

Steroidal Indoxyls, Indoles, and Quinolines¹

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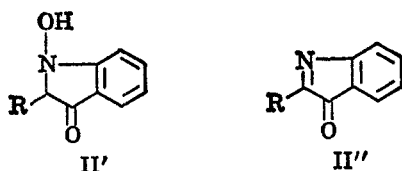
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3 β -Hydroxy-5-androsten-17-one (Ib) was converted to a steroidal indoxyl IIb by a novel reaction with *o*-nitrobenzaldehyde. Other 17-keto steroids gave similar products. The proposed structure (II) is consistent with the chemical reactions of these compounds, and is corroborated by infrared, nmr, and ultraviolet spectra. The conversion of I to II proceeded *via* the aldol intermediate XI rather than *via* the *o*-nitrobenzal ketone V. The latter intermediate (V) provides another route to steroidal quinolines. A mechanism for the formation of II which involves intramolecular carbanion attack on a nitro group is proposed and discussed.

In a previous paper² we reported that 17-keto steroids condense with *o*-aminobenzaldehyde and with isatin, respectively, to yield steroidal quinolines. In connection with our studies of syntheses of steroidal nitrogen compounds³ we investigated the condensation of *o*-nitrobenzaldehyde with 17-keto steroids. It has been reported⁴ that basic media are often unsuitable for aldol condensations of ketones with *o*-nitrobenzaldehyde and that such reactions are best performed in sulfuric acid medium. However, as acidic conditions were found ineffective in condensations of 3 β -hydroxy-5-androsten-17-one (Ib) with *o*-nitrobenzaldehyde,⁵ we turned our attention again to the investigation of this reaction under basic conditions.

The expected *o*-nitrobenzal ketone (Vb) was not formed, but we were able to isolate in good yield⁴ a yellow acidic material showing no infrared absorption for a nitro group. The possible structure VIIb (Chart I), formed by photolytic conversion of *o*-nitrobenzaldehyde to *o*-nitrosobenzoic acid and then reaction with Ib, was discarded for the product of the condensation reaction since Ib did not react with *o*-nitrosobenzoic acid. 3 β -Hydroxy-5-androsten-17-one (Ib) reacted even in the dark with *o*-nitrobenzaldehyde to give the yellow acid, the ultraviolet spectrum of which suggested a highly conjugated system (maxima at 238, 262, and 455 m μ). The acid formed a brown 2,4-dinitrophenylhydrazone and displayed fluorescence when dissolved in organic solvents. This, and other evidence shown below, strongly suggested an indoxyl structure for the acidic reaction product of 5-androsten-3 β -ol-17-one (Ib) with *o*-nitrobenzaldehyde under basic conditions.

Partial structure II' and II'' for the yellow acid, although mechanistically attractive, were eliminated from consideration, the former on the basis of elemental analysis, color, and acetylation experiments and the latter on the basis of infrared spectra (presence



(1) (a) Stereochemistry of Organic Nitrogen Compounds. XVI. Nitro Compounds. V. For paper IV, see A. Hassner and D. R. Fitchman, *Tetrahedron Letters*, 1991 (1966). (b) This work was supported by Grant CY-4474 of the National Cancer Institute, National Institutes of Health. (c) A preliminary report of part of this work has appeared in *Tetrahedron Letters*, No. 21, 975 (1962).

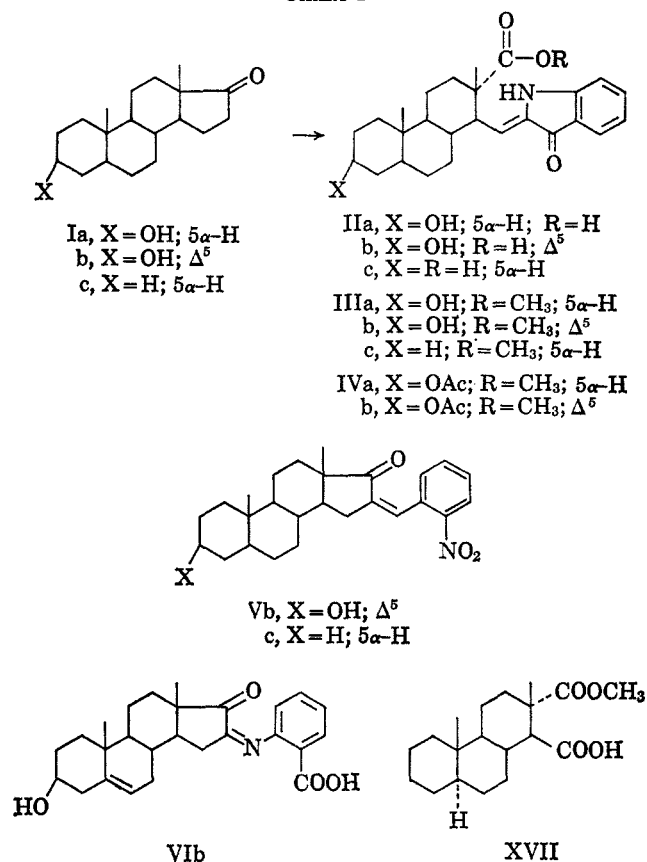
(2) A. Hassner and M. J. Haddadin, *J. Org. Chem.*, **27**, 1911 (1962).

(3) A. Hassner and C. Heathcock, *ibid.*, **30**, 1748 (1965).

(4) (a) A. Hassner and N. H. Cromwell, *J. Am. Chem. Soc.*, **80**, 893 (1958); (b) G. Singh and T. N. Ray, *J. Indian Chem. Soc.*, **7**, 638 (1930).

(5) F. Weigert and L. Kummerer, *Ber.*, **46**, 1207 (1913).

CHART I



of NH absorption). An isotogen structure is untenable for similar reasons.⁶ The long wavelength maximum in the ultraviolet spectrum of the yellow acid showed a bathochromic displacement with respect to the maximum of indoxyls⁷ (400 m μ). The infrared spectrum likewise was characteristic of indoxyls⁸ with strong bands at 3400 and 1610 cm⁻¹, a band at 1690 cm⁻¹ due to a conjugated five-membered ring ketone, and a band at 1640 cm⁻¹ for a conjugated double bond. Bands indicative of a 1,2-disubstituted phenyl system were present at 750 and 705 cm⁻¹. A carboxy group was indicated by absorption in the 2400–2750-cm⁻¹ region.

The analogous yellow acid IIa, obtained by reaction of 3 β -hydroxyandrostane-17-one (Ia) with *o*-nitrobenzaldehyde, showed in the nmr spectrum the presence of an olefinic hydrogen split by one hydrogen (a doublet at τ 4.23, J = 10.1 cps) in addition to an NH and to

(6) Isotogens (the N-oxides of II'') are known to arise from ultraviolet light catalyzed reactions of certain *o*-nitrostyrenes and α -(*o*-nitrophenyl)- β -phenylethanols; e.g., F. Kroehnke and I. Vogt, *ibid.*, **35**, 387 (1952).

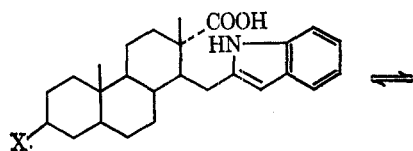
(7) B. Witkop, *J. Am. Chem. Soc.*, **73**, 614 (1950).

(8) B. Witkop and J. B. Patrick, *ibid.*, **73**, 2188 (1951).

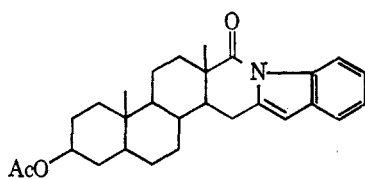
aromatic hydrogens characteristic of indoxyls or anthranilic acid type compounds. Fischer esterification or treatment with diazomethane of 3 β -hydroxy-16,17-seco-16-nor-5-androsten-15-(2'-indoxyliden)-17-oic acid (IIb) yielded a methyl ester IIIb which could be acetylated at room temperature to the corresponding 3-acetate IVb. Oppenauer oxidation converted alcohol IIIb into a Δ^4 -3-ketoindoxyl (III), indicating that the functional groups at positions 3 and 5 had been unaffected in the conversion of Ib to IIb. When indoxyl IIc, prepared by an analogous reaction of androstan-17-one (Ic) with *o*-nitrobenzaldehyde, was converted to IIIc, the latter was found to exhibit in potassium bromide as well as in chloroform solution strong NH absorption at 3350 cm^{-1} , indoxyl carbonyl and methyl ester carbonyl absorptions at 1700 and 1730 cm^{-1} , characteristic absorptions at 1640 and 1610 cm^{-1} , and an nmr doublet at τ 4.23 ($J = 10.1$ cps), all indicative of structure IIc.

Oxidation of IIIc with chromic acid gave XVII and isatin, thus providing additional evidence for the presence of the indoxyl nucleus. The latter reaction suggests the feasibility of a two-step degradation of cyclic ketones resulting in cleavage with loss of one carbon atom (Ic \rightarrow IIc \rightarrow XVII).

Indoxyl IIb was reduced by sodium borohydride in alcohol with simultaneous loss of water to yield the steroidal indole VIIIb. The latter gave a positive Ehrlich test⁹ and had an ultraviolet spectrum almost identical with that of 2-methylindole. The fact that indole VIIIb was converted by heating with acetic anhydride to the lactam IXb (no NH, COOH, or an-



VIIIa, X = OH
b, X = OH, Δ^5

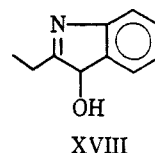


IXa
b, Δ^5

hydride bands in the infrared) also implied a 2- rather than a 3-substituted indole structure for VIIIb. Ring closure of acid VIIIb to lactam IXb probably proceeds via a mixed anhydride of the 17-oic acid with acetic acid which then acts as an internal acylating agent on the NH of the indole. The conversion of 17-oic acids to mixed anhydrides has been reported previously.¹⁰

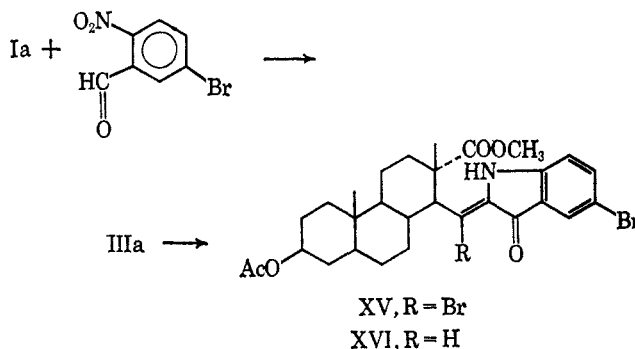
Borohydride reduction of indoxyls II can be interpreted as proceeding by reduction of the carbonyl followed by equilibration of the *exo* double bond to the *endo* position (XVIII) in the presence of base. Subsequent reduction of the C=N would be followed by elimination of water to furnish the indole product VIII.

(9) K. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds," Interscience Publishers, Inc., New York, N. Y., 1960, p 131.
(10) A. Hassner and I. H. Pomerantz, *J. Org. Chem.*, **27**, 1760 (1962).

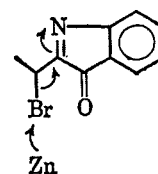


XVIII

The methyl ester IIIa, derived from IIa, the 5,6-dihydro analog of IIb, reacted readily with bromine to yield after acetylation the dibromo compound XV. The reaction can be envisaged as an addition of bromine to the 15,2' double bond, followed by elimination of hydrobromic acid,¹¹ with simultaneous substitution of bromine on the phenyl ring. Both the loss of hydrobromic acid from α,β -dibromo ketones¹² and halogenation at C-5 of indole systems¹³ have analogies in the literature. The ultraviolet spectrum of XV showed the expected bathochromic shift for β -bromo α,β -unsaturated ketones,¹⁴ and the nmr spectrum indicated clearly the absence of an olefinic hydrogen and the presence of a trisubstituted benzene ring. Debromination of XV with zinc in ethereal acetic acid gave monobromide XVI, the nmr spectrum of which showed the doublet at τ 4.23, also present in IIIa and IIIc but not

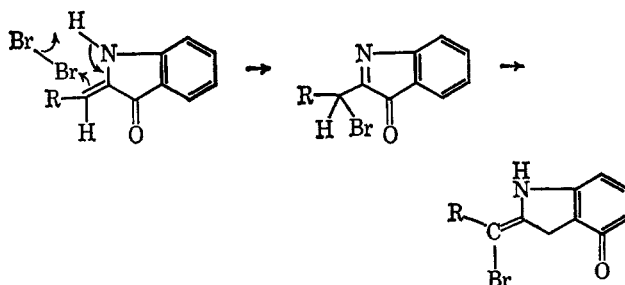


in dibromide XV. Zinc debromination of the β -bromo- α,β -unsaturated ketone XV can be explained if one assumes equilibration to XIX, which can be reduced by zinc like an α -bromo ketone. The structure of mono-



XIX

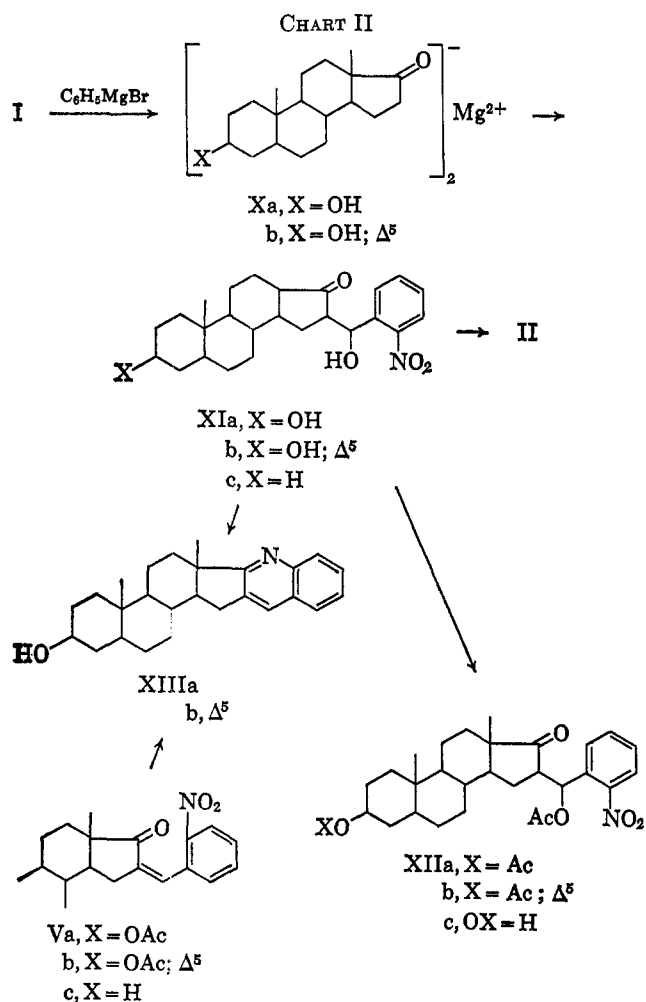
(11) An alternate pathway might be direct bromination of the enamine as shown.



(12) A. Hassner and T. C. Mead, *Tetrahedron*, **20**, 2201 (1964).

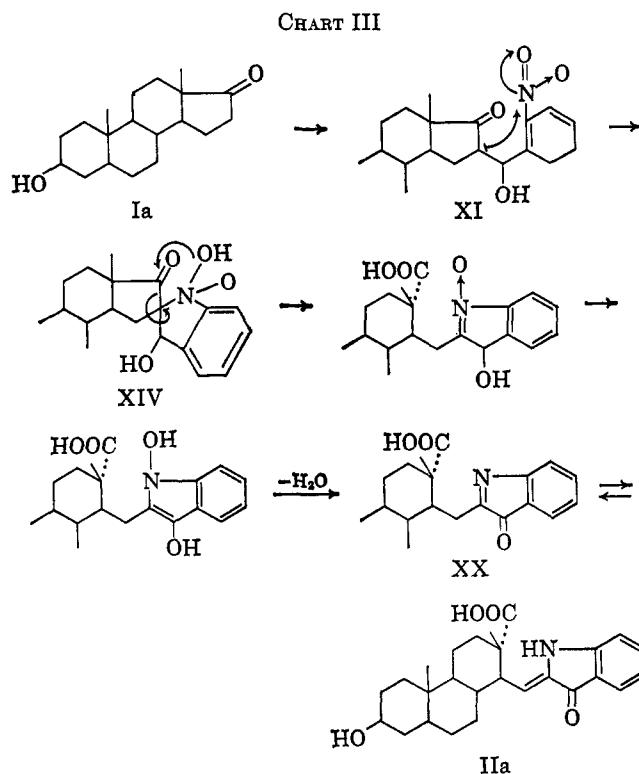
(13) Isatin and related compounds are known to be substituted by halogen *para* to the nitrogen; cf. E. Kambi, *Helv. Chim. Acta*, **24**, 93E (1941).

(14) W. Brode, E. Pearson, and G. Wyman, *J. Am. Chem. Soc.*, **76**, 1034 (1954); A. L. Nussbaum, O. Mancera, R. Daniels, G. Rosenkrantz, and C. Djerassi, *ibid.*, **73**, 3263 (1951).



bromide XVI, specifically the position of the bromine atom in the aromatic ring, was proved by independent synthesis from the reaction of Ia with 2-nitro-5-bromobenzaldehyde in base.

To help elucidate the mechanism of the transformation of I to II, we felt that isolation of an aldol condensation intermediate XI would be desirable. Since direct aldol condensation of 17-keto steroids (I) with *o*-nitrobenzaldehyde under acidic or basic conditions led only to starting material or to indoxyls II, we resorted to using X, the magnesium enolate of I in nonprotogenic solvents, in which case isolation of an aldol intermediate,¹⁵ owing to formation of its magnesium salt, should become possible. Indeed, when a suspension of enolate Xb (prepared from the hindered ketone Ib with phenylmagnesium bromide) was treated with *o*-nitrobenzaldehyde, ketol XIb was obtained. The latter was converted rapidly on contact with aqueous or alcoholic base to indoxyl IIb. As a structure proof for intermediate XI, we converted XIb by acetylation to XIIb, which, upon chromatography, lost acetic acid to give 3 β -acetoxy-16-(*o*-nitrobenzal)-5-androsten-17-one (Vb). Treatment of Vb with base did not give indoxyl IIb, but reduction with iron in acetic acid and subsequent treatment of the resulting amino intermediate with base gave the known¹ quinoline XIIIb. Reduction of XIb under the same conditions gave XIIIb directly (Chart II).



For the present, the mechanism of transformation of methylene ketones with *o*-nitrobenzaldehyde to indoxyls in the presence of base is probably best represented as indicated in Chart III. Intermediates of type XI have been isolated. Whereas aldol condensation of ketones with benzaldehydes normally leads to formation of benzal ketones (such as V), in this case the presence of an *o*-nitro group induces the aldol XI to react by preferential intramolecular carbanion attack on the nitro function. An analogy to the indoxyl formation is provided by the well-known indigo synthesis in good yield from acetone and *o*-nitrobenzaldehyde.¹⁶ Indigo also results if one substitutes pyruvic acid or acetaldehyde for acetone, facts which are consistent with the mechanism proposed above. In analogy with the steroid case, the unsaturated *o*-nitrobenzalacetone with base did not yield indigo, but the aldol 1-(*o*-nitrophenyl)butan-1-ol-3-one did. The formation of a carboxylic acid function is in line with isolation of acid II as well as with the formation of acetic acid from the reaction of acetone with *o*-nitrobenzaldehyde to yield indigo. We favor an intramolecular reaction of XIV rather than an equally plausible external attack by hydroxide ion, because the reaction, XI \rightarrow II, also proceeds with ammonium hydroxide in methanol and an attack on the hindered 17-carbonyl by a weak base seems unlikely. Furthermore, XIa is converted by anhydrous methoxide in methanol to acid IIa rather than to ester XIIIa, a product which should have resulted from external methoxide attack on XIVa.

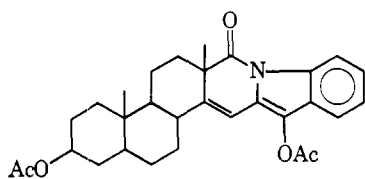
A primary product to be expected from the reaction of *o*-nitrobenzaldehyde with 17-keto steroids or with acetone would be an indoleninone (XX or II''). Indoleninone II'' (R = H), in which no substituent is present at position 2, probably reacts with the anion

(15) J. P. Collman, *J. Org. Chem.*, **26**, 3162 (1961).

(16) (a) A. Baeyer and V. Drewsen, *Ber.*, **15**, 2856 (1882); **16**, 2205 (1883); (b) see also J. D. Loudon and G. Tennant, *Quart. Rev.* (London), **18**, 389 (1964).

of one of its precursors or dimerizes to indigo, while XX isomerizes to its exocyclic unsaturated isomer. The instability of compounds of type II'' is not surprising in view of the known instability of cyclopentadienone¹⁷ and of 2-azaindoleninones.¹⁸ Two reported indoleninones (II'', R = CH₃ or C₆H₅) have been shown by us to possess a dimeric structure.¹⁹

The stereochemistry about the indoxylidene double bond in II-IV has been assigned *trans* (steroid with respect to the indoxyl carbonyl) on the basis of the strong double bond absorption at 1640 cm⁻¹, the enhanced stability of *trans*- over *cis*-alkylidenecyclopentanones,¹¹ and because IIb can be converted to lactam XXI on heating with acetic anhydride.



XXI

Experimental Section²⁰

3 β -Hydroxy-16,17-seco-16-nor-5-androsten-15-(2'-indoxylidene)-17-oic Acid (IIb).—Two grams of 3 β -hydroxy-5-androsten-17-one (Ib) was dissolved in 50 ml of methanol with warming. A solution of 2 g of potassium hydroxide in 2 ml of water was added, followed by a solution of 1.1 g of freshly steam-distilled *o*-nitrobenzaldehyde in 10 ml of methanol. The solution developed a yellow color that gradually intensified to green and finally to reddish brown on standing for 24 hr at room temperature. The solution was concentrated under reduced pressure to about 20 ml and diluted with water. The slightly turbid solution was treated with charcoal and filtered, and the clear yellow filtrate was acidified with dilute hydrochloric acid. The resulting bright yellow solid was collected by filtration, washed with water, and dried (2.82 g, mp 180–210°). On recrystallization from benzene-methanol the product (IIb) was obtained in yellow prismatic needles that melted at 267–269° (2.17 g). In acetone, benzene, or ether the compound exhibited strong green fluorescence: ν_{\max} 3400 (OH), 3300 (NH), 2750–2400 (hydrogen-bonded CO₂H), 1690 (C=O of CO₂H and C=O of conjugated C=O), 1640 (conjugated C=C), and 1610 cm⁻¹; λ_{\max} 455, 300 (sh), 275 (sh), 262, and 238 m μ (ϵ 5000, 7560, 15,500, 25,000, and 16,500, respectively). The ultraviolet spectrum of IIb did not change in basic or acidic medium (in each case 2–5 drops of 5% sodium hydroxide or concentrated hydrochloric acid were added to the cuvette containing the sample solution).

Anal. Calcd for C₂₇H₃₃NO₄: C, 74.08; H, 7.41; N, 3.32. Found: C, 74.33; H, 7.36; N, 3.45.

Methyl 3 β -Hydroxy-16,17-seco-16-nor-5-androsten-15-(2'-indoxylidene)-17-oate (IIIb).—A suspension of 100 mg of acid IIb in ether was treated with freshly prepared ethereal diazomethane. Evaporation of the excess diazomethane (as determined by the addition of a trace of acetic acid in ether to the solution) on a steam bath gave a quantitative yield of IIIb. Orange-yellow prisms, mp 264–266°, were obtained from methanol: ν_{\max} 3500 (OH), 3220 (NH), 1720 (C=O of methyl ester), 1690 (conjugated C=O), 1640 (conjugated C=C), and 1610

cm⁻¹; λ_{\max} 450–455, 295 (sh), 275 (sh), 262, 238, and 236 m μ (ϵ 4800, 7500, 15,500, 26,800, 16,100, and 16,000, respectively).

Anal. Calcd for C₂₇H₃₃NO₄: C, 74.45; H, 7.64; N, 3.22. Found: C, 74.50; H, 7.82; N, 3.35.

The methyl ester IIIb was prepared also by refluxing a solution of 0.5 g of acid IIb and 2 ml of concentrated hydrochloric acid in 20 ml of methanol on a steam bath for 2 hr. The solution became reddish. Evaporation of methanol and dilution with water gave 475 mg of a reddish solid. The product was recrystallized from methanol to furnish 320 mg of orange-yellow prisms of IIIb that melted at 265–267°.

3 β -Hydroxy-16,17-seco-16-nor-5-androsten-15-(2'-indolyl)-17-oic Acid (VIIIb).—To a solution of 0.5 g of indoxylidene compound IIb was added 4 g of sodium borohydride. Gas evolution started immediately and the yellow solution became hot. The yellow color slowly disappeared. After 14 hr at room temperature, the solution was concentrated under vacuum. The residue was diluted with 200 ml of warm water and acidified by dropwise addition of dilute hydrochloric acid. The precipitated white solid was collected by filtration, washed with hot water, and dried (0.415 g, mp 160–172° mainly softening). When recrystallized from ethanol-water the product gave thin white needles of VIIIb that melted at 255–256°. An analytical sample melted at 265–267° dec. The product gave a positive Ehrlich test. It had ν_{\max} 3400 (OH), 3320 (NH), 2750–2400 (hydrogen-bonded CO₂H), 2000 (br), and 1670 (C=O, br, s) cm⁻¹.

Anal. Calcd for C₂₆H₃₃NO₃: C, 76.62; H, 8.16; N, 3.44. Found: C, 76.64; H, 8.29; N, 3.16.

3 β -Acetoxy-16,17-seco-16-nor-5-androsten-15-(2'-indolyl)-17-oic Acid Lactam (IXb).—A solution of the indole acid VIIIb (80 mg, mp 255–257°) in 3.5 ml of hot distilled acetic anhydride was heated under reflux for 3 hr after which time 2 ml of water was added. Heating was continued for 3 min to hydrolyze the excess acetic anhydride. The product (IXb) separated as a white solid. The mixture was diluted with 10 ml of water, and the white solid was collected by filtration, washed with water, and dried (75 mg). Recrystallization of the product from absolute ethanol furnished needles of IXb: mp 268–269°; ν_{\max} 1725 (3-acetate), 1700 (amide), and 1560 cm⁻¹; λ_{\max} 243, 265, 290, and 300 m μ (ϵ 28,000, 14,000, 6750, and 6450, respectively).

Anal. Calcd for C₂₅H₃₃NO₃: C, 78.65; H, 7.78; N, 3.74. Found: C, 78.57; H, 7.77; N, 3.51.

Hydrolysis of Lactam IXb to Indole Acid VIIIb.—Lactam IXb (50 mg) was dissolved in 12 ml of 95% ethanol with heating. A 50% sodium hydroxide solution (1.5 ml) was added to the hot solution and refluxing was continued for 30 hr. After concentration to about 3 ml, the solution was diluted with water. The turbid solution was filtered and the filtrate was acidified with dilute hydrochloric acid. The precipitated white solid was collected by filtration, washed with water, and dried to yield 23 mg of VIIIb. Upon recrystallization from ethanol-water the product melted at 265–267°. Admixture with authentic VIIIb showed no depression in melting point. The infrared spectrum of the hydrolyzed product was identical with that of authentic VIIIb.

3 β -Hydroxy-16,17-seco-16-nor-5-androsten-15-(2'-indoxylidene)-17-oic Acid 2,4-Dinitrophenylhydrazone (VIIb).—A solution of 50 mg of 2,4-dinitrophenylhydrazine in 2 ml of concentrated hydrochloric acid and 10 ml of methanol was added to a solution of 50 mg of the indoxyl IIb in 2 ml of methanol. During standing at room temperature for 24 hr, the solution changed color from orange-yellow to dark red. The solution was concentrated under vacuum to about 5 ml and diluted with water. The resulting brown-red solid was collected by filtration, washed with water, and dried (60 mg, mp 135–155° dec). Attempts to recrystallize VIIb from benzene, ethyl acetate, and benzene-pentane were unsatisfactory. VIIb had ν_{\max} 3400 (OH), 3200 (NH), 1750, 1715, 1530 (NO₂), and 1335 (NO₂) cm⁻¹; the infrared spectrum showed close resemblance to that of VIIa.

Methyl 3-keto-16,17-seco-16-nor-4-androsten-15-(2'-indoxylidene)-17-oate.—A warm solution of 800 mg of alcohol IIIb in 20 ml of freshly distilled cyclohexanone was treated with 1 g of aluminum isopropoxide. The solution was heated under reflux for 3 hr. The reaction mixture was steam distilled until no smell of cyclohexanone could be detected. The mixture was made acidic with dilute hydrochloric acid and the yellow precipitate was collected by filtration, washed with dilute hydrochloric acid and water, and dried. The product (560 mg) was recrystallized from Skellysolve (bp 80–90°)-benzene to give yellow crystals of methyl 3-keto-16,17-seco-16-nor-4-androsten-15-(2'-indoxylidene)-

(17) C. H. DePuy and E. F. Zaweski, *J. Am. Chem. Soc.*, **81**, 4920 (1959).

(18) E. F. Ullman and E. A. Bartkus, *Chem. Ind. (London)*, **93** (1962).

(19) A. Hassner and M. J. Haddadin, *J. Org. Chem.*, **28**, 224 (1963).

(20) Unless mentioned otherwise, all melting points are taken on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were determined in the solid phase (KBr) using a Beckman Ir-5 spectrophotometer. Ultraviolet spectra are measured in methanol solution on a Cary Model 14 instrument. Alumina used for chromatography was neutral, activity II, Woelm. Molecular weights were determined in benzene solution using Mechrolab vapor osmometer Model 301A. Nmr spectra were run in deuteriochloroform on a Varian Associates A-60 instrument with tetramethylsilane as an internal standard. Elemental analyses were performed by A. Bernhardt, Mülheim, Germany.

den)-17-oate that melted at 157–160°. The mother liquors were extracted with ether to yield 260 mg of additional crude material. It had ν_{\max} 3350 (NH), 1725 (C=O of methyl ester), 1700 (conjugated C=O), 1640 (conjugated C=C), and 1610 cm^{-1} ; λ_{\max} 455, 300 (sh), 275 (sh), 261, and 239 $\text{m}\mu$ (ϵ 4200, 7500, 15,300, 26,600, and 27,700, respectively).

Methyl 3 β -Acetoxy-16,17-seco-16-nor-5-androsten-15-(2'-indoxyliden)-17-oate (IVb).—Alcohol IIIb (350 mg) was dissolved in 4 ml of dry pyridine and 8 ml of acetic anhydride. The next day work-up with ice-water gave 370 mg of IVb. The product was recrystallized from methanol to furnish 350 mg of yellow needles that melted at 239–241°. An analytical sample of IVb melted at 240–242° and had ν_{\max} 3380 (NH, sharp and strong), 1720, 1700 (conjugated C=O), 1640 (conjugated C=C), and 1615 cm^{-1} .

Anal. Calcd for $\text{C}_{28}\text{H}_{36}\text{NO}_5$: C, 72.93; H, 7.39; N, 2.93. Found: C, 73.13; H, 7.34; N, 3.21.

3 β -Hydroxy-16,17-seco-16-norandrostan-15-(2'-indoxyliden)-17-oic Acid (IIa).—To a solution of 0.5 g of 3 β -hydroxyandrostan-17-one (Ia, mp 175–177°) in 15 ml of 3% methanolic potassium hydroxide, there was added a solution of 0.3 g of freshly steam-distilled *o*-nitrobenzaldehyde in 2 ml of methanol. The solution was allowed to stand at room temperature for 48 hr, diluted with water, and acidified with dilute hydrochloric acid. The resulting yellow precipitate was collected by filtration, washed with water, and dried (650 mg, mp 156–172°). Recrystallization from ethyl acetate-methanol or methanol-water gave 300 mg of bright yellow crystals that melted at 258–260° dec. A second crop of 100 mg of IIa was also obtained. IIa had ν_{\max} 3400 (OH), 3300 (NH), 2500–2225 (hydrogen-bonded CO_2H), 1690 (C=O of acid and conjugated C=O), 1640 (conjugated C=C), and 1610 cm^{-1} ; λ_{\max} 450, 300 (sh), 275 (sh), 262, and 238 $\text{m}\mu$ (ϵ 5200, 7000, 15,500, 25,000, and 16,500, respectively).

Anal. Calcd for $\text{C}_{26}\text{H}_{34}\text{NO}_4$: C, 73.73; H, 7.85; N, 3.31. Found: C, 73.51; H, 7.78; N, 3.34.

Methyl β -Hydroxy-16,17-seco-16-norandrostan-15-(2'-indoxyliden)-17-oate (IIIa) and Its 3 β -Acetate (IVa).—The methyl ester IIIa was obtained in quantitative yield from acid IIa with diazomethane. Recrystallization from methanol afforded yellow prisms that melted at 263–265°: ν_{\max} 3500 (OH), 3250 (NH), 1720 (C=O of methyl ester), 1700 (conjugated C=O), 1640 (conjugated C=C), and 1610 cm^{-1} .

Acetylation with acetic anhydride-pyridine afforded yellow prisms of IVa from methanol: mp 261–262°; ν_{\max} 3390 (NH), 1725 (C=O of methyl ester and 3-acetate), 1700 (conjugated C=O), 1640 (conjugated C=C), and 1610 cm^{-1} .

3 β -Hydroxy-16,17-seco-16-norandrostan-15-(2'-indoxyliden)-17-oic Acid 2,4-Dinitrophenylhydrazone (VIIa).—A solution of 50 mg of indoxyl IIa in 2 ml of methanol was added to a solution of 50 mg of 2,4-dinitrophenylhydrazine in 1 ml of concentrated hydrochloric acid. The orange-yellow solution was let stand at room temperature for 24 hr during which time a dark brown precipitate was formed (30 mg). Repeated recrystallization from ethyl acetate gave VIIa: mp 268–270° dec; ν_{\max} 3570–3320 (OH, NH), 1755, 1715, 1620, 1580, 1525 (NO_2), and 1335 (NO_2) cm^{-1} ; λ_{\max} 440, 300–240, and 220 $\text{m}\mu$ (ϵ 2040, 1510, and 3260, respectively).

Anal. Calcd for $\text{C}_{32}\text{H}_{37}\text{N}_5\text{O}_7$: C, 63.66; H, 6.18. Found: C, 63.20; H, 6.26.

3 β -Acetoxy-16,17-seco-16-nor-14-androsten-15-(3'-acetoxy-2-indolyl)-17-oic Acid Lactam (XXI).—A solution of 1 g of indoxyl acid IIb in 30 ml of hot acetic anhydride was heated under reflux for 12 hr and then poured into ice-water, and a yellowish product was collected by filtration, washed with water, and dried (1.28 g). Two crystallizations from 95% ethanol furnished 0.95 g of white needles of XXI: mp 226–228°; ν_{\max} 1770 (enol acetate), 1725 (3-acetate), 1690 (lactam), 1640, 1240 (acetate), and 1190 (enol acetate) cm^{-1} ; λ_{\max} 335 (sh), 322, 270, 240, and 222 $\text{m}\mu$ (ϵ 15,400, 25,600, 10,350, 19,000, and 22,600, respectively).

Anal. Calcd for $\text{C}_{30}\text{H}_{38}\text{NO}_5$: C, 73.59; H, 7.21; N, 2.86; O, 16.34. Found: C, 73.40; H, 7.32; N, 2.88; O, 16.50.

3 β -Hydroxy-16,17-seco-16-norandrostan-15-(2'-indolyl)-17-oic Acid (VIIIa).—To a solution of 0.5 g of indoxylidene compound IIa in 30 ml of methanol was added 5 g of sodium borohydride. The reaction solution was left to stand at room temperature for 24 hr and then poured into water. The aqueous solution was acidified with dilute hydrochloric acid. The resulting white solid was collected by filtration, washed with hot water, and dried (320 mg). The product was recrystallized from methanol to furnish white needles of VIIIa that melted at 255–257° and gave

a positive Ehrlich test: ν_{\max} 3400 (NH, OH), 2700–2300 (hydrogen-bonded CO_2H), and 1680 cm^{-1} ; λ_{\max} 290, 280, and 222 $\text{m}\mu$ (ϵ 6910, 8790, and 44,000, respectively).

Anal. Calcd for $\text{C}_{26}\text{H}_{36}\text{NO}_3$: C, 76.24; H, 8.61; N, 3.42. Found: C, 76.36; H, 8.81; N, 3.42.

3 β -Acetoxy-16,17-seco-16-norandrostan-15-(2'-indolyl)-17-oic Acid Lactam (IXa).—A solution of 55 mg of indole acid VIIIa in 3 ml of acetic anhydride was heated under reflux for 3 hr. Excess acetic anhydride was hydrolyzed by addition of 2 ml of water to the hot solution. The precipitated white solid was collected by filtration, washed with water, and dried to yield 45 mg of IXa, mp 204–208°. Recrystallization from methanol furnished white needles that melted at 214–216° and gave no Ehrlich test: ν_{\max} 1720 (3-acetate), 1695 (lactam), and 1670 (sh) cm^{-1} ; λ_{\max} 320, 293, 266, and 243 $\text{m}\mu$ (ϵ 5500, 5500, 12,000, and 25,400, respectively).

Anal. Calcd for $\text{C}_{28}\text{H}_{36}\text{NO}_3$: C, 77.56; H, 8.14; N, 3.23. Found: C, 77.79; H, 8.27; N, 3.28.

The conversion of lactam IXa (100 mg) into indole acid VIIIa (32 mg) was carried out in the same manner described for the hydrolysis of lactam IXb into indole acid VIIIb. The identity of the hydrolysis product with VIIIa was confirmed by mixture melting point, infrared spectrum, and a positive Ehrlich test.

Methyl 3 β -Acetoxy-14,5'-dibromo-16,17-seco-16-norandrostan-15-(2'-indoxyliden)-17-oate (XV).—To a solution of 3.5 g of methyl ester IIIa in 25 ml of chloroform was added 26.5 ml of a solution of bromine in chloroform (2.5 g in 50 ml). The color of bromine disappeared rapidly on addition of a few milliliters of methanol. The solution was washed with water, dried, and evaporated to give 4.3 g of a yellow solid, mp 181–185°, softening at 161–165°. Attempts to recrystallize it failed. The product (1.5 g) was acetylated in acetic anhydride-pyridine. The usual work-up gave 1.6 g of a yellow product. Recrystallization from methanol yielded yellow needles of XV: mp 224–225°; ν_{\max} 3300, 1725, 1700, and 1620 cm^{-1} ; λ_{\max} 250, 260, 268, 290–298, 315 (sh), and 470 $\text{m}\mu$ (ϵ 18,500, 19,200, 16,000, 16,900, 10,000, and 4300, respectively).

Anal. Calcd for $\text{C}_{28}\text{H}_{36}\text{Br}_2\text{NO}_5$: C, 54.56; H, 5.68; Br, 25.03; mol wt, 638. Found: C, 54.24; H, 5.54; Br, 24.88; mol wt (benzene), 635.

Methyl 3 β -Acetoxy-16,17-seco-16-norandrostan-15-(5'-bromo-2'-indoxylidene)-17-oate (XVI). A. By Treatment of the Dibromo Derivative XV with Zinc.—To a solution of 0.5 g of XV in 15 ml of ether was added 1.5 ml of acetic acid and 1 g of zinc dust. The mixture was stirred for 10 min. Water (1 ml) was added and the mixture was stirred for 2 min. Then the supernatant liquid was decanted. The dried ether layer was evaporated to give a yellow solid (0.4 g). Recrystallization from methanol after fast chromatography over alumina furnished yellow needles of XVI: mp 276–278°; ν_{\max} 3550, 3270, 1725, 1700, 1640, and 1620 cm^{-1} ; λ_{\max} 240–250, 263, 284, 310 (sh), and 460 $\text{m}\mu$ (ϵ 20,200, 24,300, 19,200, and 4700, respectively); nmr, τ 4.23 (doublet, $J = 10.1$ cps).

Anal. Calcd for $\text{C}_{27}\text{H}_{34}\text{BrNO}_4$: C, 62.78; H, 6.63; Br, 15.49. Found: C, 62.84; H, 6.85; Br, 15.32.

B. From Ia with 2-Nitro-5-bromobenzaldehyde.—To a solution of 0.5 g of 3 β -hydroxyandrostan-17-one (Ia) in 15 ml of 3% methanolic potassium hydroxide was added 0.38 g of 2-nitro-5-bromobenzaldehyde in 3 ml of methanol. The solution was allowed to stand at room temperature for 24 hr, diluted with water, and acidified with dilute hydrochloric acid. The resulting yellow precipitate (745 mg) was collected by filtration, washed with water, and dried. Recrystallization from methanol-water gave 320 mg and a second crop of 80 mg of product: mp 275–276°; ν_{\max} 3350, 2650–2400 (hydrogen-bonded COOH), 1680 (C=O of acid and conjugated C=O), 1625 (conjugated C=C), and 1600 cm^{-1} .

The methyl ester XVI was obtained from the above acid by treatment with diazomethane or by heating with methanol-hydrochloric acid.

From 80 mg of acid was obtained 85 mg of crude ester. Recrystallization from methanol furnished 40 mg of XVI, mp 276–278°.

This product was identical by infrared and a mixture melting point experiment with XVI obtained under A.

16,17-Seco-16-norandrostan-15-(2'-indoxyliden)-17-oic Acid (IIc).—A solution of 1.0 g of androstan-17-one (mp 119–120°) in 120 ml of methanol was made basic by the addition of 3 ml of 30% sodium hydroxide. *o*-Nitrobenzaldehyde (0.6 g) in 15 ml of methanol was added to the solution. After standing at

room temperature for 36 hr the yellow solution was concentrated under vacuum and diluted with water. The clear yellow solution was acidified with dilute hydrochloric acid and the precipitated yellow solid was collected by filtration, washed with water, and dried to yield 1.34 g of IIc, mp 170–185°. On recrystallization from acetic acid–water the acid was obtained as yellow prisms that melted at 224–226° dec: ν_{\max} 3400 (NH, sharp and strong), 3200–3000, 2600 (hydrogen-bonded CO₂H), 1700 (C=O of acid and conjugated C=O), 1640 (conjugated C=C), and 1615 cm⁻¹; λ_{\max} 450, 300 (sh), 275 (sh), 262, and 238 m μ (ϵ 4500, 7500, 15,500, 25,000, and 16,200, respectively).

Methyl 16,17-Seco-16-norandrostan-15-(2'-indoxyliden)-17-oate (IIIc).—Acid IIc (50 mg) was dissolved in ether–methanol and treated with ethereal diazomethane. After usual work-up 40 mg of the methyl ester IIIc was isolated. Recrystallization from methanol furnished yellow needles that melted at 223–225°: ν_{\max} 3350 (NH, sharp and strong), 1725 (C=O of methyl ester), 1690 (C=O of conjugated C=O), 1640 (conjugated C=C), and 1610 cm⁻¹; λ_{\max} 455, 300 (sh), 275 (sh), 262, and 238 m μ (ϵ 4840, 8000, 17,000, 26,900 and 17,600, respectively); $\lambda_{\max}^{\text{cyclohexane}}$ 442 (b), 286, 277, 268, and 240 (sh) m μ (ϵ 4500, 17,700, 18,500, 25,000, and 15,000, respectively). The nmr spectrum showed a doublet at τ 4.23 ($J = 10.1$ cps).

Anal. Calcd for C₂₇H₃₆NO₃: C, 76.92; H, 8.37; N, 3.32. Found: C, 76.63; H, 8.66; N, 3.44.

Conversion of Aldol XI into Indoxyl Acid II.—When 15 mg of XIa, b, or c was dissolved in methanol and 0.1 N potassium hydroxide solution was added with warming, the solution turned immediately yellow. After 30 min of standing at room temperature, the solution was acidified with dilute hydrochloric acid. The precipitated yellow solid was collected by filtration, washed with water, and dried (13 mg). On recrystallization, pure product was obtained that showed no depression in a mixture melting point determination with the corresponding authentic acids IIa, b, or c. The product gave infrared and ultraviolet spectra identical with those of the authentic acids.

The intermediate XI is also easily converted into acid II by concentrated ammonia in methanol or by sodium methoxide in methanol.

Oxidation of Methyl 16,17-Seco-16-norandrostan-15-(2'-indoxyliden)-17-oate IIIc with Chromic Acid.—To a solution of 835 mg of IIIc in 30 ml of acetic acid there was added 596 mg of chromium trioxide in 2 ml of water. The yellow solution turned reddish with evolution of heat. After standing at room temperature for 9 hr, the solution was diluted with 200 ml of water. The resulting turbid solution was thoroughly extracted with ether. The yellow ether layer was repeatedly extracted with water. Isatin remained in the water layer. A final extraction with 5% sodium hydroxide and acidification of the basic solution with acetic acid gave XVII as a yellowish white solid that was collected by filtration, washed with water, and dried (300 mg). Treatment of a hot methanol solution of acid XVII with charcoal and filtration afforded a clear colorless solution, which on dilution with water to incipient turbidity yielded hard white prisms of methyl 14 β -carboxy-16,17-seco-15,16-bisnorandrostan-17-oate (XVII) that melted at 167–169°. An analytical sample of acid XVII melted at 168–169°: ν_{\max} 3200 (OH), 2550–2400 (hydrogen-bonded CO₂H), 1740 (methyl ester), and 1710 (C=O of COOH) cm⁻¹.

Anal. Calcd for C₁₉H₃₀O₄: C, 70.77; H, 9.38; O, 19.85. Found: C, 70.53; H, 9.43; O, 19.82.

The yellow, aqueous layer containing the isatin was extensively extracted with ether until the former was colorless. The yellow ether layer was washed with 5% sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered, and evaporated to give 125 mg of a yellow-red solid that melted at 165–185°. The product was treated with 4 ml of ether, and the ether-insoluble part was collected by filtration (75 mg): mp 197–200° (lit.²¹ 198–199°). Admixture with authentic isatin showed no depression in melting point. The infrared spectrum of the product was superimposable with that of authentic isatin.

16-(*o*-Nitro- α -hydroxybenzyl)-5-androsten-3 β -ol-17-one (XIb).—A phenylmagnesium bromide solution prepared from 0.48 g of metallic magnesium and 3.5 g of bromobenzene in 25 ml of dry ether was added at room temperature to a solution of 3 β -hydroxyandrostan-17-one (2.8 g) in dry ether (300 ml). The

addition was accompanied by boiling and a heavy cream-colored turbidity. The mixture was heated under reflux on a steam bath for 1 hr. A solution of *o*-nitrobenzaldehyde (1.5 g) in dry ether (30 ml) was added. The mixture was heated for 1 hr, then 40 ml of dilute hydrochloric acid was added. The solution separated into two distinct layers. The ether portion was washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated on a steam bath. During evaporation, a white solid appeared which was collected by filtration (730 mg, mp 240–247°). On recrystallization from methanol thin long needles were obtained that melted at 252–254°. The analytical sample of XIb melted at 253–254°: ν_{\max} 3500 (unbonded OH), 3110 (bonded OH), 1710 (C=O), 1600, 1520 (NO₂), and 1340 (NO₂) cm⁻¹.

Anal. Calcd for C₂₆H₃₃NO₅: C, 71.04; H, 7.57; N, 3.19. Found: C, 70.99; H, 7.58; N, 2.84.

3 β -Acetoxy-16-(*o*-nitro- α -acetoxybenzyl)-5-androsten-17-one (XIb).—The alcohol XIb (450 mg) was dissolved in dry pyridine (2 ml), and distilled acetic anhydride (4 ml) was added. The usual work-up gave a white solid (490 mg, mp 183–185°). Recrystallization from ethyl alcohol furnished hard needles that melted at 185–186°: ν_{\max} 1720 (C=O), 1600, 1525 (NO₂), and 1335 (NO₂) cm⁻¹.

Anal. Calcd for C₃₀H₃₇NO₇: C, 68.81; H, 7.12; N, 2.68. Found: C, 68.97; H, 7.11; N, 2.80.

3 β -Acetoxy-16-(*o*-nitrobenzal)-5-androsten-17-one (Vb).—The diacetate XIb (490 mg) was dissolved in benzene (15 ml). Woelm neutral alumina (6 g) was added and the slurry was stirred for 20 hr. The alumina was washed with benzene, and the filtrate was evaporated to give Vb (200 mg). Faint yellow needles of Vb, mp 149–150°, were obtained on recrystallization from methanol: ν_{\max} 1720, 1640 (conjugated C=O), 1630, 1610, 1525 (NO₂), and 1340 (NO₂) cm⁻¹; λ_{\max} 260 and 320 (sh) m μ (ϵ 17,000 and 5000, respectively).

Anal. Calcd for C₂₆H₃₃NO₅: C, 72.54; H, 7.18; N, 3.02. Found: C, 72.72; H, 7.29; N, 3.19.

Quinolino(3',2':16,17)-5-androsten-3 β -ol (XIIIb). A. From 16-(*o*-Nitro- α -hydroxybenzyl)-5-androsten-3 β -ol-17-one (XIb).—To a solution of 340 mg of nitro compound XIb in 15 ml of acetic acid there was added gradually 200 mg of reduced iron with swirling. The mixture was heated on the steam bath for 1 hr and filtered, and the filtrate was diluted with water to give 240 mg of XIIIb, recrystallized from methanol–water, mp 268–270°; admixture with authentic XIIIb showed no depression of melting point. The spectra of this product were superimposable with those of authentic XIIIb.²

B. From 3 β -Acetoxy-16-(*o*-nitrobenzal)-5-androsten-17-one (Vb).—Vb (200 mg, mp 147–149°) was dissolved in glacial acetic acid (4 ml) and water (6 drops) by heating on a steam bath. Reduced metallic iron (200 mg) was added gradually with occasional swirling. In 15 min the solution developed a brown color, whereupon it was cooled and diluted with water. A yellowish solid was collected by filtration, washed with water, and dried (160 mg). The product, 3 β -acetoxy-16-(*o*-amino-benzal)-5-androsten-17-one, was recrystallized from methanol to afford hard needles: mp 243–245°; ν_{\max} 3500 (sharp), 3400 (sharp), 3300 (w), 1725 (3-acetate), 1690 (CO—C=C), 1640 (conjugated C=C), and 1600 cm⁻¹.

The above amine (50 mg) was dissolved in 5 ml of 5% alcoholic potassium hydroxide. After standing for 12 hr at room temperature, the yellow solution was diluted with water. The resulting yellowish solid was collected by filtration, washed with water, and dried. On recrystallization from ethanol–water, there was obtained 35 mg of XIIIb identified by mixture melting point and infrared spectrum.

16-(*o*-Nitro- α -hydroxybenzyl)androstan-3 β -ol-17-one (XIa).—The procedure for the preparation of XIa was the same as that of XIb, except that Ia (2.8 g) was the starting material. Evaporation of the dry, clear, yellowish ether layer gave an oil. After the oil was subjected to steam distillation it was dissolved in benzene and dried over anhydrous magnesium sulfate. The benzene filtrate was concentrated to about 2 ml and poured into an alumina column (35 g) prepared in benzene. Elution with 100 ml of benzene gave mostly starting material (Ia). The product XIa was eluted with 100-ml portions of benzene–ether (9:1, 8:2, 6:4, 4:6) as an oil which solidified when rubbed with acetone (1.95 g). Recrystallization of these fractions from methanol–water or acetone furnished needles that melted at 248–250°: ν_{\max} 3450 (unbonded OH), 3320 (bonded OH), 1730 (C=O), 1700 (w), 1610, 1520 (NO₂), and 1350 (NO₂) cm⁻¹.

(21) "Handbook of Chemistry and Physics," 41st ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1958–1959, p 1050.

Anal. Calcd for $C_{26}H_{35}NO_5$: C, 70.71; H, 7.99; N, 3.17. Found: C, 70.69; H, 7.98; N, 3.29.

Conversion of Aldol XIa into Quinoline XIIIa.—The transformation of XIa (160 mg) into XIIIa (100 mg) was carried out in acetic acid (4 ml) with reduced iron (200 mg) as described for the conversion of XIb into XIIIb. The intermediate (3 β -acetate of XIIIa) was hydrolyzed in 4% methanolic sodium hydroxide (5 ml) for 12 hr at room temperature. Evaporation of the methanol left 100 mg of crude air-dried XIIIa as a yellowish solid. The product was recrystallized from ethanol-water to furnish white needles, mp 232–234°. A mixture melting point with authentic² XIIIa showed no depression. The infrared spectra of the product and that of authentic XIIIa were superimposable.

16-(*o*-Nitro- α -hydroxybenzyl)androst-17-one (XIc).—A one-tenth aliquot of a phenylmagnesium bromide solution (prepared from 0.48 g of magnesium and 3.5 g of bromobenzene in 25 ml of dry ether) was added to a solution of 0.54 g of androst-17-one in 12 ml of dry ether. The addition was accompanied by boiling. The slightly turbid solution was heated under reflux for 1.5 hr on a steam bath. *o*-Nitrobenzaldehyde (300 mg) in dry ether (10 ml) was added and heating was continued for 5 hr. The

mixture was treated with dilute hydrochloric acid and the ether layer was washed with water, dried over anhydrous magnesium sulfate, filtered, and evaporated to give a yellow oil (470 mg) that solidified partially on standing. The product could not be recrystallized. It had ν_{\max} 3450 (OH), 1725, 1650, 1630, 1530 (NO_2), and 1340 (NO_2) cm^{-1} .

16-*o*-Nitrobenzalandrost-17-one (Vc).—The alcohol XIc (300 mg) was warmed with 6 ml of pyridine-acetic anhydride (1:2) for 6 hr. The solution was cooled and poured into ice to give the acetate Vc as a yellow sticky oil (300 mg): ν_{\max} 1730 (b, s), 1600, 1525 (NO_2), and 1340 (NO_2) cm^{-1} . This crude material (290 mg) was dissolved in benzene (1 ml) and chromatographed over 10 g of alumina. The product, Vc (173 mg), was eluted with 100-ml portions of Skellysolve F (bp 40–55°)-benzene (8:2, 7:3, 6:4). It was recrystallized from methanol to give long yellowish prisms, melting at 175–177°. An analytical sample of Vc melted at 176–177°: ν_{\max} 1720, 1640 (conjugated C=O), 1530 (NO_2), and 1340 (NO_2) cm^{-1} ; λ_{\max} 260 m μ (ϵ 17,350).

Anal. Calcd for $C_{26}H_{33}NO_5$: C, 76.62; H, 8.16; N, 3.44. Found: C, 76.74; H, 8.18; N, 3.63.

A Novel Reaction of Diketene with Water

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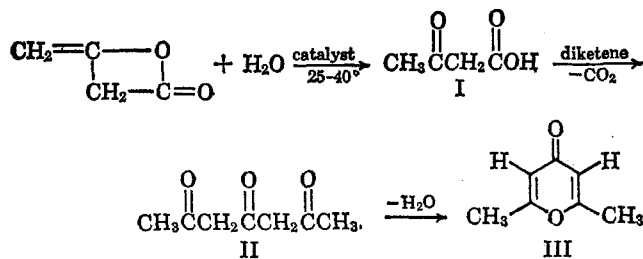
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The reaction of diketene with water in the presence of a tertiary amine catalyst is described. Under carefully controlled conditions the major products of the reaction are 2,6-dimethyl-4H-pyran-4-one and 2,4,6-heptanetrione. An nmr spectrum of the latter compound is also discussed.

In the absence of a catalyst diketene does not appear to react readily with water to form acetoacetic acid; it may even be distilled in the presence of water with little decomposition.¹ However, in the presence of acidic and basic catalysts diketene is hydrolyzed easily to give acetoacetic acid (I) (Scheme I) which in turn decomposes to acetone and carbon dioxide.^{1–3} We have now found that I in the presence of tertiary amines can react further with diketene to produce 2,4,6-heptanetrione (II) and 2,6-dimethyl-4H-pyran-4-one (III) in good yields.⁴

SCHEME I



The best catalyst for the reaction was found to be 1,4-diazabicyclo[2.2.2]octane (DABCO). Under the mildest conditions the reaction proceeded smoothly in the absence of a solvent. A less effective catalyst was pyridine. With triethylamine the yield of the two products was very poor. The desired reaction did not occur at all when a catalytic amount of concentrated

sulfuric acid was used. With hydrochloric acid a reaction appeared to occur initially, but then the reaction proceeded so violently that the reaction vessel disintegrated.

In order to obtain good yields of II and III, it was necessary to add 2 moles of diketene to 1 mole of water containing a catalytic amount of DABCO. When the molar amount of diketene with respect to water was increased to 2.5, the yield of the two products decreased. The reaction was exothermic and required a slow rate of addition or external cooling to maintain the temperature range. After the addition was complete the reaction mixture was kept at 30–40° for several hours until carbon dioxide ceased to evolve. Any low-boiling products (mainly acetone) formed during the reaction were removed on a rotatory evaporator at 25° under reduced pressure. II and III were obtained as a mixture in ratios varying from 3:1 to 2:3 depending on the reaction conditions, and the combined yield was 60–78% according to vapor phase chromatographic analyses. Separation of the two products could be accomplished by fractional recrystallization.

The yields of the desired products were also influenced by the reaction temperature. The best temperature range was 25–40°. At lower temperatures the reaction was very slow; at higher temperatures than 60° the reaction became difficult to control.

Although the detailed mechanism for the reaction is not known, a speculation concerning the possible intermediates is of interest. In an attempt to identify the intermediates, the reaction between diketene and water was followed by infrared and nmr spectroscopy. When 1 mole of diketene was allowed to react with 1 mole of water in the presence of DABCO, the product was definitely acetoacetic acid (I) which decomposed gradually into carbon dioxide and acetone. With 2

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