone, and 20 mg of *p*-toluenesulfonic acid in 100 ml of benzene was refluxed under the conditions described above for the preparation of **4b**. After the usual extraction procedure, the crude material was chromatographed on neutral alumina. Elution with benzene–chloroform (3:2) afforded 130 mg of the crystalline condensation product (**4a**) which, after recrystallization from methylene chloride–hexane, exhibited mp 291–292°; $[\alpha]_D$ +35°; RD (*c* 0.0005, dioxane), $[\Phi]_{600}$ +151°, $[\Phi]_{350}$ −815°, $[\Phi]_{301}$ −2506°, $[\Phi]_{296}$ −3842°, $[\Phi]_{284}$ −1503°, $[\Phi]_{274}$ ±0°, $[\Phi]_{256}$ +3174°, $[\Phi]_{226}$ ±0°; $\lambda_{max}^{dioxane}$ 280 mμ (log ε 4.44); $\nu_{max}^{CHCl_3}$ 3400, 1580, and 1520 cm^{-1}; nmr, 33.8 (18-H), 48.9 (19-H), 63.8 (*gem*-dimethyl), 130 (CH_2CO), 180–204 (3α-H), ~283 (NH), 309.6 cps (vinylic H of dimedonyl group). *Anal.* Calcd for $C_{29}H_{47}ON$: C, 81.82; H, 11.13; O, 3.76; N, 3.29. Found: C, 81.84; H, 11.01; O, 3.74; N, 3.39.

Dimedone Condensation Product (5) of 3β-Amino-20β-hydroxypregn-5-ene.—Holafillamine hydrochloride[13] (300 mg) in 25 ml of methanol was treated with 600 mg of sodium borohydride. At the end of the reaction, water was added and the compound extracted with chloroform. The organic layer was washed, dried, filtered, and evaporated *in vacuo*. The crude extract (265 mg), devoid of absorption in the carbonyl region, was dissolved in 70 ml of benzene. After addition of 117 mg of dimedone and 50 mg of *p*-toluenesulfonic acid, the reaction mixture was treated as described above. The dimedonyl derivative, isolated as its hydrochloride (*vide supra*), was treated with a water solution of 5% sodium bicarbonate. The precipitate which formed was filtered, dried (280 mg), and recrystallized from acetone–hexane solution to provide the analytical sample of **5** with the following properties: mp 294–296°; $[\alpha]_D$ +82°; RD (*c* 0.0005, dioxane), $[\Phi]_{600}$ −353°, $[\Phi]_{350}$ −2032°, $[\Phi]_{293}$ −6626°, $[\Phi]_{288}$ −14799°, $[\Phi]_{270}$ ±0°, $[\Phi]_{260}$ +3534, $[\Phi]_{242}$ ±0°, $[\Phi]_{231}$ −884°, $[\Phi]_{224}$ ±0°, $[\Phi]_{212}$ +12370°; $\lambda_{max}^{dioxane}$ 280 mμ (log ε 4.43); $\nu_{max}^{CHCl_3}$ 3600, 1580, and 1520 cm^{-1}; nmr, 47 (18-H), 61 (19-H), 63 (*gem*-dimethyl), 61.72 (21-H), ~132 (CH_2CO), 170–195 (3α-H), 308.5 (vinylic H of dimedonyl group), 324.5 cps (C-6H). *Anal.* Calcd for $C_{29}H_{45}O_2N$: C, 79.22; H, 10.32; O, 7.28; N, 3.19. Found: C, 79.07; H, 10.25; O, 7.35; N, 3.33.

N-Methyldihydro-5α-paravallarine (6a).[7]—RD (*c* 0.005, dioxane), $[\Phi]_{360}$ ±0°, $[\Phi]_{280}$ −190°, $[\Phi]_{256}$ ±0°, $[\Phi]_{247}$ +210°, $[\Phi]_{240}$ ±0°, $[\Phi]_{215}$ −4500°, and CD (*c* 0.06, dioxane), $[\theta]_{270}$ ±0, $[\theta]_{235}$ +3100 (extremum not reached), were properties shown by **6a**.

N-Methyldihydro-5α-20-isoparavallarine (6b).[7]—RD (*c* 0.005, dioxane), $[\Phi]_{350}$ ±0°, $[\Phi]_{260}$ −520°, $[\Phi]_{233}$, −1830°, $[\Phi]_{210}$ −530°, and CD (*c* 0.04, dioxane), $[\theta]_{260}$ ±0°, $[\theta]_{236}$ −2100 (extremum not reached), were properties shown by **6b**.

Registry No.—**1a**, 13084-70-3: **3**, 13084-71-4; **4a**, 13084-72-5; **4b**, 13084-73-6; **5**, 13084-74-7.

(10) Microanalyses were done by Dr. A. Bernhardt, Mühlheim, Germany. Melting points were determined with a Bausch and Lomb apparatus; they are corrected. Rotations were taken between 16 and 22° with a 1-dm tube at sodium D light. RD curves were taken with an automatic recording JASCO/UV-5 spectropolarimeter. CD curves have been obtained with a ORD-CD JACSO instrument and with a Jouan dichrograph at the University of California and Braunschweig, Germany, through the kind cooperation of Professor J. Cymerman Craig and Dr. H. Wolf. Infrared spectra were taken with a Perkin-Elmer Model 21 NaCl prism. Ultraviolet absorption spectra were obtained with a Beckman spectrophotometer, Model DU. The nmr spectra were recorded at 60 Mcps using 5–8% w/v solutions of substance in chloroform containing tetramethylsilane (TMS) as an internal reference. Resonance frequencies, ν, are quoted as cps downfield from the TMS reference (0.0 cps) and are accurate to ±1 cps. We are indebted to Dr. L. Throop, Syntex Research, Palo Alto, Calif., for several RD curves and nmr spectra and to Syntex S.A., Mexico, for a generous gift of steroid used as starting material in this work.

(11) M. M. Janot, Q. Khuong-Huu, X. Lusinchi, and R. Goutarel, *Bull. Soc. Chim. France*, 1669 (1960).

(12) C. W. Shoppee, D. E. Evans, H. C. Richards, and G. H. R. Summers, *J. Chem. Soc.*, 1649 (1956).

(13) M. M. Janot, A. Cavé, and R. Goutarel, *Bull. Soc. Chim. France*, 896 (1959).

Steroids. VII. The Synthesis and Reactions of Some α,β-Unsaturated α′-Oximino-3-keto Steroids[1a]

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The conversion of a number of 3-keto steroids into the corresponding 2,4-bisoximino 3-ketones was described in the previous paper of this series.[1a] We now report the results of the nitrosation of several α,β-unsaturated 3-keto steroids. The products of these reactions were of interest to us as precursors of new types of unsaturated α-diazo ketones.

(1) (a) Part VI of this series: M. P. Cava, E. J. Glamkowski, and P. M. Weintraub, *J. Org. Chem.*, **31**, 2755 (1966). (b) To whom all correspondence should be addressed at the Department of Chemistry, Wayne State University, Detroit, Mich. 48202.

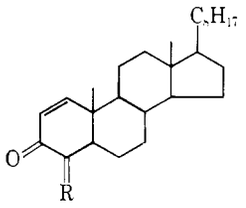
Base-catalyzed nitrosation of cholest-1-en-3-one (I) afforded, in moderate (32%) yield, 4-oximinocholest-1-en-3-one (II), mp 174–175° dec. The oxime function of II was found to be *anti* to the carbonyl group, as evidenced by the formation of colored metal complexes.[1a,2] The ultraviolet spectrum of II exhibits a single maximum at 240 mμ in neutral solution; in basic solution, maxima at both 236 and 325 mμ are observed. In contrast, saturated α-oximino ketones having the *anti* configuration show only a single bathochromically shifted maximum in basic solution.[1a,3,4]

Oximino ketone II was treated with chloramine in an attempt to prepare 4-diazocholest-1-en-3-one (III). The presence of III in the amorphous reaction product was indicated by the presence of a typical diazo absorption band at 4.79 μ; however, since pure crystalline III could not be isolated, this material was not further investigated.

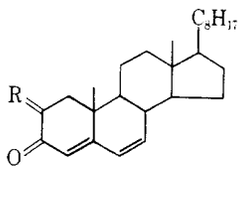
Base-catalyzed nitrosation of cholesta-4,6-dien-3-one (IV) afforded a single crystalline oximino ketone, mp 235–237°, in good (61%) yield; this compound was assigned the structure of 2-oximinocholesta-4,6-dien-3-one (V) for the following reasons, which effectively eliminate the two alternate structures Va and Vb. The new oximino ketone gives colored complexes with various metal ions, behavior typical only of an α-oximino ketone of *anti* configuration. This fact eliminated from further consideration structure Vb, which is not an α-oximino ketone. Confirmation of structure V, opposed to structure Va, was then obtained by its catalytic reduction, which gave a mixture of two isomeric saturated α-oximino ketones, both of which were shown to be *anti* oximes by their positive color tests with metal ions. The first reduction product, mp 273°, was identical with the known 2-oximinocholestan-3-one (VI).[3b] The second reduction product, mp 192°, was therefore the previously unreported 2-oximinocoprostan-3-one (VII).

Oximino ketone V reacted with acetic anhydride in pyridine to give 2-acetoximocholesta-4,6-dien-3-one (VIII), mp 118–119°. This compound was recovered totally unchanged after being heated for 1 hr in refluxing acetone; it was hydrolyzed in good yield to oximino ketone V by hydrochloric acid in aqueous acetone at room temperature. The reluctance of acetate VIII to undergo the Beckmann rearrangement is in marked contrast to the behavior of the D-ring α-acetoximino ketone IX, which is reported to undergo a second-order Beckmann cleavage on treatment with aqueous acid or base or even on attempted recrystallization from aqueous methanol.[5] The reaction of oximino ketone V with chloramine afforded, in satisfactory (50%) yield, the bright yellow 2-diazocholesta-4,6-dien-3-one (X), mp 104–105°. The infrared spectrum of X showed a strong diazo band at 4.77 μ, as well as bands at 6.15 and 6.43 μ, characteristic of the conjugated unsaturated ketone system.

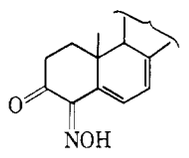
Attempts to effect a photochemical Wolff rearrangement of diazo ketone X to an acid of structure XI were completely unsuccessful, since no bicarbonate-soluble material was produced by photolysis in aqueous tetrahydrofuran or in a two-phase benzene–water mixture. It seems likely that the carbene formed by loss of nitrogen from X preferentially undergoes a hydride shift to give trienone XII; the further photochemical transformation of XII to a very complex mixture of ketonic and phenolic products is to be expected.[6] The procedures used in the preparation of V and X were readily applied in the androstane series to the synthesis of the testosterone-related compounds 2-oximinoandrosta-4,6-



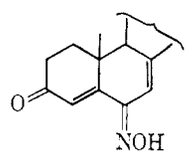
I, R = H, H
II, R = NOH
III, R = N_2



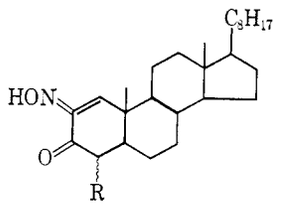
IV, R = H, H
V, R = NOH
VIII, R = $NOCOCH_3$
X, R = N_2



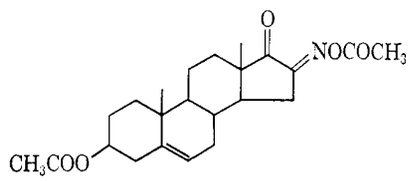
Va



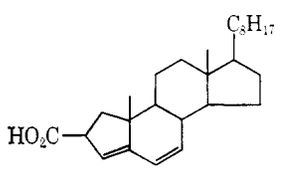
Vb



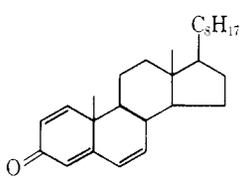
VI, R = α-H
VII, R = β-H



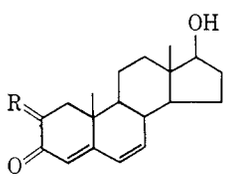
IX



XI



XII



XIII, R = NOH
XIV, R = N_2

(2) N. V. Sidgwick, "The Organic Chemistry of Nitrogen," Oxford University Press, Oxford, 1937, p 195.

(3) (a) M. P. Cava and B. R. Vogt, *J. Org. Chem.*, **30**, 3775 (1965); (b) M. P. Cava, P. M. Weintraub, and E. J. Glamkowski, *ibid.*, **31**, 2015 (1966).

(4) D. H. R. Barton and J. Beaton, *J. Am. Chem. Soc.*, **83**, 4083 (1961).

(5) A. Hassner and I. H. Pomerantz, *J. Org. Chem.*, **27**, 1760 (1962).

(6) H. Dutler, C. Ganter, H. Ryf, E. C. Utzinger, K. Weinberg, K. Schaffner, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **65**, 2346 (1962); see also C. Ganter, E. C. Utzinger, K. Schaffner, D. Arigoni, and O. Jeger, *ibid.*, **65**, 2403 (1962).

dien-17β-ol-3-one (XIII) and 2-diazoandrosta-4,6-dien-17β-ol-3-one (XIV).

Experimental Section[7]

4-Oximinocholest-1-en-3-one (II).—Cholest-1-en-3-one[3a] (5.00 g) was dissolved in a stirred solution of commercial potassium *t*-butoxide (6.00 g) in dry *t*-butyl alcohol (250 ml) kept under a nitrogen atmosphere. *n*-Butyl nitrite (2.50 ml) was added through a dropping funnel and the resulting purple solution was stirred for 4 hr at room temperature. The resulting thick suspension of potassium salt was diluted with water (250 ml), ether (500 ml) was added, and the mixture was acidified with dilute hydrochloric acid. The organic phase was washed successively with aqueous sodium bicarbonate and water, dried, and evaporated *in vacuo*. Crystallization of the resulting foam (3.00 g) from ether–hexane afforded pure II (1.71 g, 32%) as pale yellow flakes: mp 174–175° dec; $[\alpha]^{27}D$ +50.0° (*c* 0.52); λ_{max} 3.06, 5.88, and 6.15 μ; $\lambda_{max}^{neutral}$ 240 mμ (ε 9000); λ_{max}^{basic} 236 mμ (ε 11,600) and 325 mμ (ε 4960).

Anal. Calcd for $C_{27}H_{44}O_2N$: C, 78.21; H, 10.69; N, 3.38. Found: C, 78.12; H, 10.41; N, 3.45.

The metal complexes of oximino ketone II were observed by adding 1 drop of a 5% aqueous solution of the metal cation [M-(OAc)$_2$] to a solution (2 mg/ml) of II in ethanol. The following complexes were observed: Ni^{2+} (brownish yellow), Cu^{2+} (green), Co^{2+} (crimson), Fe^{2+} (deep blue, becoming green).

Attempted Preparation of 4-Diazocholest-1-en-3-one (III).—Oximino ketone II (7.20 g) was treated with chloramine by the usual procedure (see ref 3a for typical examples) and the crude product was purified by chromatography on Woelm alumina (neutral III, benzene eluent). The resulting yellow gum (3.70 g) showed moderate absorption (infrared) at 4.79 μ, but it could be neither crystallized nor further purified by rechromatography.

Cholesta-4,6-dien-3-one (IV).—This compound was prepared by the chloranil dehydrogenation method of Agnello and Laubach.[8] Since these authors give no details for the specific preparation of IV and since we have found detailed directions to be of considerable utility for large-scale preparations, our procedure is reproduced below. A stirred mixture of cholest-5-en-3-one[9] (25.00 g), chloranil (60 g), and *t*-butyl alcohol (1500 ml) was refluxed for 3 hr. Excess chloranil was removed by filtration from the cooled solution and the filtrate was evaporated *in vacuo*. The brown residue was dissolved in warm benzene (*ca.* 30 ml) and adsorbed on a tall column of Alcoa alumina (700 g), the column being eluted with benzene until a yellow eluate no longer passed through. The eluate was evaporated and the resulting oil was crystallized from methanol to give IV as pale yellow needles (12.5 g, 50%), mp 82–82.5° (lit.[10] 80.5–81.5°).

2-Oximinocholesta-4,6-dien-3-one (V).—The procedure employed was the same as that described above for the preparation of II, except that only 100 ml of *t*-butyl alcohol was used as the reaction solvent. The crude reaction product from 5.00 g of cholesta-4,6-dien-3-one (IV) was crystallized twice from ethanol to give oximino ketone V (6.56 g, 61%) as pale yellow plates: mp 235–237° dec; $[\alpha]^{29}D$ −36.8° (*c* 1.06); λ_{max} 3.09, 5.91, 61.5, 6.20, and 6.28 μ; $\lambda_{max}^{neutral}$ 311 mμ (ε 28,800); λ_{max}^{basic} 299 mμ (ε 25,900) and 344 mμ (ε 11,100).

Anal. Calcd for $C_{27}H_{41}O_2N$: C, 78.78; H, 10.04; N, 3.40. Found: C, 78.90; H, 10.14; N, 3.17.

Using a solution (4 mg/ml) of V in ethanol, the following metal complexes were observed: Ni^{2+} (green, precipitate), Co^{2+} (orange, precipitate), Cu^{2+} (dark green, precipitate), Fe^{2+} (blue, becoming green and finally brown).

Catalytic Reduction of 2-Oximinocholesta-4,6-dien-3-one.—A solution of 2-oximinocholesta-4,6-dien-3-one (0.100 g) in dry purified tetrahydrofuran (25 ml) containing 5% palladium on charcoal (0.100 g) was hydrogenated at atmospheric pressure. After 11 min, 2 equiv of hydrogen was taken up and the reduction was interrupted. Evaporation of the filtered solution afforded a residue which was dissolved in a small volume of tetrahydrofuran and applied to a silica gel preparative thin layer plate. Development of the plate by 1:1 benzene–ethyl acetate caused the separation of three zones (A, R_f 0.95; B, R_f 0.87; C, R_f 0.70), which were detectable under ultraviolet light. The zones were removed from the plate and extracted repeatedly with 1:1 tetrahydrofuran–methanol. Zone A yielded only a small amount of brown gum which was rejected. Zone B yielded, after crystallization from tetrahydrofuran–methanol, small white crystals (0.035 g, 35%) of 2-oximinocoprostan-3-one (VII): mp 192°; $[\alpha]^{25}D$ +2.5° (*c* 1.26 tetrahydrofuran); λ_{max} 2.90, 5.90, 6.20, 9.72, 9.85, 10.06, 12.60, and 13.59 μ; $\lambda_{max}^{neutral}$ 246 mμ (ε 9220); λ_{max}^{basic} 303 mμ (ε 19,900).

Anal. Calcd for $C_{27}H_{45}O_2N$: C, 78.02; H, 10.91; N, 3.37. Found: C, 78.18; H, 10.76; N, 3.74.

Compound VII formed an orange-brown Co^{2+} complex and a green Cu^{2+} complex, indicating the *anti* configuration of the oxime function.

Zone C, obtained above, yielded, after crystallization from tetrahydrofuran–methanol, small white crystals of 2-oximinocholestan-3-one (VI): mp 273° (lit.[3b] mp 268–270°), $[\alpha]^{26}D$ +50.7° (*c* 0.41, tetrahydrofuran). This material was identical (infrared, ultraviolet, tlc, metal complex colors) with an authentic sample prepared from cholestan-3-one.[3b]

2-Acetoximinocholesta-4,6-dien-3-one (VIII).—A solution of 2-oximinocholesta-4,6-dien-3-one (0.500 g) in a mixture of pyridine (5 ml) and acetic anhydride (2 ml) was kept for 6 hr at room temperature. Water (350 ml) was added and the product was extracted into ether. Evaporation of the washed and dried ethereal layer gave a residue (0.421 g) which crystallized from ether–petroleum ether as yellow-green platelets (0.271 g, 49%): mp 118–119°; λ_{max} 5.65, 5.96, 6.17, 6.24, and 6.29 μ; λ_{max} 220 mμ (ε 9530) and λ_{max} 315 mμ (ε 24,700).

Anal. Calcd for $C_{29}H_{43}O_3N$: C, 76.78; H, 9.55; N, 3.08. Found: C, 76.79; H, 9.28; N, 3.22.

Metal ions (Ni^{2+}, Cu^{2+}, and Co^{+2}) gave no immediate color with alcoholic solutions of VIII, but color appeared gradually on standing owing to hydrolysis of the acetyl group and formation of V.

Hydrolysis of 2-Acetoximinocholesta-4,6-dien-3-one.—A solution of acetate VIII (1.25 g) in a mixture of acetone (50 ml), water (10 ml), and concentrated hydrochloric acid (5 ml) was kept for 24 hr at room temperature. The gradual addition of water, followed by cooling, caused the separation of crystalline 2-oximinocholesta-4,6-dien-3-one (0.984 g, 87%), the infrared spectrum of which was superimposable on that of an authentic specimen.

2-Diazocholesta-4,6-dien-3-one (X).—A suspension of 2-oximinocholesta-4,6-dien-3-one (10.0 g) in a mixture of tetrahydrofuran (20 ml), 5 *N* sodium hydroxide solution (15 ml), and concentrated ammonium hydroxide (20 ml) was stirred to effect solution of the solid. The brownish red solution was cooled to 1–2° and benzene (300 ml) and a 5.25% solution of sodium hypochlorite (40 ml of Clorox) were added. The mixture was stirred an additional 3 hr without external cooling. The washed and dried organic layer was evaporated *in vacuo*. Crystallization of the residue from ether–hexane afforded the diazo ketone X (4.95 g, 50%) as bright yellow prisms: mp 105–106°; $[\alpha]^{30}D$ −108.0° (*c* 1.00); λ_{max} 4.78, 6.15, 6.43, 7.24, and 7.38 μ; λ_{max} 234 mμ (ε 7950), 288 mμ (ε 19,600), and 345 mμ (ε 10,600).

Anal. Calcd for $C_{27}H_{40}ON_2$: C, 79.36; H, 9.87; N, 6.86. Found: C, 79.27; H, 9.86; N, 6.83.

Photolysis of 2-Diazocholesta-4,6-dien-3-one.—A solution of diazo ketone X (0.500 g) in a mixture of tetrahydrofuran (50 ml) and water (50 ml) containing sodium bicarbonate (1.0 g) was irradiated with a low-pressure Hanovia lamp for 45 min, after which time nitrogen evolution ceased. Extraction of the mixture with ether afforded a red neutral gum (~0.50 g) which showed no diazo absorption in the infrared and from which no crystalline product could be isolated either by direct crystallization or by chromatography on silicic acid. Acidification of the aqueous bicarbonate solution from the irradiation afforded no acid fraction.

2-Oximinoandrosta-4,6-dien-17β-ol-3-one (XIII).—Testosterone was dehydrogenated with chloranil in the manner described for the preparation of dienone IV. Crystallization from aqueous ethanol afforded androsta-4,6-dien-17β-ol-3-one

(7) All melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 237 spectrophotometer (potassium bromide disks). Ultraviolet absorption spectra were determined in 95% ethanol and with a Perkin-Elmer Model 4000 Spectracord; basic solutions were obtained by adding a few drops of 0.1 *N* aqueous sodium hydroxide to the neutral solutions. All optical rotations were measured in chloroform solution, unless otherwise indicated. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., and by Dr. A. Bernhardt, Mülheim, Germany.

(8) E. J. Agnello and G. D. Laubach, *J. Am. Chem. Soc.*, **82**, 4293 (1960).

(9) L. F. Fieser, *ibid.*, **75**, 5421 (1953).

(10) A. L. Wilds and C. Djerassi, *ibid.*, **68**, 1712 (1946).

(48% yield) as pale yellow needles, mp 205–206° (lit.[11] mp 204–205°). *n*-Butyl nitrite (2.50 ml) was added slowly to a stirred solution (N_2 atmosphere) of androsta-4,6-dien-17β-ol-3-one (5.00 g) and potassium *t*-butoxide (6.00 g) in dry *t*-butyl alcohol. After 2 hr, the thick suspension was diluted with water (250 ml) and the solution was extracted with two 250-ml portions of ether. The aqueous phase was covered with ethyl acetate (500 ml) and the stirred mixture was acidified with dilute hydrochloric acid. The organic phase was washed successively with aqueous sodium bicarbonate and water, dried, and evaporated *in vacuo*. Crystallization of the resulting residue (4.10 g) from acetone afforded oximino ketone XIII (3.80 g, 69%) as yellow needles: mp 241–242° dec; $[\alpha]^{29}D$ +8.3° (*c* 0.78); λ_{max} 2.96–3.05, 6.03, 6.17, and 6.25 μ; $\lambda_{max}^{neutral}$ 310 mμ (ε 20,400); λ_{max}^{basic} 297 mμ (ε 20,000) and 343 mμ (ε 11,400).

Anal. Calcd for $C_{19}H_{25}O_3N$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.28; H, 8.01; N, 4.41.

Using a solution (6 mg/ml) of XIII in ethanol, the following metal complexes were observed, indicative of the *anti* configuration of the oxime function: Ni^{2+} (brown), Co^{2+} (crimson), Cu^{2+} (green), and Fe^{2+} (blue, becoming green).

The acetylation of 2-oximinoandrosta-4,6-dien-17β-ol-3-one with acetic anhydride in pyridine at room temperature afforded, after the usual work-up (see preparation of VIII), yellow rosettes (from benzene–ether) of 17β-acetoxy-2-acetoximinoandrosta-4,6-dien-3-one: mp 185–187° dec; λ_{max} 5.64, 5.79, 5.97, 6.22, and 6.34 μ; λ_{max} 222 mμ (ε 8500) and 313 mμ (ε 22,500).

Anal. Calcd for $C_{23}H_{29}O_5N$: C, 69.15; H, 7.32; N, 3.51. Found: C, 69.30; H, 7.41; N, 3.60.

2-Diazoandrosta-4,6-dien-17β-ol-3-one (XIV).—To a stirred solution of 2-oximinoandrosta-4,6-dien-17β-ol-3-one (0.700 g) in tetrahydrofuran (10 ml) and 1 *N* sodium hydroxide (5 ml) was added ether (500 ml, precooled to 5°), followed by concentrated ammonium hydroxide (3 ml) and 5.25% sodium hypochlorite (10 ml of Clorox). The two-phase system was stirred at 0–5° for 1 hr and then at room temperature for 2 hr. The washed and dried ethereal phase, on concentration to a small volume, deposited diazo ketone XIV as long yellow needles, decomposing at *ca.* 165° without melting: $[\alpha]^{30}D$ −77.0° (*c* 1.00); λ_{max} 2.92, 4.77, 6.22, 6.37, 7.25, and 7.34 μ; λ_{max} 243 mμ (ε 7960), 287 mμ (ε 20,500), and 345 mμ (ε 10,700).

Anal. Calcd for $C_{19}H_{24}O_2N_2$: C, 73.04; H, 7.74; N, 8.97. Found: C, 72.62; H, 7.54; N, 8.85.

Registry No.—II, 13341-54-3; IV, 566-93-8; V, 13341-55-4; VI, 6901-58-2; VII, 13341-57-6; VIII, 13341-58-7; X, 13341-59-8; XIII, 5541-21-9; XIV, 13341-61-2; 17β-acetoxy-2-acetoximinoandrosta-4,6-dien-3-one, 13341-62-3.

Acknowledgment.—This investigation was supported by Public Health Service Research Grants CY-4498 and CA-04498, National Institutes of Health.

(11) C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufmann, and J. Pataki, *J. Am. Chem. Soc.*, **72**, 4534 (1950).

Autoxidation of Steroid $\Delta^{3,5}$-dien-3-ol Ethers. A Simple Route to 6β-Hydroxy Δ^4-3-Ketones

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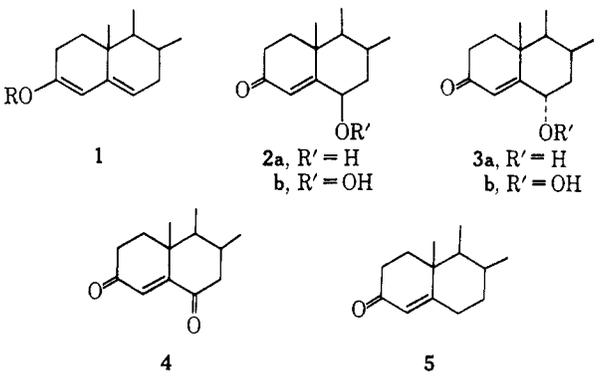
Steroids hydroxylated at C-6 are of current interest for metabolic studies. Formation of 6-hydroxy Δ^4-3-ketones from the enol ethers of the corresponding Δ^4-3-ketones by per acid oxidation[1,2] has been reported by Smith, *et al.*,[3] and by Dusza, *et al.*[4] We wish to report on the preparation of 6β-hydroxy Δ^4-3-keto steroids by a different reaction, still starting from $\Delta^{3,5}$-dienol ethers.

The main degradative process of enol ethers **1**, of course in the absence of acids, is autoxidation to give 6β- and 6α-hydroxy Δ^4-3-ketones (**2a** and **3a**). This occurs in both solution and solid state.



1 **2a**, R′ = H; **b**, R′ = OH **3a**, R′ = H; **b**, R′ = OH **4** **5**

Experiments carried out in different solvents and the analogy to other autoxidations suggest that the reaction is a free-radical chain process. It is initiated by the light and by radical generators such as benzoyl peroxide or azobisisobutyronitrile and inhibited by antioxidants such as tocopherols or butylhydroxyanisol and by inorganic and organic bases, the latter being effective only if having a pK_b lower than 6. The time required for the complete disappearance of the enol ether, as shown by thin layer chromatography, varied in the light between 2 and 35 hr according to the nature of the solvent and of the irradiation (direct sunlight, diffuse daylight, fluorescent lamp, incandescent photolamp), being least in direct sunlight. In the dark and in the presence of radical generators, at least 50 hr are necessary. As to the solvent, autoxidation proceeded at the highest rate in alcoholic solution. In direct sunlight, in ethanol, and without initiators, enol ethers **1** reacted practically completely in 2 hr at an average temperature of 30°, yielding 6β-hydroxy Δ^4-3-ketones (**2a**) as the main products.

The nature of the etherifying alcohol did not seem to affect sensibly the reaction rate, at least for the aliphatic and cycloaliphatic types.[5] Among the enol ethers tested, only the phenyl and benzyl ethers survived autoxidation conditions. Except for the substitutions at C-6, the influence of the nature of the parent steroid could not be easily settled, although it seemed generally unimportant. The marked increase of reaction time observed with certain compounds was very likely due to their low solubility and to the necessity of using different solvent mixtures. As to the 6-substituted derivatives, enol ethyl ether of 6-chloroprogesterone did not undergo autoxidation, while enol ethyl ether of 6-methyl-17α-hydroxy-pregn-4-ene-3,20-dione did, but only in low yield, owing to the formation of remarkable amounts of the hydrolysis product.

Iodometric titration of the alcoholic solution after autoxidation revealed variable amounts of active

(1) For the same reaction on Δ^2- and Δ^3-enol ethers of 5α-3-ketones, see R. Gardi, P. P. Castelli, and A. Ercoli, *Tetrahedron Letters*, 497 (1962).

(2) Similar results have been obtained by *t*-butyl chromate oxidation of Δ^4-3-ketone enol ethers and enol acetates by K. Ysuda, *Chem. Pharm. Bull.* (Tokyo), **11**, 1167 (1963); *Chem. Abstr.*, **59**, 12864 (1963).

(3) L. L. Smith, J. J. Goodman, H. Mendelsohn, J. P. Dusza, and S. Bernstein, *J. Org. Chem.*, **26**, 974 (1961).

(4) J. P. Dusza, J. P. Joseph, and S. Bernstein, *ibid.*, **27**, 4046 (1962).

(5) Experiments carried out on suitable derivatives proved that the nonsteroidal alcoholic moiety of the enol ethers can be recovered as alcohol.