[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. CIX.[1] Studies in Nitro Steroids. Part 1. The Synthesis of 6α- and 6β-Nitrotestosterone and 6α- and 6β-Nitroprogesterone[2]

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Nitration of Δ^5-androstene-3β,17β-diol diacetate (Ib) afforded the Δ^5-6-nitro compound IIIb. Acid hydrolysis of IIIb to the corresponding diol IVa proceeded normally, but alkaline hydrolysis was accompanied by rearrangement and gave 6β-nitro-Δ^4-androstene-3β,17β-diol (VIa).

The transformation of VIa into the 6α- and 6β-nitro derivatives of Δ^4-androstene-3,17-dione and testosterone is described.

An analogous series of reactions in the pregnane series led to the synthesis of both 6α-nitroprogesterone (IXc) and 6β-nitroprogesterone (VIIIb).

As long ago as 1903 the nitration of cholesterol acetate (Ia) was reported to afford 6-nitrocholesterol acetate[3] (IIIa). This vinyl-nitro compound has been widely utilized as an intermediate for the preparation of 6-ketocholestanol acetate which it readily affords upon reduction with zinc and acetic acid followed by acid hydrolysis.[3,4]

Similarly Δ^4-cholestene affords cholestan-4-one[5] by an analogous series of reactions. However, apart from similar studies with Δ^5-stigmastene[6] no other investigations of nitrosteroids were made until 1954 when Anagnostopoulos and Fieser[7] reported nitration studies with Δ^5-, Δ^7-, $\Delta^{9(11)}$- and $\Delta^{7,9(11)}$-unsaturated steroids. They introduced two experimental nitration techniques into steroid chemistry, namely fuming nitric acid in ether and nitrogen tetroxide and oxygen in ether. Using the latter conditions they showed, for example, that cholesterol acetate afforded the 6β-nitro-5α-nitrate ester II, a compound which readily eliminated the elements of nitric acid upon treatment with ammonia to afford 6-nitrocholesterol acetate (IIIa). This compound was also obtained by the direct nitration of cholesteryl acetate (Ia) with fuming nitric acid in ether.[7]

Only tentative structural assignments were made to the nitration products obtained from the other unsaturated steroids studied, but this work clearly indicated the general feasibility of nitrating unsaturated steroids.

Our interest in nitro steroids stems from a broad investigation being carried out in these laboratories into the correlation of structure with biological activity of modified steroid hormones. In particular, we have synthesized recently the 6α- and 6β-fluoro analogs of many of the steroid hormones[8a,b] and the biological activity of some of these compounds has been markedly enhanced.[9] It was important, therefore, to establish whether this increase in biological activity was due to an inherent feature of the fluorine atom or whether substitution of other powerful electronegative groups at C-6 would have a similar effect. In this connection we chose to study a series of 6-nitro-steroid hormones and this paper describes the synthesis of the 6α- and 6β-nitro analogs of Δ^4-androstene-3,17-dione, testosterone and progesterone.

Initial efforts were directed toward the direct displacement of the bromine atom in 6β-bromotestosterone acetate[10] by a nitro group, following procedures shown by Kornblum and his co-workers[11] to be successful with many saturated aliphatic primary and secondary bromides. This method essentially involves treatment of a bromo compound with sodium nitrite in dimethylformamide, but in no case were we able to isolate any nitro steroid from 6β-bromotestosterone.

Thus we turned to more indirect approaches. Nitration of Δ^5-androstene-3,17-diol diacetate (Ib) (Fig. 1) with a large excess of fuming nitric acid in ether solution led in 70% yield to the vinyl-nitro diacetate IIIb.[12] The vinyl nitro group of IIIb was characterized by a strong band in the infrared at 1515 cm.$^{-1}$ and maximum absorption in the ultraviolet at 260 mμ, ε 1,820.[13a,b]

Hydrolysis of IIIb with perchloric acid in methanol[14] smoothly afforded the corresponding diol IVa which had spectral characteristics similar to those of the diacetate IIIb which it reformed on acetylation with acetic anhydride and pyridine. Alkaline hydrolysis of the vinyl-nitro diacetate IIIb, however, was accompanied by structural changes. A product was obtained which was different from IVa and which did not exhibit in the infrared the characteristic band of a vinyl nitro group. Instead, the alkaline hydrolysis product displayed a strong band at 1540 cm.$^{-1}$ characteristic of a saturated nitro group[14] and in the ultraviolet it exhibited maximum

(1) Steroids. CVIII. H. J. Ringold, O. Mancera, C. Djerassi, A. Bowers, E. Batres, H. Martinez, E. Necoechea, J. Edwards, M. Velasco and R. I. Dorfman, THIS JOURNAL, **80**, 6464 (1958).

(2) Presented in part by A. B. at the Steroids and Natural Products Section of the Gordon Research Conference, August, 1958.

(3) (a) A. Windaus, *Ber.*, **36**, 3752 (1903); (b) J. Mauthner and W. Suida, *Monatsh.*, **24**, 648 (1903).

(4) I. M. Heilbron, H. Jackson, E. R. H. Jones and F. S. Spring, *J. Chem. Soc.*, 102 (1938).

(5) A. Windaus, *Ber.*, **53**, 488 (1920).

(6) A. Windaus and C. Brunken, *Z. physiol. Chem.*, **140**, 52 (1924).

(7) C. R. Anagnostopoulos and L. F. Fieser, THIS JOURNAL, **76**, 532 (1954).

(8) (a) A. Bowers and H. J. Ringold, *Tetrahedron*, **3**, 14 (1958); (b) THIS JOURNAL, **80**, 4423 (1958).

(9) See for example ref. 8b and J. A. Hogg, G. B. Spero, J. L. T. Thompson, B. J. Magerlein, W. P. Schneider, D. H. Peterson, O. K. Sebek, H. C. Murray, J. C. Babcock, R. I. Pederson and J. A. Campbell, *Chemistry & Industry*, 1002 (1958).

(10) C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufmann and J. Pataki, THIS JOURNAL, **72**, 4534 (1950).

(11) N. Kornblum, H. O. Larson, R. K. Blackwood, D. D. Mooberry, E. P. Oliveto and G. E. Grabam, *ibid.*, **78**, 1497 (1956).

(12) Considerable care must be exercised in nitrations of this type. If the temperature of the reaction mixture is allowed to exceed 15° a violent exothermic reaction takes place. *Cf.* Experimental section and footnote 24.

(13) (a) The spectral data are in accord with those reported for 6-nitrocholesteryl acetate; *cf.* ref. 7. (b) For an excellent discussion of the infrared spectra of nitro compounds see J. F. Brown, THIS JOURNAL, **77**, 6341 (1955).

(14) *Cf.* J. Fried and E. F. Sabo, *ibid.*, **79**, 1130 (1957).

absorption at 280–286 mμ, ε 115. This compound was also obtained by an alkaline treatment of the vinyl-nitrodiol IVa.[15]

The most probable structure for this alkaline hydrolysis product was 6β-nitro-Δ⁴-androstene-3β,-17β-diol (VIa). In a strong alkaline solution IVa would be present as the anion of the *aci* form of the nitro compound Va and acidification of this anion would be expected to afford a 6-nitro-Δ⁴-3β-alcohol. The 6β-stereochemistry was assigned to the nitro group on the basis of some recent work by Zimmerman and Nevins.[16] These authors showed that protonation of the enolate ion derived from *trans*-1-nitro-2-phenylcyclohexane affords the thermodynamically less stable *cis* isomer, steric hindrance to prototopic attack being the controlling factor. Thus prototopic attack of Va should occur from the α-face and afford the 6β-nitro-allyl alcohol VIa.

The structure and stereochemistry assigned to VIa were confirmed in the following way. Oxidation of VIa with 8 *N* chromic acid afforded 6β-nitro-Δ⁴-androstene-3,17-dione (VIIIa), λ_{max} 232–234 mμ, ε 11,750. Proof that inversion of the nitro group or other structural rearrangements did not occur during the oxidation of VIa was obtained when reduction of VIIIa with sodium borohydride in aqueous dioxane solution regenerated VIa. Thus, if the assigned stereochemistry of the nitro group was correct, very mild alkaline treatment of the 6β-nitro(axial)-Δ⁴-3-ketone should invert the nitro group to the thermodynamically more stable 6α-nitro(equatorial)-Δ⁴-3-ketone. In fact, this was the case. Treatment of a solution of VIIIa in methanol containing 0.5% of potassium hydroxide at 0° for 1 minute followed by acidification with acetic acid and precipitation with water afforded in good yield 6α-nitro-Δ⁴-androstene-3,17-dione (IXa), λ_{max} 232 mμ, ε 14,790. It is pertinent to point out that treatment of 6β-nitro-Δ⁴-androstene-3,17-dione (VIIIa) with a very dilute solution of a strong base is fundamentally different from the treatment of 6-nitro-Δ⁵-androstene-3β,17β-diol (IVa) with a much more concentrated solution of the same base. In the latter case the compound is "frozen" as the sodium salt of the anion of the *aci* form (Va) and kinetic factors control the nature of the product when this anion is protonated. In dilute alkaline solution the 6β-nitro-Δ⁴-3-ketone VIIIa is in equilibrium with its 6α-nitro epimer, *via* the enolate anion, the important factor, however, being that the concentration of the anion is very low. The net result is that a thermodynamically controlled equilibrium ensues which favors a high conversion of the

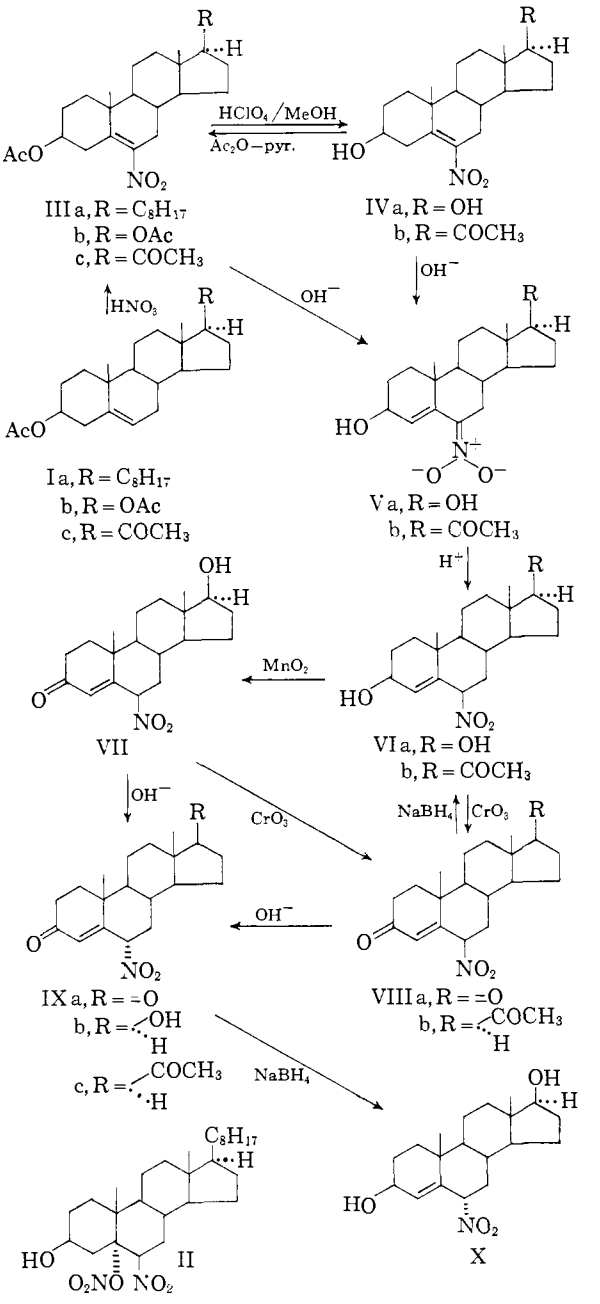


Fig. 1.

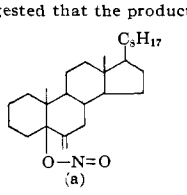
6β-nitro(axial)-Δ⁴-3-ketone VIIIa into the 6α-nitro(equatorial)-Δ⁴-3-ketone IXa.

Sodium borohydride reduction of IXa gave after purification a homogeneous product which was tentatively formulated as 6α-nitro-Δ⁴-androstene-3β,17β-diol (X), although the stereochemistry at C-3 was not proved.

Both VIIIa and IXa exhibited bands in the infrared at 1545 cm.⁻¹ (characteristic of a nitro group attached to a saturated carbon atom)[14] and the doublet at 1680 and 1620 cm.⁻¹ due to the Δ⁴-3-ketone chromophore.

A striking difference was observed between the specific rotations of 6α-nitro-Δ⁴-androstene-3,17-dione (IXa) and 6β-nitro-Δ⁴-androstene-3,17-dione (VIIIa) which appears to be a characteristic dif-

(15) One of the referees has kindly pointed out that alkaline rearrangements of Δ⁵-6-nitro steroids have been reported previously, T. Mitui, *Bull. Agr. Chem. Soc., Japan*, **16**, 144 (1940); *C. A.*, **35**, 4390 (1941). Mitui suggested that the product from alkali treatment



(a)

of 6-nitro-Δ⁵-cholestene was (a), a structure which is not compatible with the evidence presented in this paper.

(16) H. E. Zimmerman and T. E. Nevins THIS JOURNAL, **79**, 6559 (1957).

TABLE I

Compound	Substituent at C-6	$[M]_D$ (6α)	$[M]_D$ (6β)	$\Delta[M]_D$ (6α–6β)
Δ^4-Androstene-3,17-dione	Nitro[a]	+483	−166	+649
Testosterone	Nitro[a]	+ 97	−483	+580
Progesterone	Nitro[a]	+556	−180	+736
Desoxycorticosterone	Hydroxy[b]	+484	+218	+266
Desoxycorticosterone	Acetoxy[b]	+589	+469	+120
Progesterone	Methyl[c]	+650	+445	+205
Δ^4-Cholestene-3-one	Chloro[d]	+247	+ 65	+182
Δ^4-Cholestene-3-one	Bromo[e]	+245	+ 28	+217
Testosterone	Fluoro[f]	+312	± 0	+312

[a] This paper. [b] P. T. Herzig and M. E. Ehrenstein, *J. Org. Chem.*, 16, 1050 (1951). [c] H. J. Ringold, E. Batres and G. Rosenkranz, *ibid.*, **22**, 99 (1957). [d] D. H. R. Barton and E. Miller, THIS JOURNAL, **72**, 370 (1950). [e] *Ibid.*, **72**, 1066 (1950). [f] A. Bowers and H. J. Ringold, *Tetrahedron*, **3**, 14 (1958).

ference between epimeric 6-nitro-Δ^4-3-ketones (*cf.* Table I).

In addition these rotation measurements fully supported the stereochemical assignments made for the nitro groups in VIIIa and IXa, for there is sufficient evidence available to demonstrate that in any epimeric pair of 6α- and 6β-substituted Δ^4-3-ketones the 6α-substituted compound is always more dextrorotatory than the 6β-epimer. In Table I examples of C-6 epimeric hydroxy, acetoxy, methyl, bromo, chloro and fluoro Δ^4-3-ketones are also listed and in each example the 6α-epimer always has the more dextrorotatory specific rotation. This rotation difference which is at its maximum in the epimeric nitro compounds manifests itself even more clearly in the rotatory dispersion curves. Figure 2 reproduces the rotatory dispersion curves of Δ^4-androstene-3,17-dione[17] and the two C-6 epimeric nitro analogs VIIIa and IXa. While the curve of the 6α-nitro(equatorial)-Δ^4-3-ketone IXa is quite similar to the parent compound Δ^4-androstene-3,17-dione, the 6β-nitro(axial)-Δ^4-3-ketone VIIIa is strikingly different. The most probable explanation for this effect is that the bulky 6β-nitro group being 1,3-diaxially orientated to the C-10 methyl group causes some distortion of the ring system which is reflected in the rotatory dispersion curve. However electronic factors clearly play a part in this effect since the $\Delta[M]_D$ (6α-6β) value is greater for 6-fluoro-Δ^4-3-ketones than for the bulkier 6-bromo-Δ^4-3-ketones.[18]

6β-Nitrotestosterone (VII) was then obtained from 6β-nitro-Δ^4-androstene-3β,17β-diol (VIa) by a selective oxidation of the C-3 allylic alcohol with manganese dioxide.[19] Oxidation of VII with 8 *N* chromic acid smoothly afforded 6β-nitro-Δ^4-androstene-3,17-dione (VIIIa) identical with the compound obtained by the oxidation of 6β-nitro-Δ^4-androstene-3β,17β-diol (VIa → VIIIa).

Mild alkaline treatment of 6β-nitrotestosterone (VII) inverted the nitro group to afford 6α-nitrotestosterone (IXb). The characteristically large difference in the specific rotations between epimeric C-6 nitro-Δ^4-3-ketones was observed also with the testosterone analogs (see Table I).

By an analogous series of reactions this work was extended to the preparation of 6α-nitroprogesterone (IXc) and 6β-nitroprogesterone (VIIIb).

Nitration of pregnenolone acetate (Ic) readily afforded 6-nitropregnenolone acetate (IIIc) with the characteristic spectral features of a vinyl nitro system. Hydrolysis of the acetate group of IIIc with perchloric acid in methanol gave the corresponding 3β-alcohol IVb. Acetylation of IVb reformed the original acetate IIIc indicating that no structural changes had occurred during the hydrolysis.

However alkaline hydrolysis of IIIc afforded a non-crystalline product, and by analogy with the preparation of VIa from either IIIb or IVa it was assigned the structure VIb, 6β-nitro-Δ^4-pregnen-3β-ol-20-one. Its spectral properties were in full accord with this formulation, namely, λ_{max}^{KBr} 1550 cm.$^{-1}$ (nitro group attached to a saturated carbon atom) and no selective absorption in the ultraviolet. Oxidation of this non-crystalline hydrolysis product (VIb) afforded 6β-nitroprogesterone (VIIIb), which readily gave 6α-nitroprogesterone (IXc) after a mild treatment with base. The spectral data and rotatory dispersion curves of these two epimeric C-6 nitro-analogs of progesterone (see Fig. 3) were in full accord with their assigned structures.

Both 6α- and 6β-nitrotestosterone (IXb and VII) assayed in the parabiotic rat at one and two mg. total doses were inactive as gonadotrophin suppressive, mytrophic or androgenic agents; 6α- and 6β-nitroprogesterone, in the guinea pig copulatory assay exhibited less than one-eighth the progestational activity of progesterone.[20]

Acknowledgments.—In this and the following two papers we are indebted to Professor Carl Djerassi for his interest and valuable advice. Helpful discussions with Professor Gilbert Stork and Professor Arthur J. Birch are gratefully acknowledged.

Experimental[21]

6-Nitro-Δ^5-androstene-3β,17β-diol Diacetate (IIIb).—Fuming nitric acid[22] (150 cc.) was added dropwise over 1 hour with efficient stirring to a solution of Δ^5-androstene-3β,17β-diol diacetate[23] (10 g.) in anhydrous ether (200 cc.), keeping the temperature between −5 to 0° (acetone–solid

(17) C. Djerassi, E. W. Foltz and A. E. Lippman, THIS JOURNAL, **77**, 4354 (1955).

(18) For a discussion of this and related topics see: (a) C. Djerassi, O. Halpern, V. Halpern and B. Riniker, *ibid.*, **80**, 4001 (1958); (b) C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, *ibid.*, **80**, 1216 (1958).

(19) See for example F. Sondheimer, C. Amendolla and G. Rosenkranz, *ibid.*, **75**, 5930 (1953).

(20) Biological assays by Endocrine Laboratories, Madison, Wisc. All assays by subcutaneous route.

(21) Melting points were determined in capillary tubes and are uncorrected. Rotations were measured in chloroform and ultraviolet light absorption spectra in 95% ethanol solution. The rotatory dispersion measurements were obtained with a Rudolph spectropolarimeter in dioxane solution using a xenon arc lamp (250–350 mμ) and a zirconium arc lamp (350–700 mμ). We are grateful to Dr. L. Throop and his staff for these measurements and for the infrared spectra which were obtained with a Perkin–Elmer model 21 spectrophotometer with a sodium chloride prism. The elemental analyses were carried out by Dr. A. Bernhardt, Mülheim (Ruhr), Germany.

(22) Our best results were obtained with fuming nitric acid which had a density at 20° between 1.5015 and 1.5040, prepared by distilling commercial concentrated nitric acid from concentrated sulfuric acid (60 cc. of sulfuric acid per 100 cc. of nitric acid). Two distillations were usually necessary.

(23) Prepared by the reduction of Δ^5-androsten-3β-ol-17-one with sodium borohydride followed by acetylation with acetic anhydride–pyridine; m.p. 164–166°, $[\alpha]_D$ −66°. *Cf.* P. Wieland and K. Miescher *Helv. Chim. Acta*, **32**, 1769 (1949).

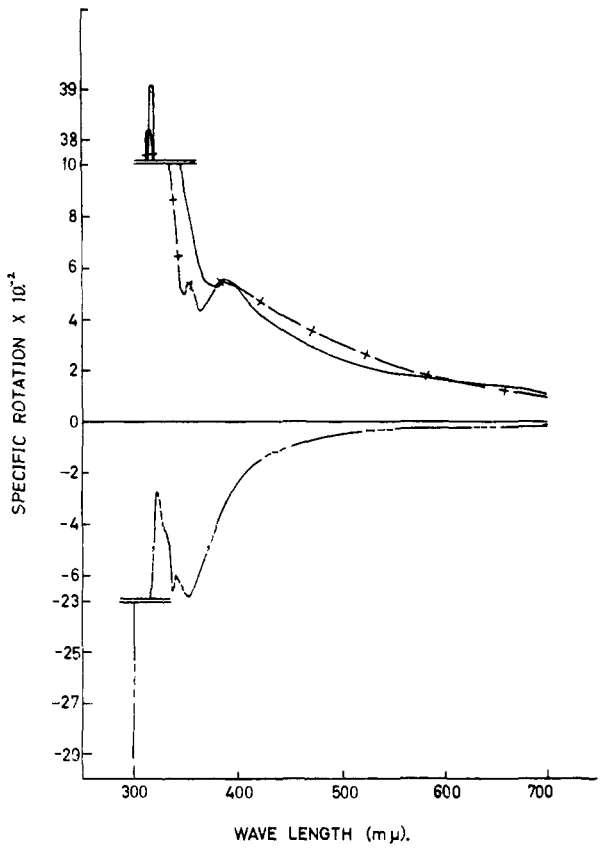


Fig. 2.—6α-Nitro-Δ⁴-androstene-3,17-dione (IXa), ———; 6β-nitro-Δ⁴-androstene-3,17-dione (VIIIa), —·—·—; Δ⁴-androstene-3,17-dione (XI), [17]—+—.

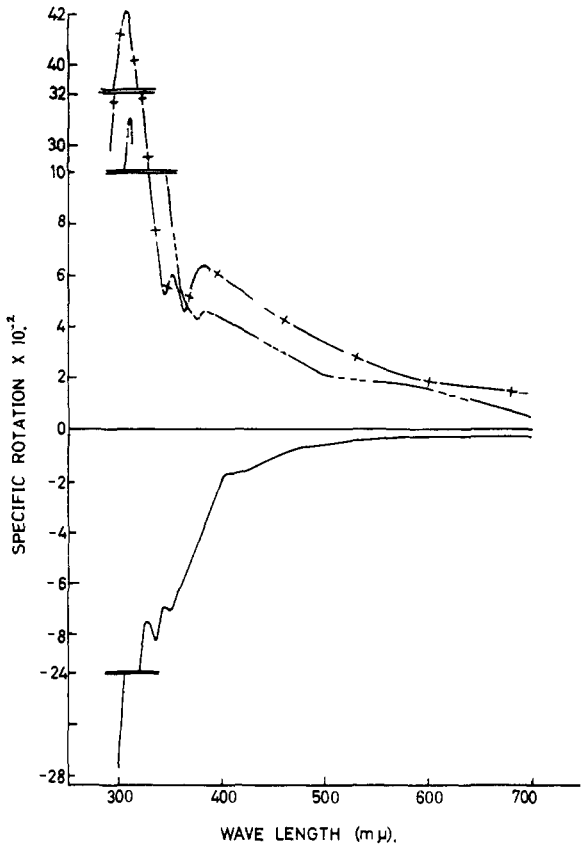


Fig. 3.—6α-Nitroprogesterone (IXc), ———; 6β-nitroprogesterone (VIIIb), ———; progesterone (XII), —+—; *cf.* E. W. Foltz, A. E. Lippman and C. Djerassi, THIS JOURNAL, **77**, 4359 (1955).

CO_2-bath).[24] After a further 2 hours at 0° the solution is allowed to warm up to 15° with good stirring when cold water (300 cc.) was added in one portion. The reaction mixture was then diluted with ether (200 cc.) and the ether solution was washed with water and then cold sodium bicarbonate solution (5%) until the bicarbonate solution just began to develop a brown color. Finally the solution was washed with water, dried (Na_2SO_4) and the solvent removed *in vacuo*. Crystallization of the product from methanol afforded 6-nitro-Δ⁵-androstene-3β,17β-diol diacetate (IIIb) (6.8 g.), m.p. 164–166°, raised by several crystallizations from methanol to 169–170°, $[\alpha]D$ −94° λ_{max}^{EtOH} 260 mμ, ε 1,820; $\lambda_{max}^{CHCl_3}$ 1725 and 1515 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{33}O_6N$: C, 65.85; H, 7.93; N, 3.34. Found: C, 65.61; H, 8.07; N, 3.27.

The above experiment was reproduced many times but in one instance just after the completion of the addition of the nitric acid the temperature of the reaction mixture began to rise in spite of intensive external cooling. Immediate addition of water and isolation of the product as described above led after chromatography over neutral alumina to a different product in 24% yield; m.p. 186–187°, $[\alpha]D$ −75°, λ_{max}^{EtOH} 266 mμ, ε 490; $\lambda_{max}^{CHCl_3}$ 1725, 1648, 1575 cm.$^{-1}$.

Anal. Found: C, 55.53, 55.82; H, 6.80, 6.83; N, 8.50, 8.24; O, 28.69.

(24) It is recommended that these nitrations are carried out in a hood with adequate shielding for the operator. Eye protection is indispensable. The temperature must be carefully noted throughout the experiment for in some instances (apparently identical to those in which a smooth reaction took place) the temperature of the reaction mixture began to rise and could not be controlled by intensive cooling. In these cases addition of cold water to the reaction mixture before the temperature reached 15° quenched the reaction; if the temperature was allowed to rise much above 15° a vigorous evolution of gas and spraying of acid occurred. This exothermic reaction was encountered in approximately 10% of our nitrations.

6-Nitro-Δ⁵-androstene-3β,17β-diol (IVa).—Perchloric acid (70%) (3.5 cc.) was added to a solution of 6-nitro-Δ⁵-androstene-3β,17β-diol diacetate (IIIb) (2.0 g.) in methanol (100 cc.). After heating under reflux for 3 hours in a nitrogen atmosphere the solution was evaporated *in vacuo* to approximately 30 cc. Addition of water and filtration afforded the diol IVa (1.3 g.), m.p. 98–102°, raised by several crystallizations from aqueous methanol to 104–106°, $[\alpha]D$ −94°, λ_{max}^{EtOH} 264–266 mμ, ε 2,140, λ_{max}^{KBr} 3450 and 1515 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{29}O_4N \cdot {}^1/_2MeOH$: C, 66.82; H, 8.84; N, 3.96. Found: C, 67.19; H, 8.57; N, 4.12.

Acetylation of this diol IVa (acetic anhydride–pyridine, 20°, 16 hours) afforded the diacetate IIIb in high yield, identical in every respect with the authentic sample.

6β-Nitro-Δ⁴-androstene-3β,17β-diol (VIa). (a) By Alkaline Hydrolysis of the Diacetate (IIIb).—6-Nitro-Δ⁵-androstene-3β,17β-diol diacetate (IIIb) (5.0 g.) in methanol (300 cc.) containing potassium hydroxide (3.0 g.) was heated under reflux for 1.5 hours in an atmosphere of nitrogen. Acidification with acetic acid, addition of water and isolation with ethyl acetate afforded a product which was crystallized from aqueous methanol to yield 6β-nitro-Δ⁴-androstene-3β,17β-diol (VIa) (1.83 g.), m.p. 178–181°, raised by several crystallizations from aqueous methanol to 196–197°, $[\alpha]D$ −134°, λ_{max}^{EtOH} 280–286, ε 115; λ_{max}^{KBr} 3450, 1540 and 1528 (m) cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{29}O_4N$: C, 68.03; H, 8.71; N, 4.18. Found: C, 68.14; H, 8.68; N, 4.39.

(b) By Alkali Treatment of the Δ⁵-3β,17β-Diol IVa.—A solution of 6-nitro-Δ⁵-androstene-3β,17β-diol (IVa) (200 mg.) in methanol (15 cc.) containing potassium hydroxide (150 mg.) was heated under reflux for 1.5 hours in an atmosphere of nitrogen. After acidification with acetic acid and evaporation to approximately 5 cc., addition of water afforded a precipitate (120 mg.), m.p. 163–170° raised by

one crystallization from acetone–hexane to 181–183°, $[\alpha]_D$ −126°. Further crystallizations from acetone–hexane raised the m.p. to 194–196° undepressed on admixture with a sample prepared as in method (a). The infrared spectra of the two compounds were identical.

6β-Nitro-Δ⁴-androstene-3,17-dione (VIIIa).—6β-Nitro-Δ⁴-androstene-3β,17β-diol (VIa) (300 mg.) in acetone (15 cc.) was treated with an excess of 8 *N* chromic acid[25] at 0° for 2 minutes. Addition of water and filtration afforded 6β-nitro-Δ⁴-androstene-3,17-dione (VIIIa) (245 mg.), m.p. 193–196°, raised by several crystallizations from acetone–hexane to 198–200°, $[\alpha]_D$ −45°, λ_{max}^{EtOH} 232–234 mμ, ε 11,750; $\lambda_{max}^{CHCl_3}$ 1735, 1680, 1620 and 1545 cm.$^{-1}$; rotatory dispersion curve (*c* 0.016 in dioxane): $[\alpha]_{700}$ −18.0, $[\alpha]_{589}$ −22.9°, $[\alpha]_{350}$ −702.5°, $[\alpha]_{337.5}$ −593°, $[\alpha]_{335}$ −675°, $[\alpha]_{320}$ −275.5°, $[\alpha]_{300}$ −2,970°.

Anal. Calcd. for $C_{19}H_{25}O_4N$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.84; H, 7.78; N, 4.22.

Sodium Borohydride Reduction of 6β-Nitro-Δ⁴-androstene-3,17-dione (VIIIa).—Sodium borohydride (75 mg.) in water (1.0 cc.) and dioxane (9 cc.) was added to a solution of 6β-nitro-Δ⁴-androstene-3,17-dione (VIIIa) (300 mg.) in dioxane (15 cc.). After 2 hours at room temperature, addition of water, extraction with ethyl acetate and crystallization of the crude product from acetone–hexane afforded 6β-nitro-Δ⁴-androstene-3β,17β-diol (VIa) (150 mg.), m.p. 176–184°, raised by crystallization from acetone–hexane to 193–195°, undepressed on admixture with an authentic sample. The infrared spectra of the two compounds were identical.

6α-Nitro-Δ⁴-androstene-3,17-dione (IXa).—6β-Nitro-Δ⁴-androstene-3,17-dione (VIIIa) (100 mg.) in methanol (5 cc.) containing potassium hydroxide (25 mg.) was kept at room temperature for 2 minutes. After acidification with acetic acid, addition of water afforded 6α-nitro-Δ⁴-androstene-3,17-dione (IXa) (80 mg.), m.p. 190–197°, raised by several crystallizations from acetone–hexane to 202–203°, $[\alpha]_D$ +146°, λ_{max}^{EtOH} 232 mμ, ε 14,790; λ_{max}^{KBr} 1740, 1680, 1615 and 1550 cm.$^{-1}$; rotatory dispersion curve (*c* 0.0610 in dioxane): $[\alpha]_{700}$ +111.5°, $[\alpha]_{589}$ +164°, $[\alpha]_{385}$ +542°, $[\alpha]_{375}$ +517°, $[\alpha]_{320}$ +3920°, $[\alpha]_{300}$ +1585°.

Anal. Calcd. for $C_{19}H_{25}O_4N$: C, 68.86; H, 7.60; N, 4.23. Found: C, 69.04; H, 7.68; N, 4.30.

Sodium Borohydride Reduction of 6α-Nitro-Δ⁴-androstene-3,17-dione (IXa).—Sodium borohydride (125 mg.) in water (1.2 cc.) and dioxane (7.0 cc.) was added to a solution of 6α-nitro-Δ⁴-androstene-3,17-dione (IXa) (500 mg.) in dioxane (15 cc.). After 2 hours at room temperature, addition of water, extraction with chloroform and crystallization of the crude product from acetone–hexane afforded 6α-nitro-Δ⁴-androstene-3β,17β-diol (X) (200 mg.), m.p. 118–120°, raised by crystallizations from acetone–hexane to 125–126°, $[\alpha]_D$ +47°. It exhibited no selective absorption in the ultraviolet λ_{max}^{KBr} 3325 and 1545 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{29}O_4N$: C, 68.03; H, 8.71; N, 4.18. Found: C, 67.63; H, 8.02; N, 3.92.

6β-Nitrotestosterone (VII).—Manganese dioxide[19] (10 g.) was added to a solution of 6β-nitro-Δ⁴-androstene-3β,17β-diol (VIa) (1.0 g.) in chloroform (100 cc.) and the suspension was stirred for 8 hours at room temperature. Filtration through Celite, removal of the solvent *in vacuo* and crystallization of the residue from acetone–hexane afforded 6β-nitrotestosterone (VII) (620 mg.), m.p. 168–175°, raised by one crystallization from acetone–hexane to 200–202° (290 mg.). The analytical sample had m.p. 203–205°, $[\alpha]_D$ −145°, λ_{max}^{EtOH} 234–236 mμ, ε 10,720; λ_{max}^{KBr} 3500, 1677, 1620 and 1547 cm.$^{-1}$; rotatory dispersion curve (*c* 0.0635 in dioxane): $[\alpha]_{700}$ −70.8°, $[\alpha]_{589}$ −104°, $[\alpha]_{307.5}$ −3,180°, $[\alpha]_{300}$ −2,970°.

Anal. Calcd. for $C_{19}H_{27}O_4N$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.66; H, 8.12; N, 3.99.

6α-Nitrotestosterone (IXb).—A solution of potassium hydroxide (25 mg.) in methanol (2.5 cc.) was added to 6β-nitrotestosterone (VII) (150 mg.). After stirring at 5–10° for 30 seconds a complete solution was obtained. After an additional 1 minute the mixture was acidified with acetic acid and diluted slowly with water to afford a precipitate of 6α-nitrotestosterone (IXb) (95 mg.), m.p. 168–175° raised by crystallization from acetone–hexane to 188–192°, $[\alpha]_D$ +29°, λ_{max}^{EtOH} 234 mμ, ε 13,180; λ_{max}^{KBr} 3500, 1680, 1620 and 1550 cm.$^{-1}$; rotatory dispersion curve (*c* 0.0635 in dioxane): $[\alpha]_{700}$ ±0°, $[\alpha]_{589}$ +9.5°, $[\alpha]_{367.5}$ −349°, $[\alpha]_{332.5}$ −59.8°, $[\alpha]_{330}$ −105.5, $[\alpha]_{329.5}$ +59.8°, $[\alpha]_{305}$ −6.3, $[\alpha]_{300}$ +37.8°.

Anal. Calcd. for $C_{19}H_{27}O_4N$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.37; H, 8.03; N, 4.35.

6-Nitro-Δ⁵-pregnen-3β-ol-20-one 3-Acetate (IIIc).—Pregnenolone acetate (Ic) (10 g.) was nitrated exactly as described for Δ⁵-androstene diacetate (Ib → IIIb) and afforded in 62% yield 6-nitro-Δ⁵-pregnene-3β-ol-20-one 3-acetate (IIIc), m.p. 173–176°, raised by several crystallizations from methanol to 183–184°, $[\alpha]_D$ −49°, λ_{max}^{EtOH} 258–260 mμ, ε 1,950; $\lambda_{max}^{CHCl_3}$ 1730, 1705 and 1520 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{33}O_5N$: C, 68.46; H, 8.24; N, 3.47. Found: C, 68.30; H, 8.24; N, 3.50.

6-Nitro-Δ⁵-pregnene-3β-ol-20-one (IVb).—6-Nitro-Δ⁵-pregnene-3β-ol-20-one 3-acetate (IIIc) (3.0 g.) in methanol (100 cc.) containing 70% perchloric acid (5.0 cc.) was heated under reflux in an atmosphere of nitrogen for 2 hours. Concentration of the solution to approximately 75 cc. under vacuum, addition of water and filtration afforded a precipitate (2.5 g.), m.p. 79–85°. A solution of this product in benzene (100 cc.) was adsorbed onto a mixture of silica (25 g.) and Celite (25 g.). Elution with benzene (500 cc.) and benzene–ether (90:10, 500 cc.) afforded 6-nitro-Δ⁵-pregnene-3β-ol-20-one (IVb) as crystals (1.01 g.) from acetone–hexane, m.p. 138–142°, raised by several crystallizations from acetone–hexane to 141–143°, $[\alpha]_D$ −17°, λ_{max}^{EtOH} 262–264 mμ, ε 1905; λ_{max}^{KBr} 3400, 1705 and 1515 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{30}O_4N$: C, 69.77; H, 8.65; N, 3.88. Found: C, 69.75; H, 8.68; N, 3.97.

Acetylation of 6-Nitro-Δ⁵-pregnene-3β-ol-20-one (IVb).—Acetylation (acetic anhydride-pyridine, room temperature, 18 hours) afforded in 70% yield 6-nitro-Δ⁵-pregnen-3β-ol-20-one 3-acetate (IIIc), m.p. 179–182°, undepressed on admixture with an authentic sample. The infrared spectra of the two compounds were identical.

6β-Nitroprogesterone (VIIIb).—6-Nitro-Δ⁵-pregnene-3β-ol-20-one 3-acetate (IIIc) (600 mg.) in methanol (25 cc.) containing potassium hydroxide (1.25 g.) was heated under reflux in an atmosphere of nitrogen for 30 minutes. After acidification with acetic acid the solution was concentrated to approximately 10 cc. Addition of water and isolation with ether gave a non-crystalline product (mainly VIb) which resisted all attempts at crystallization. It had no selective absorption in the ultraviolet, λ_{max}^{KBr} 1700(s), 1550(s) and 1518(weak) cm.$^{-1}$.

The total crude product in acetone (25 cc.) was oxidized with an excess of 8 *N* chromic acid at 0° for 2 min. Addition of water and filtration afforded 6β-nitroprogesterone (VIIIb) (310 mg.), m.p. 153–165°, raised by several crystallizations from acetone–hexane to 178–180°, $[\alpha]_D$ −50°, λ_{max}^{EtOH} 234–236 mμ, ε 12,020; λ_{max}^{KBr} 1710, 1680, 1625 and 1550 cm.$^{-1}$; rotatory dispersion curve (*c* 0.0525 in dioxane): $[\alpha]_{700}$ −24.8°, $[\alpha]_{559}$ −24.85°, $[\alpha]_{347.5}$ −712.5°, $[\alpha]_{340}$ −695°, $[\alpha]_{335}$ −828°, $[\alpha]_{330}$ −755°, $[\alpha]_{300}$ −2770°.

Anal. Calcd. for $C_{21}H_{29}O_4N$: C, 70.17; H, 8.13; N, 3.90. Found: C, 69.96; H, 8.23; N, 3.76.

6α-Nitroprogesterone (IXc).—6β-Nitroprogesterone (VIIIb) (120 mg.) was dissolved in methanol (6 cc.) containing potassium hydroxide (50 mg.) and kept at 10° for 1–2 minutes. Acidification with acetic acid and addition of water afforded 6α-nitroprogesterone (IXc) (110 mg.), m.p. 176–178°, raised by several crystallizations from acetone–hexane to 180–182°, $[\alpha]_D$ +155°, λ_{max}^{EtOH} 232–234 mμ, ε 15,850, λ_{max}^{KBr} 1700, 1680, 1620 and 1550 cm.$^{-1}$; rotatory dispersion curve (*c* 0.045 in dioxane): $[\alpha]_{700}$ +48.8°, $[\alpha]_{589}$ +155.5°, $[\alpha]_{382.5}$ +457.5°, $[\alpha]_{330}$ +427° $[\alpha]_{310}$ +3115°, $[\alpha]_{300}$ +2035°.

Anal. Calcd. for $C_{21}H_{29}O_4N$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.40; H, 8.11; N, 3.81.

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(25) *Cf.* A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).