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

Steroids. CX.[1] Studies in Nitro Steroids (Part 2).[1] A New Route to 6-Nitro Steroid Hormones. 6α-Nitro-17α-acetoxyprogesterone and 6α-Nitrocortisone[2]

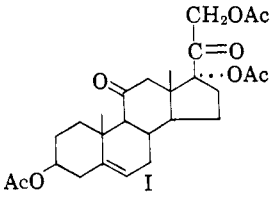
BY A. BOWERS, LAURA CUÉLLAR IBÁÑEZ AND H. J. RINGOLD

RECEIVED NOVEMBER 3, 1958

A new method for the transformation of steroid Δ^4-3-ketones into their 6β- and 6α-nitro analogs by the direct nitration of their derived $\Delta^{3,5}$-dienylacetates is described. Application of this method led to a new synthesis of 6α-nitrotestosterone and the syntheses of 6α-nitro-17α-acetoxyprogesterone and 6α-nitrocortisone. 6β-Nitro-Δ^4-3-ketones undergo mutarotation in methanol solution to an equilibrium mixture of the 6α and 6β-nitro-Δ^4-3-ketones. The fission of a steroid 5α,6α-epoxide with fuming nitric acid is described.

Previous publications from these laboratories[3,4] have described the syntheses of several C-6 fluorosteroid hormones. A remarkable enhancement of biological activity in many of these compounds was noted and in particular the high oral progestational activity of 6α-fluoro-17α-acetoxyprogesterone[4] and the high antiinflammatory activity of the 6α-fluorocortical hormones[4,5] may be mentioned. It was thus of considerable interest to establish whether this enhancement of biological activity was an inherent feature of the fluorine atom or whether the introduction of other strongly electronegative groups at C-6(α) would have a similar effect on biological activity. In this connection we wished to extend our work on nitro steroids to the synthesis of 6α-nitro-17α-acetoxyprogesterone (XIa) and 6α-nitrocortisone (XIb). In the preceding paper[1] we described the synthesis of the 6α-nitro and 6β-nitro analogs of testosterone and progesterone by a route which appears to be generally applicable for the synthesis of 6-nitro-Δ^4-3-ketones from the corresponding Δ^5-3β-hydroxy acetates.

However, adoption of this route for the synthesis of 6α-nitrocortisone required an 11-oxygenated-Δ^5-3β-hydroxy derivative such as the triester I. Such a compound was not readily available when



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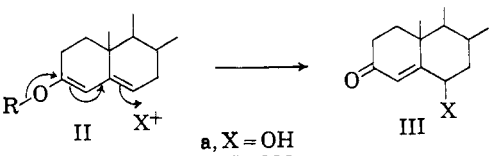
this work was initiated,[6] thus an alternate method for the preparation of 6-nitro steroid hormones utilizing the parent hormone as the starting material was investigated.

Several years ago it was shown in these laboratories that the peracid oxidation of a steroid $\Delta^{3,5}$-dienyl acetate (II) yielded directly the 6β-hydroxy-Δ^4-3-ketone IIIa. This reaction is very probably a concerted reaction initiated by electrophilic attack at C-6 by the peracid as depicted in the formulas II → III. The 6β-(axial) configuration for the introduced hydroxyl group is in accord with current view on the stereochemistry of processes involving electrophilic attack on cyclic enolate anions, enols or enol esters.[8]



a, X = OH
b, X = NO_2

In addition we have demonstrated recently that reaction of steroid $\Delta^{3,5}$-dienyl-3-ethyl ethers with Cl^+ directly yields 6β-chloro-Δ^4-3-ketones.[9]

Thus, it seemed to us, that mechanistically it was feasible to visualize the direct formation of 6β-nitro-Δ^4-3-ketones by treatment of a $\Delta^{3,5}$-dienyl acetate or dienyl ether system (II) with a source of electrophilic nitronium ions (NO_2^+); II → IIIb.

Indeed, this was the case. A suitable source of nitronium ions was fuming nitric acid[10] and studies with the enol acetate of testosterone acetate[11] (IV) led to satisfactory conditions being established for the direct obtention of 6β-nitrotestosterone acetate (V) (Fig. 1). The reaction involved adding a large excess of fuming nitric acid to an ether solution of the enol acetate at 0°. Isolation of the product and direct crystallisation of the reaction mixture afforded 6β-nitrotestosterone acetate (V) in 20% yield, λ_{max}^{EtOH} 234–236 mμ, ε 10,000. In the infrared it exhibited bands at 1730, 1680, 1615 and 1545

(1) Steroids CIX and Part 1, A. Bowers, Maria Blanca Sanchez and H. J. Ringold, THIS JOURNAL, **81**, 3702 (1959).

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

(3) A. Bowers and H. J. Ringold, *Tetrahedron*, **3**, 14 (1958).

(4) A. Bowers and H. J. Ringold, THIS JOURNAL, **80**, 4423 (1958).

(5) Simultaneous with our communication a preliminary announcement from the Upjohn Laboratories also described a series of 6α-fluoro-steroid hormones; J. A. Hogg, G. B. Spero, J. L. Thompson, B. J. Magerlein, W. P. Schneider, D. H. Peterson, O. K. Sebek, H. C. Murray, J. C. Babcock, R. L. Pederson and J. A. Campbell, *Chemistry & Industry*, 1002 (1958).

(6) E. S. Rothman and M. E. Wall, THIS JOURNAL, **81**, 411 (1959), report the synthesis of Δ^5-pregnene-3β,17α,21-triol-11,20-dione (private communication from Dr. Monroe E. Wall); O. Halpern and C. Djerassi, *ibid.*, **81**, 439 (1959) report the synthesis of Δ^5-pregnene-3β,11α,17α-triol-20-one (private communication from Dr. Carl Djerassi).

(7) J. Romo, G. Rosenkranz, C. Djerassi and F. Sondheimer, *J. Org. Chem.*, **19**, 1509 (1954).

(8) See for example (a) W. S. Johnson, *Chemistry & Industry*, 167 (1956); (b) J. L. Beton, T. G. Halsall, E. R. H. Jones and D. C. Phillips, *J. Chem. Soc.*, 753 (1957); (c) R. Howe and F. J. McQuillin, *ibid.*, 1194 (1958).

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

(10) At −10° absolute nitric acid has been shown to ionize to the extent of 4.1%, according to the equation $2HNO_3 = NO_2^+ + NO_3^- + H_2O$; D. J. Millen and W. H. Lee, private communication to C. K. Ingold; *cf.* "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, N. Y., 1953, p. 277, footnote 107.

(11) L. Ruzicka and W. H. Fischer, *Helv. Chim. Acta*, **19**, 1371 (1936).

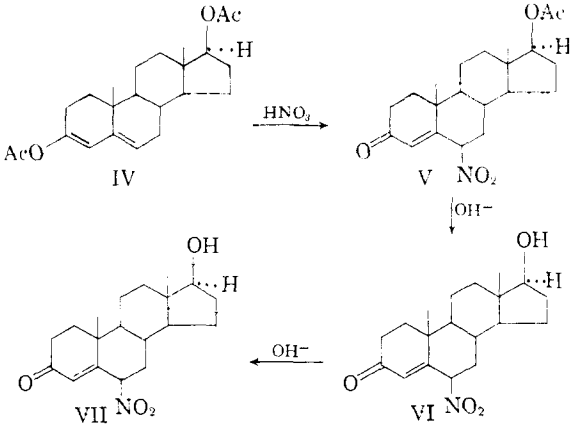


Fig. 1.

cm.$^{-1}$ (characteristic of a nitro group attached to a saturated carbon atom).[12]

The structure and stereochemistry assigned to V followed from its mode of preparation, elemental analysis, spectral data, its characteristically high negative rotation at the sodium *D* line ($[\alpha]_D$ −120°) and the marked similarity of its rotatory dispersion curve with that of 6β-nitrotestosterone and complete disimilarity with that of 6α-nitrotestosterone.[13] Attempts to prepare crystalline V by the room temperature acetylation of 6β-nitrotestosterone with acetic anhydride in pyridine were unsuccessful. It appears that neither 6β- nor 6α-nitro-Δ^4-3-ketones are stable to mild acetylation conditions since both 6α-nitrotestosterone and 6α-nitrocortisone also failed to afford recognizable products after treatment with acetic anhydride in pyridine at room temperature.

Hydrolysis of the 17β-acetoxy group of V with 2% methanolic potassium hydroxide for 18 hours at room temperature followed by acidification with acetic acid and precipitation with water led to a mixture of both 6α- and 6β-nitrotestosterone as evidenced by the rotation of the crude product. Crystallization of the mixture led only to the isolation of 6β-nitrotestosterone (VI), identical in every respect with an authentic sample.[1] Very mild alkaline treatment of VI afforded 6α-nitrotestosterone (VII), identical with an authentic sample.[1]

The isolation of the thermodynamically less stable 6β-nitrotestosterone (VI) by a relatively vigorous alkaline hydrolysis of the 17-acetate V (which involves formation of the salt of the *aci* form of the nitro group) and the isolation of 6α-nitrotestosterone (VII) by a very mild alkali treatment of 6β-nitrotestosterone (VI) is analogous to the case described in the previous paper.[1]

These results with the enol acetate of testosterone clearly established the feasibility of obtaining 6-nitro-Δ^4-3-ketones from the corresponding Δ^4-3-ketones by the direct nitration of their derived enol acetates. Although we have not exploited this method in other than the steroid nucleus it should be capable of wide application and would appear to offer a method for converting cyclic or alicyclic α,β-unsaturated ketones into their γ-nitro analogs *via* the nitration of their derived enol esters.

Application of this method led to a facile synthesis of 6α-nitro-17α-acetoxyprogesterone (XIa) (Fig. 2). Treatment of 17α-acetoxyprogesterone (VIIIa) with acetyl chloride and acetic anhydride smoothly afforded the corresponding Δ^{3,5}-dienyl-acetate IXa. Nitration of this enol acetate (IXa) yielded a crude product which, without purification, was treated with alkali under very mild conditions to afford 6α-nitro-17α-acetoxyprogesterone (XIa), λ_{max}^{EtOH} 232–234 mμ, ε 14,130.

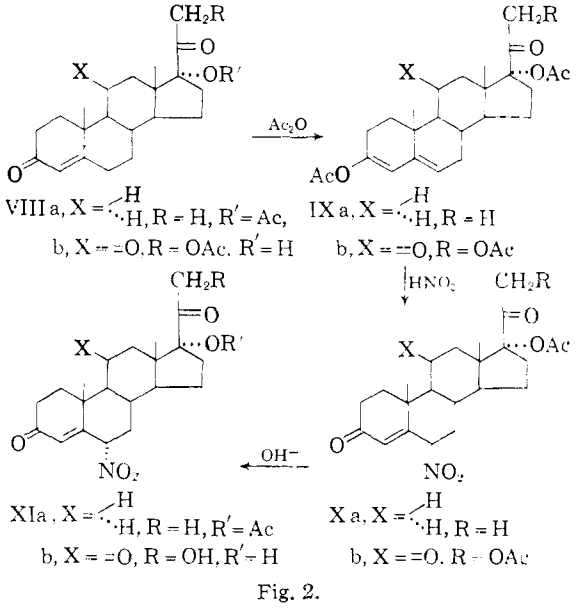


Fig. 2.

A similar approach led to the synthesis of 6α-nitrocortisone (XIb). Cortisone acetate (VIIIb) was treated for 72 hours at room temperature with acetic anhydride containing *p*-toluenesulfonic acid to afford in 63% yield the Δ^{3,5}-dienyl-3,17α,21-triacetate (IXb). Nitration of IXb following the usual procedure led to the isolation of 6β-nitrocortisone 17,21-diacetate (Xb) in 49% yield. This compound had the very characteristic negative rotatory dispersion curve of a 6β-nitro-Δ^4-3-ketone.[1]

Finally, mild alkaline treatment of Xb at 0° in an atmosphere of nitrogen afforded 6α-nitrocortisone (XIb), λ_{max}^{EtOH} 228–230 mμ, ε 14,130. The rotatory dispersion curve of XIb and its spectral properties were in full accord with its assigned structure.

In connection with some rotatory dispersion studies we have observed that 6β-nitro-Δ^4-3-ketones are unstable in methanol solution. A closer examination revealed that 6β-nitroprogesterone,[1] for example, mutarotates at 20° to afford after 72 hours an equilibrium mixture which on the basis of its rotation would correspond to a mixture containing 60% of the 6β-nitro epimer and 40% of the 6α-nitro epimer. The mutarotation was followed by measurement of the specific rotation of the methanol solution at 325 mμ.[14] Unfortunately

(12) For a well documented account of the infrared spectra of nitro compounds see J. F. Brown, THIS JOURNAL, **77**, 6341 (1955).

(13) For a discussion of the difference in the rotatory dispersion curves of 6α- and 6β-nitro-Δ^4-3-ketones see ref. 1.

(14) At 325 mμ the specific rotations of 6α-nitroprogesterone and 6β-nitroprogesterone are +1622 and −750°, respectively, making any conversion of 6β-nitroprogesterone to its 6α-nitro epimer readily

the composition of the mixture could not be confirmed by either paper or column chromatography and we cannot rule out the possibility of complete inversion with partial decomposition, or of a rotationally significant amount of *aci* form being present at equilibrium.

In connection with a general study of the fission of steroid epoxides being carried out in these laboratories[15] we investigated the reaction of fuming nitric acid in anhydrous ether solution on 5α,6α-oxidopregnane-3β-ol-20-one 3-acetate[3] (XII) (Fig. 3). As was to be expected from the known course of ionization of absolute nitric acid[10] nucleophilic attack at C-6β by the nitrate ion afforded in good yield the diaxial glycol mononitrate ester, pregnane-3β,5α,6β-triol-20-one 3-acetate 6-nitrate (XIII). The structure of XIII followed from elemental analysis, a strong band in the infrared at 1640 cm.$^{-1}$ (characteristic of a nitrate ester)[12] its stability toward oxidation with 8 *N* chromic acid and its transformation into the known 3β-hydroxy-5α,6α-epoxide (XIV) upon treatment with alkali. Acetylation of XIV afforded pregnenolone acetate α-epoxide (XII). In the ease with which the nitrate ester undergoes nucleophilic displacement to form the epoxide it closely resembles mesylate or tosylate esters.[16]

In the Clauberg assay, oral route, 6α-nitro-17α-acetoxyprogesterone exhibited 3–4 times the oral progestational activity of 17α-acetoxyprogesterone.[17]

Experimental[18]

6β-Nitro-Δ^4-androstene-17β-ol-3-one 17-Acetate (V).—Fuming nitric acid (75 cc.)[19] was added during 1 hour with good stirring to a solution of Δ^{3,5}-androstadiene-3,17β-diol diacetate (IV) (10 g.) in anhydrous ether (300 cc.), keeping the temperature at 0°.[20] After keeping at 0° for a further 2 hours, ice-water (350 cc.) was added in one portion and the product isolated with ether. The ether solution was washed with cold 5% sodium bicarbonate solution until the alkaline solution just turned brown and then several times with water. The dried solution (Na_2SO_4) was evaporated to dryness *in vacuo* and the product crystallized from ether–ethyl acetate–hexane to afford 6β-nitro-Δ^4-androstene-17β-ol-3-one 17-acetate (V) (1.96 g.), m.p. 163–171°, raised by several crystallizations from ethyl acetate–hexane to 170–173°, $[\alpha]D$ −120°, λ_{max}^{EtOH} 234–236 mμ, ε 10,000; λ_{max}^{KBr} 1730, 1680, 1615 and 1545 cm.$^{-1}$; rotatory dispersion curve (*c* 0.0570 in dioxane): $[\alpha]_{700}$ −21.1°, $[\alpha]_{589}$ −72°, $[\alpha]_{307.5}$ −3,255°, $[\alpha]_{305}$ −3065°.

Anal. Calcd. for $C_{21}H_{29}O_3N$: C, 67.18; H, 7.79; N, 3.73. Found: C, 67.58; H, 7.54; N, 3.81.

6β-Nitrotestosterone (VI).—The crude non-crystalline nitration product[21] from the preceding experiment ($[\alpha]D$ −60°), (2.0 g.) in methanol (60 cc.) containing potassium hydroxide (1.2 g.) was kept at room temperature for 18 hours. After neutralizing the reaction mixture with acetic acid, concentration of the solution to 30 cc. and careful addition of water afforded a crystalline product (1.16 g.),[22] m.p. 180–190°, $[\alpha]D$ −88°, raised by three crystallizations from methanol to 202–204° (310 mg.), $[\alpha]D$ −144°, λ_{max}^{EtOH} 234–236 mμ, ε 10,800. The m.p. was undepressed on admixture with an authentic sample of 6β-nitrotestosterone.[1] The infrared spectra of the two compounds were identical.

The conversion of the above product (m.p. 202–204°) into 6α-nitrotestosterone (VII) was carried out as previously described and afforded a product identical in every respect with an authentic sample.[1]

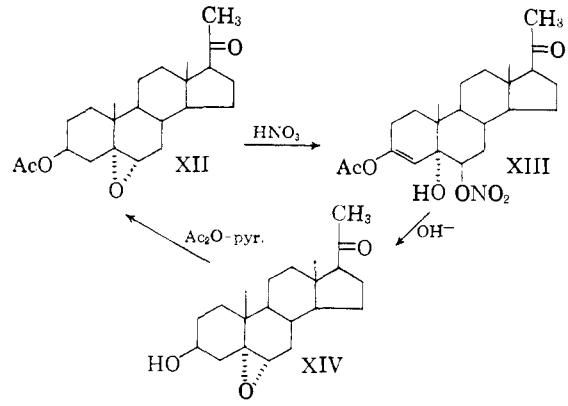


Fig. 3.

Δ^{3,5}-Pregnadiene-3,17α-diol-20-one 3,17-Diacetate (IXa).—17α-Acetoxyprogesterone[23] (10 g.) (VIIIa) in acetic anhydride (30 cc.) and acetyl chloride (30 cc.) was heated under reflux in an atmosphere of nitrogen for 2 hours. After cooling the reaction mixture in ice for 2 hours, filtration afforded Δ^{3,5}-pregnadiene-3,17α-diol-20-one 3,17-diacetate (IXa) (4.9 g.), m.p. 193–195°, raised by several crystallizations from methanol to 205–206°, $[\alpha]D$ −127°, λ_{max}^{EtOH} 234 mμ, ε 20,000; λ_{max}^{KBr} 1760(s), 1740(s), 1575(m) and 1540(m) cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27; O, 19.30. Found: C, 72.41; H, 8.46; O, 19.20.

6α-Nitro-17α-acetoxyprogesterone (XIa).—Fuming nitric acid (15 cc.) was added over 30 minutes with good stirring to a solution of Δ^{3,5}-pregnadiene-3,17α-diol-20-one 3,17-diacetate (IXa) (2.2 g.) in anhydrous ether (60 cc.) at 0°. After a further two hours at 0° ice-water (100 cc.) was added in one portion and the product isolated with ether. The ether solution was washed with 5% sodium bicarbonate solution until the alkaline solution just turned brown and then several times with water. After drying (Na_2SO_4) the solvent was removed *in vacuo* and the residue triturated with hexane to afford an amorphous solid (1.55 g.), m.p. 102–120°, $[\alpha]D$ −80°. In the ultraviolet it displayed an inflection at 230–234° mμ, ε 7,890. All attempts to crystallize this product were unsuccessful and chromatography over alumina or silica gel failed to yield a pure product.

The crude nitration product (950 mg.) was dissolved in methanolic potassium hydroxide solution (50 cc. of 1%) and kept at 5–10° for 2 minutes. The solution was then neutralized with acetic acid, diluted with water and extracted with ether. The extract was washed well with water, dried (Na_2SO_4) and evaporated to the point of crystallization to afford 6α-nitro-17α-acetoxyprogesterone (XIa) (570 mg.), m.p. 201–203°, raised by two crystallizations from acetone–hexane to 203–205°, $[\alpha]D$ +54°, λ_{max}^{EtOH} 232–234 mμ, ε 14,130; λ_{max}^{KBr} 1730, 1695(infl.), 1680, 1620 and 1550 cm.$^{-1}$; rotatory dispersion curve (*c* 0.0590 in dioxane): $[\alpha]_{700}$ +30.5°, $[\alpha]_{589}$ +55.9°, $[\alpha]_{390}$ +203.5°, $[\alpha]_{370}$ +164.5°, $[\alpha]_{307.5}$ +2,230°, $[\alpha]_{300}$ +1740°.

Anal. Calcd. for $C_{23}H_{31}O_6N$: C, 66.16; H, 7.48; N, 3.36. Found: C, 66.51; H, 7.73; N, 3.65.

detectable. The measurements were made with a Rudolph Spectropolarimeter with a xenon arc source.

(15) *Cf.* refs. 3 and 4 and forthcoming publications from these laboratories.

(16) See for example A. Furst and F. Koller, *Helv. Chim. Acta*, **30**, 1454 (1947).

(17) Biological assays by Endocrine Laboratories, Madison, Wisc.

(18) For general directions see the preceding paper. All crystallizations of nitro steroids were carried out as rapidly as possible in an atmosphere of nitrogen.

(19) The nitric acid used in this work had a density at 20° between 1.5015 and 1.5040. For details of its preparation see the preceding paper footnote 21.

(20) The importance of temperature control in nitrations of this type is discussed in ref. 1, footnote 23.

(21) Due to the low yield of 6β-nitrotestosterone acetate which could be isolated by direct crystallization, it was found advantageous to hydrolyze the total crude nitration product.

(22) The yield of crystalline material was not constant and varied from 20–56%.

(23) Prepared according to the method of H. J. Ringold, B. Loken, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **78**, 816 (1956).

$\Delta^{3,5}$-Pregnadiene-3,17α,21-triol-11,20-dione 3,17,21-Triacetate (IXb).—A stirred suspension of cortisone acetate (VIIIb) (10 g.) in acetic anhydride (500 cc.) containing *p*-toluenesulfonic acid monohydrate (7.0 g.) was kept at room temperature for 72 hours (after 1 hour a complete solution was obtained). The reaction mixture was then added with stirring to 3.5 kg. of ice and water. After keeping overnight at 5° filtration afforded a product (10.25 g.), m.p. 123–128°, which after one crystallization from methanol containing a few drops of pyridine yielded $\Delta^{3,5}$-pregnadiene-3,17α,21-triol-11,20-dione triacetate (IXb) (7.0 g.), m.p. 158–161°. The analytical sample had m.p. 168–169°, $[\alpha]_D$ −65°, λ_{max}^{EtOH} 234 mμ, ϵ 20,890.

Anal. Calcd. for $C_{27}H_{34}O_8$: C, 66.65; H, 7.04. Found: C, 66.56; H, 7.08.

6β-Nitro-Δ^4-pregnene-17α,21-diol-3,11,20-trione 17,21-Diacetate (6β-Nitrocortisone Diacetate) (Xb).—Fuming nitric acid (75 cc.) was added over 2 hours with good stirring to a suspension of $\Delta^{3,5}$-pregnadiene-3,17α,21-triol-11,20-dione 3,17,21-triacetate (IXb) (10 g.) in anhydrous ether (300 cc.) at 0°. Most of the steroid had dissolved after this time. The solution was then stirred at 0° for a further 2 hours when ice-water (400 cc.) was added in one portion. Ethyl acetate (250 cc.) was then added and the combined organic phase was washed with cold 5% sodium bicarbonate solution until the alkaline solution just turned brown and then several times with water. The dried solution (Na_2SO_4) was evaporated *in vacuo* at 40° and the residue crystallized from ethyl acetate–ether to afford 6β-nitrocortisone 17,21-diacetate (Xb) (3.97 g.), m.p. 220–223°, $[\alpha]_D$ −56°, and a second crop (960 mg.), m.p. 219–223°. The analytical sample from ethyl acetate–hexane had m.p. 226–228°, $[\alpha]_D$ −57°, λ_{max}^{EtOH} 226–228 mμ, ϵ 11,480; λ_{max}^{KBr} 1748-(sh.), 1735, 1710, 1680, 1625 and 1555 cm.$^{-1}$; rotatory dispersion curve (*c* 0.0615 in dioxane): $[\alpha]_{700}$ −30.9°, $[\alpha]_{650}$ −9.75°, $[\alpha]_{589}$ −37.4°, $[\alpha]_{425}$ −102.5°, $[\alpha]_{400}$ −73.2°, $[\alpha]_{302.5}$ −3340°.

Anal. Calcd. for $C_{25}H_{31}O_9N$: C, 61.34; H, 6.38; N, 2.86. Found: C, 61.70; H, 6.55; N, 2.79.

6α-Nitrocortisone (XIb).—6β-Nitrocortisone diacetate (Xb) (500 mg.) was added to a solution of potassium hydroxide (100 mg.) in methanol (5 cc.) at 0° and stirred for 2 hours under nitrogen. The steroid dissolved readily and after 90 minutes a precipitate began to settle out. After acidification with acetic acid the solution was heated to dissolve the precipitate and then concentrated and finally careful addition of water afforded 6α-nitrocortisone (XIb) (220 mg.), m.p. 215–220°, raised by crystallization from methanol to 230–232°, $[\alpha]_D$ +149° (dioxane); λ_{max}^{KBr} 3450, 1710, 1670, 1625 and 1550 cm.$^{-1}$; λ_{max}^{EtOH} 228–230 mμ, ϵ 14,130; rotatory dispersion curve (*c* 0.0560): $[\alpha]_{700}$ +100°, $[\alpha]_{589}$ +150°, $[\alpha]_{315}$ +2,390°, $[\alpha]_{300}$ +1,535°.

Anal. Calcd. for $C_{21}H_{27}O_7N$: C, 62.21; H, 6.71; N, 3.46. Found: C, 61.95; H, 6.63; N, 3.31.

Pregnane-3β,5α,6β-triol-20-one 3-Acetate 6-Nitrate (XIII).—Fuming nitric acid (5.0 cc.) was added with stirring to a solution of 5α,6α-oxidopregnane-3β-ol-20-one 3-acetate (XII) (1.0 g.) in anhydrous ether (30 cc.) at 0°. After keeping at 0–5° for 17 hours the precipitate which had settled out was removed by filtration to afford pregnane-3β,5α,6β-triol-20-one 3-acetate 6-nitrate (XIII) (650 mg.), m.p. 182–186°, raised by several crystallizations from methanol to 194–196°, $[\alpha]_D$ −37°; λ_{max}^{KBr} 3425, 1730, 1695 and 1640 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{35}O_7N$: C, 63.14; H, 8.06; N, 3.20. Found: C, 63.02; H, 7.99; N, 3.28.

A solution of XIII (500 mg.) in acetone (50 cc.) was treated with an excess of 8 *N* chromic acid[24] at 15° for 5 minutes.

Addition of water and filtration afforded unchanged starting material in high yield.

Treatment of Pregnane-3β,5α,6β-triol-20-one 3-Acetate 6-Nitrate (XIII) with Alkali.—Potassium hydroxide (100 mg.) was added to a solution of the nitrate ester XIII (250 mg.) in methanol (12 cc.) and heated under reflux in an atmosphere of nitrogen for 45 minutes. After neutralization with acetic acid, addition of ice-water and filtration afforded 5α,6α-oxidopregnane-3β-ol-20-one (XIV) (170 mg.), m.p. 183–185°, raised by crystallizations from ethyl acetate–hexane to 185–187°, $[\alpha]_D$ −5°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.44 Found: C, 75.54; H, 9.79; O, 14.82.

Acetylation of this product (acetic anhydride–pyridine, 16 hours, 20°) afforded 5α,6α-oxidopregnane-3β-ol-20-one 3-acetate (XII), m.p. 167–168°, undepressed on admixture with an authentic sample, $[\alpha]_D$ +14°, λ_{max}^{KBr} 1737 and 1708 cm.$^{-1}$. The infrared spectra were identical.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15; O, 17.09. Found: C, 74.05; H, 8.87; O, 17.40.

(24) See for example A. Bowers, T. G. Halsall, E. R. H. Jones and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

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

Steroids. CXI.[1] Studies in Nitro Steroids. Part 3.[1] The Synthesis of 21-Nitroprogesterone[2]

BY A. BOWERS AND H. J. RINGOLD

RECEIVED NOVEMBER 3, 1958

20-Dihydrodesoxicorticosterone (IV) was prepared from desoxycorticosterone acetate (I) by sodium borohydride reduction of its derived 3-cycloethylene-ketal II. Cleavage of IV with periodic acid gave 17β-formyl-Δ^4-androstene-3-one (V). Condensation of V with nitromethane and a final oxidative step afforded 21-nitroprogesterone (VII).

In recent years an increasing amount of empirical evidence has accumulated which indicates that introduction of certain atoms or groups or further unsaturation in key positions throughout the steroid nucleus leads to an enhancement or a desirable modification of the biological activity. Notable among these modifications has been the introduction of a fluorine atom at C-9(α),[3] C-12(α),[4] C-21[5] and C-6(α).[6]

In every case these fluorinated steroid hormones exhibited increased biological activity when com-

(1) Steroids CX and Part 2, A. Bowers, L. C. Ibañez and H. J. Ringold, THIS JOURNAL, **81**, 3707 (1959).

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

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