Tetrahedron, 1964, Vol. 20, pp. 373 to 385. Pergamon Press Ltd. Printed in Northern Ireland

THE SYNTHESIS OF CERTAIN α-NITRO KETO STEROIDS

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(*Received 5 September* 1963; *in revised form*: 7 *October* 1963)

Abstract—Various 2- and 4-nitro-3-ketones and some 16-nitro-17-ketones were prepared by reaction of the corresponding steroid ketone with potassium t-butoxide and amyl nitrate or (one instance) by reaction of amyl nitrate with a steroid enolate anion developed by lithium-liquid ammonia treatment of a conjugated ketone. The enolic character of the various nitro ketones is discussed.

IN THIS paper we describe the preparation of certain α-nitro keto steroids. These compounds, having the nitro group at the 2-, 4- or 16-position, are in most instances simple derivatives of structures known to have hormonal activity and as such are of interest *per se* for biological evaluation and as potential intermediates for the preparation of other steroid hormone analogs.[1]

An initial attempt to introduce the nitro group into the steroid nucleus *via* the reaction of amyl nitrate with the sodium salt of an alkoxalylated keto steroid (the 2-methoxalyl derivative of 17α,20:20,21-bismethylenedioxycortisone)[6] was unsuccessful.[7] In all experiments either starting material or, when the conditions were too vigorous, the parent dealkoxalylated keto steroid was isolated (see Experimental). An alternative approach was based on a long-known procedure, as recently modified by Feuer *et al.*,[12] involving nitration of an alicyclic ketone with an alkyl nitrate in the presence of potassium t-butoxide. Application of this method to appropriate steroid ketones afforded the desired mononitro derivatives.

[1] Several nitro substituted steroids have been reported; among these are some 6-nitrocholesteryl derivatives,[2] the 6-nitro derivatives of progesterone,[3] testosterone,[3] cortisone[4] and certain related compounds,[3,4] and 21-nitroprogesterone.[5] Of these, apparently only 6α-nitro-17-acetoxyprogesterone is of biological interest.[4] After the completion of this investigation Hassner and Larkin [*J. Amer. Chem. Soc.* **85**, 2181 (1963)] reported the preparation by the same procedure described in this paper of 2-nitrocholestanone, 16-nitro-3β-hydroxyandrost-5-en-17-one (mixture of 16α and β epimers) and of the corresponding 5,6-dihydro derivatives.

[2] See L. F. Fieser and M. Fieser, *Steroids* p. 43. Reinhold, New York (1959), for references and a brief review.

[3] A. Bowers, M. B. Sánchez and H. J. Ringold, *J. Amer. Chem. Soc.* **81**, 3702 (1959).

[4] A. Bowers, L. C. Ibáñez and H. J. Ringold, *J. Amer. Chem. Soc.* **81**, 3707 (1959).

[5] A. Bowers and H. J. Ringold, *J. Amer. Chem. Soc.* **81**, 3710 (1959).

[6] C. E. Holmlund, L. I. Feldman, H. M. Kissman and M. J. Weiss, *J. Org. Chem.* **27**, 2122 (1962).

[7] 2-Alkoxalyl-3-keto steroids are known to undergo bromination,[8] fluorination with perchloryl fluoride,[9] and alkylation[10] smoothly. However, an attempt to effect cyanation with a cyanogen halide failed.[11]

[8] J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Hanze, W. P. Schneider, P. F. Beal and J. Korman, *J. Amer. Chem. Soc.* **77**, 4438 (1955).

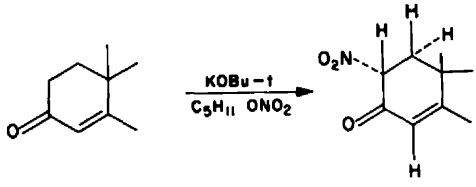
[9] H. M. Kissman, A. M. Small and M. J. Weiss, *J. Amer. Chem. Soc.* **82**, 2312 (1960).

[10] J. A. Hogg, F. H. Lincoln, R. W. Jackson and W. P. Schneider, *J. Amer. Chem. Soc.* **77**, 6401 (1955).

[11] H. M. Kissman, A. S. Hoffman and M. J. Weiss, *J. Org. Chem.* **27**, 3168 (1962).

[12] H. Feuer, J. W. Shepherd and C. Savides, *J. Amer. Chem. Soc.* **78**, 4364 (1956). For a review, see N. Kornblum, *Org. Reactions* **12**, 101 (1962).

Submission of the Δ^4-3-keto system (I) to this procedure furnished the corresponding 2α-nitro-Δ^4-3-ketone (II). The assignment of the nitro group to C_2 is based on spectroscopic evidence, in that the positions of the UV maximum ($\lambda_{max}^{CH_3OH}$ 243–245 mμ, ε 13,900–16,700) and the C=C absorption band (λ_{max}^{KBr} 6·15–6·19 μ) in the IR were not significantly shifted from that of the parent unsubstituted Δ^4-3-ketones, as would be expected for 2-substituted but not for 4- or 6-substituted derivatives. In the one instance (2α-nitrotestosterone 17-tetrahydropyranyl derivative) where it was determined, the NMR spectrum fully confirmed the assignment of the 2-position. This spectrum clearly showed the presence of the C-4 vinylic hydrogen and of a second low field hydrogen, split into a complex multiplet, and thus was only consistent with the formulation of the nitro product as a 2-nitro-Δ^4-3-ketone. Thus, base-catalyzed nitration of Δ^4-3-keto steroids follows the course of base-catalyzed acylation, leading to C-2 substituted products, rather than the course taken by base-catalyzed alkylations which lead to C-4 substitution.



I II

The 2-nitro group is assigned to the more stable α(equatorial)-position, since the products (α-nitro ketones) should be readily equilibrated, and in fact, at least in methanolic solution, are in equilibrium with a small amount of enol as is evidenced by weak UV absorption at about 370 mμ. Support for this assignment is forthcoming from the observed differences in molecular rotation between the 2-nitro derivatives and the respective parent compounds (Table 1). These differences, with one exception, are in the range +272 to +359, which is in general agreement with the effect on molecular rotation resulting from substitution by halogen,[13] hydroxyl,[14] acetoxyl,[14] methyl[15] and cyano[11] groups at the 2α-position. It is also interesting to note that introduction of the 2α-nitro group consistently results in a hypsochromic shift of the 3-carbonyl band in the IR (Table 1). Analogous shifts are observed on the introduction of 2α-halo[16] and 2α-cyano[11] substitutents adjacent to the Δ^4-3-keto system and have been attributed to electrostatic repulsion between the negatively charged halogen[17] or cyano[11] nitrogen and the negatively charged carbonyl oxygen. A similar repulsion is conceivable between the oxygen atoms of the nitro group and that of the carbonyl group.

In the course of this study, the 2α-nitro derivatives of several steroid hormones having the Δ^4-3-keto moiety were prepared. In the C_{21} series, nitrations were carried out with the appropriate 20-ketal derivatives. Thus, condensation of progesterone 20-ethylene ketal,[18] deoxycorticosterone 20-ethylene ketal[11] and hydrocortisone

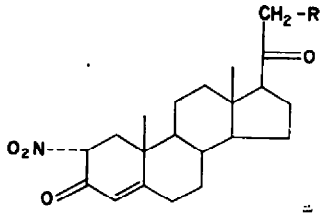
[13] B. Ellis and V. Petrow, *J. Chem. Soc.* 1179 (1956).
[14] G. Rosenkranz, O. Mancera and F. Sondheimer, *J. Amer. Chem. Soc.* **77**, 145 (1955).
[15] H. J. Ringold and G. Rosenkranz, *J. Org. Chem.* **21**, 1333 (1956).
[16] M. Fieser, M. A. Romero and L. F. Fieser, *J. Amer. Chem. Soc.* **77**, 3305 (1955); E. G. Cummins and J. E. Page, *J. Chem. Soc.* 3847 (1957).
[17] E. J. Corey, *J. Amer. Chem. Soc.* **76**, 175 (1959); R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, *J. Amer. Chem. Soc.* **74**, 2828 (1952).
[18] M. Gut, *J. Org. Chem.* **21**, 1327 (1956).

TABLE 1. INFRARED SHIFTS AND MOLECULAR ROTATION DIFFERENCES RESULTING FROM INTRODUCTION OF A NITRO GROUP

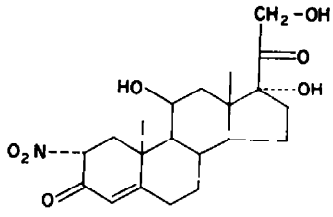
	Nitro deriv.		Parent compounds		Differences	
	Infrared 3-C=O band, μ	M_D,[a]	Infrared 3-C=O band, μ	M_D,[a]	$\Delta\mu$[b]	ΔM_D[c]
2α-Nitroprogesterone 20-ethylene ketal	5·92[d]	+698	5·94[e]	+426[f]	0·02	+272
2α-Nitroprogesterone (III)	5·92[d]	+940	5·94[e]	+639[g]	0·02	+301
2α-Nitrodeoxycorticosterone 20-ethylene ketal	5·88[h]	+705	5·94[h]	+378	0·06	+327
2α-Nitrodeoxycorticosterone (IV)	5·88[h]	+925	5·93[h]	+615	0·05	+310
2α-Nitro-17-methyltestosterone (VI)	5·92[i]	+282	6·00[i]	+242	0·08	+40
2α-Nitrotestosterone-17-tetrahydropyranyl derivative	5·92[j]	+562	6·02[j]	+279[k]	0·10	+283
2α-Nitrotestosterone· CH_3OH (VII)	5·88[h]	+696	5·93[h]	+337	0·05	+359
2α-Nitro-17β-hydroxy-17α-methyl-5α-androstan-3-one (VIII)	5·78[h]		5·83[h]		0·05	
2α-Nitro-17β-(tetrahydropyran-2-yloxy)-5α-androstan-3-one	5·77[h]		5·83[h]		0·06	
2α-Nitro-17β-hydroxy-5α-androstan-3-one (IX)	5·76[h]		5·83[h]		0·07	
4-Nitro-17β-hydroxy-5α-androstan-3-one (XIV)	5·80		5·83[h]		0·03	
4β-Nitro-17β-hydroxy-5β-androstan-3-one (XV)	5·70[h]		5·80[h]		0·10	

[a] All rotations measured in chloroform at a concentration of 0·5–1·0%.
[b] $\lambda_{max}^{Parent}-\lambda_{max}^{Product}$
[c] $M_D^{Product}-M_D^{Parent}$
[d] Measured in bromoform.
[e] Measured in carbon tetrachloride.
[f] Ref. 18
[g] A Lardon, *Helv. Chem. Acta* **32**, 1517 (1949).
[h] Measured in acetonitrile.
[i] Measured in a KBr disc
[j] Measured in chloroform.
[k] Ref. 19

20-ethylene ketal with potassium t-butoxide and amyl nitrate followed by ketal hydrolysis afforded 2α-nitroprogesterone (III), 2α-nitrodeoxycorticosterone (IV) and 2α-nitrohydrocortisone (V), respectively. The yield on nitration with progesterone 20-ketal was 70%, with deoxycorticosterone 20-ketal it was 18% and with hydrocortisone 20-ketal it was probably about 5%. Thus, it is conceivable that free hydroxyl groups interfere with this reaction.[12]

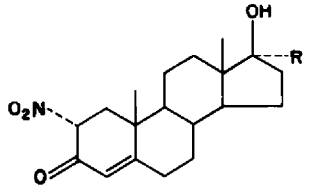


III, R=H
IV, R=OH

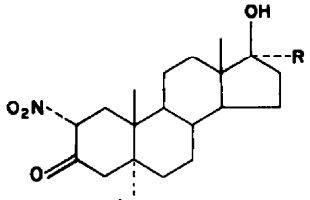


V

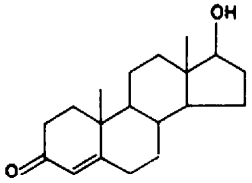
In the C_{19} series, 17-methyltestosterone and testosterone 17-O-tetrahydropyranyl derivative[19] afforded 2α-nitro-17-methyl-testosterone (VI) and 2α-nitrotestosterone (VII) (after acid hydrolysis of the tetrahydropyranyl blocking group). Although the condensation yield was 9% with 17-methyltestosterone, it was 42% with the tetrahydropyranyl testosterone derivative, in which molecule there are no free hydroxyl groups.



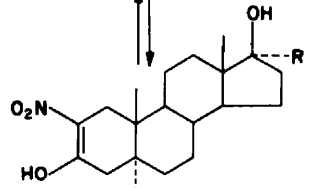
VI, R=CH₃
VII, R=H



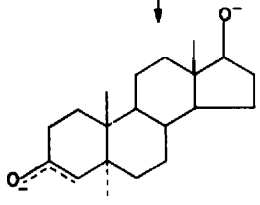
VIII, R=CH₃
IX, R=H



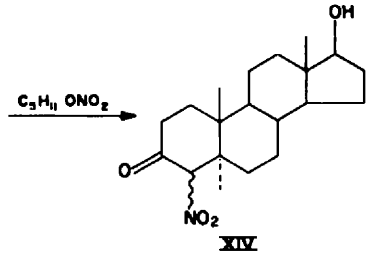
X



XI, R=CH₃
XII, R=H



XIII



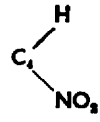
XIV

[19] A. C. Ott, M. F. Murray and R. L. Pederson, *J. Amer. Chem. Soc.* 74, 1239 (1952).

Continuing our study into the 3-keto 5α-series,[1] nitration of 17β-hydroxy-17α-methyl-5α-androstan-3-one and of 17β-tetrahydropyranyloxy-5α-androstan-3-one (followed by tetrahydropyranyloxy hydrolysis) afforded a mixture of the 2α-nitro-3-ketone and the corresponding Δ^2-enol (VIII ⇄ XI and IX ⇄ XII). The keto-enol mixture was indicated by moderate to weak carbonyl absorption at 5·76–5·78 μ (representing a hypsochromic shift of 0·05–0·07 μ from that of the unsubstituted 3-ketone), strong C=C absorption at 6·14–6·17 μ, a split of the asymmetric nitro band into bands at 6·38–6·40 μ (keto form)[20] and 6·58–6·60 μ (enol form), and a major UV absorption maximum in neutral medium at 330 mμ, the intensity of which varied with solvent. The C_2-position for these products is assigned by analogy to the usual course of reaction taken by 3-keto-5α-steroids.

The preparation of a 4-nitro derivative in the 5α-series appears to have been achieved by reaction of amyl nitrate with the enolate anion XIII developed by lithium-liquid ammonia treatment[21] of testosterone (X). Although the product (XIV) so prepared, was subjected to intensive efforts at chromatographic purification, it could not be crystallized and a completely satisfactory analysis was not obtained. Nevertheless, we believe the formation of a 4-nitro-5α-3-ketone to be reasonably well-substantiated by the available data and the method of preparation. Particularly pertinent is the observation from UV and IR absorption data that this product is completely ketonic which, in view of the strong enolic character of the 2-nitro-3-keto system in the 5α series, eliminates a structure of this type as a possibility. In fact, the observed lack of enolic character supports the formulation of this product as a 4-nitro-5α-3-ketone, inasmuch as there are several examples already in the literature wherein the β-keto ester moiety of a 4-carbalkoxy-3-keto *trans* A-B system is also non-enolic.[22–24] This latter phenomenon has been attributed to the unfavorable energetics of the Δ^3-*trans* system and to a steric repulsion which would develop in the enolic form between the 4-carbalkoxy group and the $C_{6\alpha}$-hydrogen.[22] In view of the apparent inability of this substance to undergo enolization (also see below), the more stable equatorial configuration for the 4-nitro group cannot be assumed and an assignment of configuration therefore has not been made.

In the 5β-series, nitration in the usual manner of 17β-hydroxy-5β-androstan-3-one afforded a product in 32% yield to which we assigned the 4β-nitro structure XV. Inasmuch as the formylation of 5β-3-ketones recently has been shown to proceed to a significant extent at C-2,[25] it was necessary to prove the assigned structure. Proof that this product is indeed a 4-substituted, rather than a 2-substituted, derivative was forthcoming from the NMR spectrum, which exhibited a low field proton as a doublet and therefore is attributable to a



[20] The asymmetric nitro band for the various 2α-nitro-Δ^4-3-ketones was observed between 6·36 and 6·42 μ.

[21] R. E. Schaub and M. J. Weiss, *Chem. & Ind.* 2003 (1961); G. Stork, P. Rosen and N. L. Goldman, *J. Amer. Chem. Soc.* **83**, 2965 (1961).

[22] E. Wenkert and B. G. Jackson, *J. Amer. Chem. Soc.* **81**, 5601 (1959).

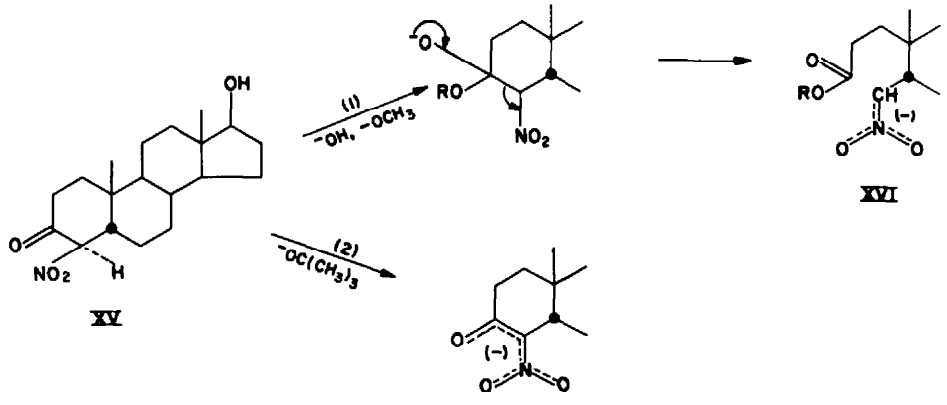
[23] N. A. Nelson and R. N. Schut, *J. Amer. Chem. Soc.* **80**, 6630 (1958).

[24] M. E. Kuehne, *J. Amer. Chem. Soc.* **83**, 1492 (1961).

[25] R. O. Clinton, R. L. Clarke, F. W. Stonner, A. J. Manson, K. F. Jennings and D. K. Phillips, *J. Org. Chem.* **27**, 2800 (1962).

moiety. The assignment of the 4β-equatorial configuration is based on the magnitude of the coupling constant ($J_{4\alpha H5\beta H}$ = 13·0 c.p.s.) which agrees with Jaa reported[26] for 2α-acetoxycholestan-3-one and 3β-acetoxycholestan-2-one.[27] Although 3-keto 5β-steroids, in general, can enolize towards C-4, solution UV and IR data and the NMR spectrum[28] indicate that this compound has no enolic character. The reluctance of XV to assume the enolic form may be ascribed to steric interference between the 6α-hydrogen and the 4-nitro group in the Δ^3-enolic form.

The UV spectra of XV in solution with various bases are particularly interesting. In solutions containing sodium hydroxide or sodium methoxide the spectra [$\lambda_{max}^{0.1N\ NaOH}$ 235 mμ (ϵ 11,900), 338 mμ (ϵ 503);[29] $\lambda_{max}^{0.1N\ NaOCH_3}$ 239 mμ (ϵ 8,950), 347 mμ (ϵ 588)[29]] are approximately the same as that given by 1-nitrobutane in sodium hydroxide solution (λ_{max} 233 mμ, ϵ 9,900), whereas in solution with potassium t-butoxide the spectrum (λ_{max} 348 mμ, ϵ 6,030) is similar to the base spectra of the readily enolized 2-nitro-5α-3-ketones ($\lambda_{max}^{0.1N\ NaOH}$ 338–340 mμ, ϵ ~11,000). These observations may be interpreted as follows. The reaction of XV with a base can take either of two courses: (1) attack at the 3-carbonyl group resulting in the rupture of ring A and formation of a 3,4-*seco*-steroid (XVI) having a nitro alkyl moiety, which in base gives the usual nitro alkane UV spectrum; or (2) removal of the C_4-proton and formation of a β-nitro ketone enolate anion (XVII). With the smaller anions, such as hydroxide or methoxide, reaction is directed to the carbonyl group, presumably because formation of the enolate anion is energetically unfavorable. However, with the sterically demanding t-butoxide anion, the balance of factors leads to removal of the C_4-proton and formation of the enolate anion. In accordance with these considerations, acidification of a potassium t-butoxide solution of XV afforded a 90% recovery of crystalline XV, whereas acidification of a sodium methoxide solution gave a complex mixture which on partition chromatography was resolved into three non-crystaline major components, each of which, according to IR and NMR determinations, contained a carbomethoxy group although two showed only trace evidence of a



XV XVI XVII

[26] K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.* **83**, 4623 (1961).

[27] Examination of Dreiding models indicates a dihedral angle between 5β-hydrogen and 4α-hydrogen slightly less than 180°.

[28] The enolic protons in XI and XII 17-tetrahydropyranyl derivative appear at about 840 c.p.s.

[29] The 338 mμ and 347 mμ absorption peaks are indicative of enolate anion formation, probably about 5%.

nitro group (possible Nef reaction with XVI). Further investigation of these substances was not undertaken. With the 4-nitro-5α-3-ketone XIV, where, as discussed above, there are at least two unfavorable factors to the formation of the Δ^3-enol, even. t-butoxide appears to attack the 3-carbonyl groups as is evidenced by the typical nitroalkane UV spectrum obtained with it.

Nitration by the t-butoxide-amyl nitrate procedure of the corresponding 17-ketones afforded good yields of the 16-nitro derivatives XVIII and XIX.[1] At least in duetero-chloroform solution, these products are present as two species in approximately equal amounts. This was evidenced by the NMR spectra in deuterochloroform which showed a split of the C_{18} angular methyl peak into two peaks of about equal intensity, the position of both peaks representing a shift downfield from the position of the C_{18} methyl group in the respective parent compounds. Inasmuch as the IR and UV spectra of these substances in chloroform solution indicated, at most, only a slight amount of enolic character and since no enolic proton could be discerned in the NMR spectrum,[28] we presume that these species are the respective 16β and 16α-nitro epimers.[30] In the more polar solvents methanol and dimethylsulfoxide considerable enolic character was evident (UV).

Several attempts to effect the reduction of the 17-keto group in XIX with metal hydrides failed, presumably because of enolate anion formation, although an attempt with diborane also was unsuccessful. However, in one experiment with lithium borohydride a low yield of a nitro alcohol was obtained. In view of the usual course of reduction of 16-substituted-17-ketones,[31c,32] we have assigned the 17β-ol structure XX to this product.

EXPERIMENTAL

General. M.p. were taken in open capillary tubes and are uncorrected. UV spectra, unless otherwise stated, were determined in methanol with a Cary recording spectrophotometer. Aliquots were diluted 1:10 with 0·1N HClaq. for the acid spectra and 1:10 with 0·1N NaOHaq. for the base spectra. IR spectra were determined with a Perkin-Elmer spectrophotometer (model 21). Polarimetric data were obtained in chloroform solution of concentration 0·5–1·0%. NMR spectra were determined with a Varian model A-60 spectrometer in deuterochloroform with tetramethylsilane as an internal standard. Unless otherwise specified, the petroleum ether used was that fraction boiling at 60–70°. Solutions were dried ($MgSO_4$) and evaporations were carried out under reduced pressure. The material used in the partition chromatography columns was Celite 545[33] diatomaceous earth which had been washed with 6N HCl and then distilled water until the washings were neutral, and finally with methanol. The substance then was dried to a fluffy powder.[34]

Treatment of the sodium salt of 2-methoxalyl-17α,20:20,21-bismethylenedioxypregn-4-ene-3,11-dione

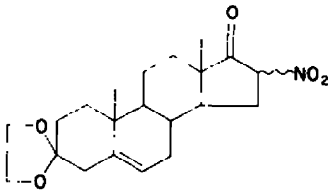
[30] There are several examples in the literature, wherein apparent equilibration of a 16-substituted-17 ketone leads to a mixture of C_{16} epimers, with the 16β-epimer usually predominating.[31] A similar observation has been reported for 16-nitro-3β-hydroxyandrost-5-en-17-one.[31d]

[31] [a] J. H. Fried, A. N. Nutile, G. E. Arth and L. H. Sarett, *J. Org. Chem.* **27**, 682 (1962) (16-methyl);
[b] W. S. Johnson, B. Gastambide and R. Pappo, *J. Amer. Chem. Soc.* **79**, 1991 (1957) (16-acetoxy);
[c] G. P. Mueller and W. F. Johns, *J. Org. Chem.* **26**, 2403 (1961) (16-halo);
[d] A. Hassner and J. Larkin, *J. Amer. Chem. Soc.* **85**, 2181 (1963) (16-nitro).

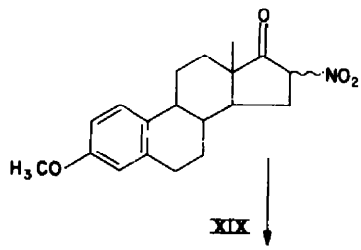
[32] [a] W. R. Biggerstaff and T. F. Gallagher, *J. Amer. Chem. Soc.* **22**, 1220 (1957);
[b] J. Fishman and W. R. Biggerstaff, *J. Amer. Chem. Soc.* **23**, 1190 (1958).
[c] B. Ellis, D. Patel and V. Petrow, *J. Chem. Soc.* 800 (1958);
[d] A. Bowers, P. G. Holton, E. Necoechea and F. A. Kincl, *J. Chem. Soc.* 4057 (1961);
[e] G. R. Allen, Jr. and M. J. Weiss, *J. Org. Chem.* **27**, 4681 (1962).

[33] Celite is the trademark of Johns-Manville Co. for diatomaceous earth products.

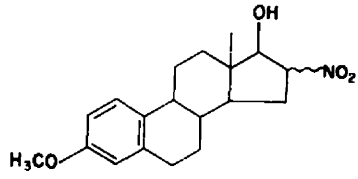
[34] For a detailed description of the partition chromatography procedure, see C. Pidacks *et al.*, *Tetrahedron.*



XVIII



XIX



XX

with amyl nitrate. To a stirred suspension of 2-methoxalyl-17α,20:20,21-bismethylenedioxy-pregn-4-ene-3,11-dione[8] (1.0 g) in 50 ml reagent methanol was added 2·05 ml (1 mmole) of 1N methanolic sodium methoxide, solution being complete in a few min. After the addition of 2 ml amyl nitrate the solution was allowed to stand at room temp for 24 hr. This solution gave a deep red color when treated with alcoholic ferric chloride solution.

One-half of the solution was heated at the reflux temp for 72 hr at which time the enol test with $FeCl_3$aq. was negative. The solution was acidified with acetic acid, concentrated to a small volume, cooled and the crystalline material was collected by filtration to give 333 mg 17α,20:20,21-bismethylenedioxypregn-4-ene-3,11-dione, m.p. 252–254°. This material was identical with an authentic sample[85] according to IR comparison and mixture m.p. No material showing a nitro band in the IR was found in the mother liquors.

The other half of the reaction mixture was kept at room temp for 30 days at which time this solution still gave a deep red color when treated with alcoholic $FeCl_3$. Acidification with acetic acid followed by filtration gave 300 mg of a semisolid material which did not contain nitrogen. The material was not investigated further.

General procedure for t-butoxide-amyl nitrate nitrations

Preparation of 2α-nitroprogesterone 20-ethylene ketal (20-ethylenedioxy-2α-nitropregn-4-en-3-one (The following preparation serves to illustrate this procedure). A solution of 20-ethylenedioxypregn-4-en-3-one[18] (3·0 g) in 65 ml purified tetrahydrofuran was added at −30° to a stirred solution of sublimed potassium t-butoxide (1·55 g) in 40 ml tetrahydrofuran. After the addition of 3 ml purified t-butanol to effect solution, 15 ml tetrahydrofuran containing 1·84 g amyl nitrate was added. The resulting solution was kept at −30° for 30 min and then was allowed to come to room temp during approximately 45 min. The resulting mixture was acidified with 2N HCl, water was added and the resulting aqueous-tetrahydrofuran solution was extracted twice with methylene chloride. The combined extracts were washed with water, dried and evaporated to dryness. Recrystallization of the residue from methylene chloride–ether furnished 2·35 g (70%) product, m.p. 213–217° dec. Further recrystallization from the same solvent pair gave pale-yellow crystals, m.p. 222–224° dec.; $[\alpha]_D^{25}$ +173° (±7·40); λ_{max} 244 mμ (ε 15,700) and 370 mμ (ε 1,800); $\lambda_{max}^{0\cdot1N\ HCl}$ 252 mμ (ε 16000); $\lambda_{max}^{0\cdot1N\ NaOH}$ 242 mμ (ε 8,700), 269 mμ (ε 8,450), 353 mμ (ε 12,700); $\lambda_{max}^{CHBr_3}$ 3·591 6·18, 6·42, 7·28, 9·53 μ. (Found: C, 68·05; H, 8·23; N, 3·86; Calc. for $C_{23}H_{32}NO_6$ (403·50): C, 68·46; H, 8·24; N, 3·47%).

2α-Nitroprogesterone (2α-nitropregn-4-ene-3,20-dione, III). A solution of 20-ethylenedioxy-2α-nitropregn-4-en-3-one (750 mg) in 100 ml methanol containing 4 ml 8% (V/V) H_2SO_4 was refluxed on the steam-bath for 45 min. After concentration to a small volume, water was added and the solids were filtered to give 622 mg (93%) III, m.p. 151–154° (gas). Recrystallization from methylene chloride–ether afforded pale-yellow crystals, m.p. 166–168°; $[\alpha]_D^{25}$ +262° (±4·9°); λ_{max} 243 mμ

[85] R. E. Beyler, F. Hoffman and L. H. Sarett, *J. Amer. Chem. Soc.* **82**, 178 (1960).

(ε 16,700) and 378 mμ (ε 719); $\lambda_{max}^{0.1N\ HCl}$ 252 mμ (ε 16,000); $\lambda_{max}^{0.1N\ NaOH}$ 242 mu (ε 8,600), 265 mμ (ε 8,600) and 356 mμ (ε 12,900); $\lambda_{max}^{CHBr_3}$ 3·590, 6·18, 6·41, 7·26 μ. (Found: C, 69·85; H, 8·41; N, 3·78; Calc. for $C_{21}H_{29}NO_4$ (359·45): C, 70·17; H, 8·13; N, 3·90%).

2α-Nitrodeoxycorticosterone 20-ethylene ketal (*20-ethylenedioxy-21-hydroxy-2α-nitropregn-4-en-3-one*, IV). Treatment of a solution of 20-ethylenedioxy-21-hydroxypregn-4-en-3-one[11] (1·0 g) and sublimed potassium t-butoxide (780 mg) in 30 ml purified tetrahydrofuran containing 2 ml t-butanol with a solution of amyl nitrate (925 mg) in 5 ml tetrahydrofuran in the manner described above for the preparation of 20-ethylenedioxy-2α-nitropregn-4-en-3-one gave 1 g amorphous material. This material was dissolved in 15 ml benzene and was chromatographed on 50 g silica gel. The column was washed with 400 ml benzene and then with 400 ml 5% ether-in-benzene; these washings were discarded. Elution with about 600 ml 10% ether-in-benzene and evaporation of the eluate gave 200 mg intractable syrup. Continued elution (1000 ml 10% ether-in-benzene) and evaporation of the eluate furnished a crystalline residue which upon recrystallization from ether–pet ether gave 200 mg (18%) product, m.p. 189–192°. Recrystallization from the same solvent pair afforded pale-yellow crystals, m.p. 192–194°; $[\alpha]_D^{25}$ +168°; λ_{max} 245 mμ (ε 15,500) and 375 mμ (ε 630); $\lambda_{max}^{0.1N\ HCl}$ 252 mμ (ε 15,000); $\lambda_{max}^{0.1N\ NaOH}$ 245 mμ (ε 7,750), 268 mμ (ε 8,000) and 354 mμ (ε 12,000); $\lambda_{max}^{CH_3CN}$ 2·82, 5·88, 6·15, 6·37 μ. (Found: C, 65·66; H, 7·85; N, 3·36; Calc. for $C_{28}H_{39}NO_6$ (419·50); C, 65·85; H, 7·93; N, 3·34%).

2α-Nitrodeoxycorticosterone (*21-hydroxy-2α-nitropregn-4-ene-3,20-dione*, IV). 20-Ethylenedioxy-21-hydroxy-2α-nitropregn-4-en-3-one (78 mg) was hydrolized by the procedure described above for the preparation of III to give, after recrystallization from acetone–pet ether, 52 mg (75%) IV m.p. 161–163°; $[\alpha]_D$ +247°; λ_{max} 245 mμ (ε 13,900) and 370 mμ (ε 750); $\lambda_{max}^{0.1N\ HCl}$ 253 mμ (14,300); $\lambda_{max}^{0.1N\ NaOH}$ 243 mμ (ε 6,750), 268 mμ (ε 7,100) and 355 mμ (ε 10,900); $\lambda_{max}^{CH_3CN}$ 2·82, 5·88, 6·15, 6·38 μ (Found: C, 66·36; H, 7·70; N, 4·21; Calc. for $C_{21}H_{29}NO_5$ (375·45): C, 67·18; H, 7·79; N, 3·73%).

2α-Nitrohydrocortisone (*11β,17α,21-trihydroxy-2α-nitropregn-4-ene-3,20-dione*, V). Treatment of 20-ethylenedioxy-11β,17α,21-trihydroxypregn-4-en-3-one[9] (1 g) in a solution of purified tetrahydrofuran (40 ml) containing 1·24 g sublimed potassium t-butoxide and 2 ml purified t-butanol with a solution of amyl nitrate (1·48 g) in 5 ml tetrahydrofuran in the manner described (prep. of 20-ethylenedioxy-2α-nitropregn-4-en-3-one) gave 600 mg amorphous material. This material was subjected to partition chromatography on Celite diatomaceous earth. The system heptane–ethyl acetate–methanol–water (55:45:12:8) was used; the column was packed with 570 g Celite diatomaceous earth and the recording spectrophotometer was set at 240 mμ. The first liter of effluent contained a negligible amount of material; the next liter of effluent contained the major peak which on evaporation afforded 85 mg crude *20-ethylenedioxy-11β,17α,21-trihydroxy-2α-nitropregn-4-en-3-one*.

Ketal hydrolysis was accomplished as described above for the preparation of III. There was obtained, after one recrystallization from ether–pet. ether, 33 mg V, m.p. 175–180° dec.; λ_{max}^{KBr} 2·90, 5·85, 5·95, 6·20, 6·45, 7·30 μ. (Found: C, 61·78; H, 7·52; N, 3·14; Calc. for $C_{21}H_{29}NO_7$ (407·45): C, 61·90; H, 7·17; N, 3·44%).

2α-Nitro-17-methyltestosterone (*17β-hydroxy-17α-methyl-2α-nitroandrost-4-en-3-one*, VI). Treatment of 17-methyltestosterone (1 g) in a solution of tetrahydrofuran (30 ml) containing 780 mg potassium t-butoxide and 2 ml t-butanol with a solution of amyl nitrate (485 mg) in 3 ml tetrahydrofuran (prep. of 20-ethylenedioxy-2α-nitropregn-4-en-3-one) gave 1·2 g amorphous material. This material was dissolved in 50 ml benzene and chromatographed on 50 g silica gel. The column was washed with 200 ml 5% ether-in-benzene and 200 ml 10% ether-in benzene, which washings were discarded. Elution with 500 ml 15% ether-in-benzene and evaporation of the eluate furnished crystalline material, recrystallization of which from ether–pet. ether furnished 100 mg (9%) VI, m.p. 199–200° dec., $[\alpha]_D^{24}$ +81·5°; λ_{max} 241 mμ (ε 9,400); absorption at 360 mμ (ε 174) was much weaker than that shown by other 2α-nitro- Δ^4-3-ketones; λ_{max}^{KBr} 2·90, 3·11, 5·91, 6·16, 6·50, 7·30 μ. (Found: C, 68·83; H, 8·23; N, 3·66; Calc. for $C_{20}H_{29}NO_4$ (347·44): C, 69·13; H, 8·41; N, 4·03%).

2α-Nitro-17β-(tetrahydropyran-2-yloxy)-androst-4-en-3-one. Treatment of a solution of 17β-(tetrahydropyran-2-yloxy)-androst-4-en-3-one[10] (3·3 g) in a solution of tetrahydrofuran (100 ml) containing 1·65 g sublimed potassium t-butoxide with a solution of amyl nitrate (1·95 g) in 16 ml tetrahydrofuran (prep. of 20-ethylenedioxypregn-4-en-3-one) furnished 4 g crude product. This material was dissolved in 25 ml benzene and chromatographed on 120 g silica gel. The column was washed with 300 ml benzene and this washing was discarded. Elution with 1,000 ml 5% ether-in-benzene and evaporation of the eluate afforded an amorphous residue which was crystallized from acetone–pet ether to give

1·55 g (42%) product, m.p. 161–163° (gas). Recrystallization from acetone–pet ether gave yellow needles, m.p. 164–166° (gas); $[\alpha]_D^{25}$ +135°; λ_{max} 245 mμ (ε 14,200) and 375 mμ (ε 1,040); $\lambda_{max}^{0.1N\ HCl}$ 253 mμ (ε 15,000); $\lambda_{max}^{0.1N\ NaOH}$ 246 mμ (ε 7,300), 268 mμ (ε 7,500) and 355 mμ (ε 11,200); λ_{max}^{KBr} 5·91, 6·18, 6·42, 7·25 μ; NMR: 330 c.p.s. (center of complex multiplet, H—C_2—NO_2), 358 c.p.s. (C_4—H). (Found: C, 69·15; H, 8·71; N, 3·35; Calc. for $C_{24}H_{35}NO_5$ (417·53): C, 69·03; H, 8·45; N, 3·35%).

2α-Nitrotestosterone (*17β-hydroxy-2α-nitroandrost-4-en-3-one*, VII). A suspension of 2α-nitro-17β-(tetrahydropyran-2-yloxy)-androst-4-en-3-one (197 mg) in 35 ml methanol containing 5 ml water and 0·5 ml 8% (V/V) H_2SO_4 was stirred at room temp for 18 hr. The resulting solution was concentrated to a small volume (red. press.) and then extracted twice with methylene chloride. The combined extracts were washed with water, dried and evaporated to dryness affording a glass, crystallization of which from aqueous methanol gave 132 mg (84%) VII as a methanolate, m.p. 95–99° (gas). Recrystallization from pet ether–methanol gave yellow plates, m.p. 98–101° (gas); $[\alpha]_D^{25}$ +191°; λ_{max} 244 mμ (ε 14,600) and 370 mμ (ε 910); $\lambda_{max}^{0.1N\ HCl}$ 252 mμ (ε 14,800); $\lambda_{max}^{0.1N\ NaOH}$ 242 mμ (ε 7,300), 268 mμ (ε 7,700) and 355 mμ (ε 11,900); $\lambda_{max}^{CH_2ON}$ 2·78 (s), 5·87, 6·14, 6·36 μ. (Found: C, 65·51; H, 8·72; N, 3·90; Calc. for $C_{19}H_{27}NO_4 \cdot CH_3OH$ (365·46): C, 65·73; H, 8·55; N, 3·82%).

17α-Methyl-2-nitro-5α-androst-2-ene-3,17β-diol (XI) *and* *17β-hydroxy-17α-methyl-2α-nitro-5α-androstan 3-one* (VIII). Treatment of a solution of 17β-hydroxy-17α-methyl-5α-androstan-3-one (1·0 g) in a solution of tetrahydrofuran (30 ml) containing 772 mg potassium t-butoxide and 2 ml t-butanol with a solution of amyl nitrate (482 mg) in 3 ml tetrahydrofuran (prep. of 20-ethylenedioxy-2α-nitropregn-4-en-3-one) gave 1·07 g amorphous material. This material was dissolved in 15 ml benzene and chromatographed on 50 g silica gel. The column was washed with 200 ml benzene, 200 ml 5% ether-in-benzene and 200 ml 10% ether-in-benzene, which washings were discarded. Elution with 400 ml 15% ether-in-benzene and evaporation of the eluate furnished 587 mg syrupy material which crystallized after standing for several days. Recrystallization of a portion from ether–pet. ether afforded buff-colored crystals, m.p. 85° (gas); $[\alpha]_D^{25}$ +91°; λ_{max} 330 mμ (ϵ^{CH_3OH} 6,650, ϵ^{CHCl_3} 6,040, ϵ^{CH_3CN} 5,330); $\lambda_{max}^{0.1N\ HCl}$ 337 mμ (ε 4,900); $\lambda_{max}^{6N\ HCl\text{-}CH_3OH}$ 345 mμ (ε 4,850); $\lambda_{max}^{0.1N\ NaOH}$ 230 mμ (ε 4,360) and 338 mμ (ε 11,720); $\lambda_{max}^{CH_3CN}$ 2·83, 5·77, 6·40 μ; λ_{max}^{KBr} 2·88, 5·77 (w), 6·16 (s), 5·40 (m), 6·60 (m), 7·45 μ; visual estimation of the IR curves obtained with Nujol[86] mincral oil mull, KBr disc and chloroform solution indicated in each instance about the same ratio of keto-enol forms; NMR: 840 c.p.s. (about one-half proton, 3-OH in enol form), 213 c.p.s. (center of quartet, J = 7 c.p.s., about one-half proton, C_3—H in keto form). (Found: C, 68·65; H, 9·39; N, 3·90; Calc. for $C_{20}H_{31}NO_4$ (349·46): C, 68·74; H, 8·94; N, 4·01%).

Continued elution of the column with 25% ether-in-benzene furnished 100 mg crystalline material, m.p. 189–190°, identified as starting material by mixture m.p. and IR comparison.

17β-(Tetrahydropyran-2-yloxy)-5α-androstan-3-one. A suspension of 17β-hydroxy-5α-androstan-3-one (2 g) and 66 mg p-toluenesulfonic acid in 0·945 ml dihydropyran was stirred at room temp for 1 hr. The resulting solution was then allowed to stand for 18 hr and then was washed with saturated $NaHCO_3$aq., water, dried and evaporated to dryness. The residue was triturated with pet. ether (b.p. 20–40°) and the resulting crystalline product was collected by filtration to give 1·77 g (69%), m.p. 98–99°.

From another experiment, in which the reaction time was extended to 72 hr, there was obtained 803 mg (31%) of product, m.p. 120°; $[\alpha]_D^{24}$ −8°; $\lambda_{max}^{CH_3CN}$ 5·83 μ. (Found: C, 77·00; H, 10·41; Calc. for $C_{24}H_{38}O_3$ (374·54): C, 76·96; H, 10·23%).

2-Nitro-17β-(tetrahydropyran-2-yloxy)-5α-androst-2-3-ol and 2α-nitro-17β-(tetrahydropyran-2-yloxy)-5α-androstan-3-one. Treatment of a solution of 17β-(tetrahydropyran-2-yloxy)-5α-androstan-3-one (700 mg) in a solution of tetrahydrofuran (25 ml) containing 315 mg sublimed potassium t-butoxide with a solution of amyl nitrate (374 mg) in 3 ml tetrahydrofuran (prep. of 20-ethylenedioxy-2α-nitropregn-4-en-3-one) gave a semisolid. Recrystallization from a minimum amount of pet ether furnished 402 mg (52%) product, m.p. 147–150°; $[\alpha]_D^{25}$ +43°; λ_{max} 227 mμ (ε 3,087) and 331 mμ (ε 8,160); $\lambda_{max}^{0.1N\ HCl}$ 230 mμ (shoulder) (ε 9,400) and 339 mμ (ε 9,200), $\lambda_{max}^{0.1N\ NaOH}$ 230 mμ (shoulder) (ε 5,650) and 340 mμ (ε 10,300); $\lambda_{max}^{CH_3CN}$ 5·76, 6·41 μ; λ_{max}^{KBr} 2·78, 5·76 w, 6·17 (s), 6·39 w, 6·58 (m), 7·43 μ; visual estimation of the IR curves obtained with Nujol mull, KBr disc, and chloroform solution indicated in each instance about the same ratio of keto-enol form; NMR: 839 c.p.s. (about ⅔ proton, 3-OH in enol form). (Found: C, 68·95; H, 9·28; N, 3·61; Calc. for $C_{24}H_{37}NO_5$ (419·54): C, 68·70; H, 8·89; N, 3·34%).

[86] Nujol is the trademark of Plough, Inc. for mineral oil.

2-Nitro-5α-androst-2-ene-3,17β-diol (XII) *and 17β-hydroxy-2α-nitro-5α-androstan-3-one* (IX). A suspension of 2-nitro-17β-(tetrahydropyran-2-yloxy)- 5α-androst-2-en-3-ol (183 mg) in 35 ml methanol containing 5 ml water and 0·5 ml 8% (V/V) H_2SO_4 was stirred at room temp for 18 hr. The resulting solution was neutralized by the addition of Duolite A-4[87] resin and then filtered. The mother liquor was concentrated to near dryness, diluted with methylene chloride and the resulting solution was washed with water, dried and evaporated to dryness. Crystallization of the residue from ether–pet. ether afforded 83 mg (47%) product, m.p. 135–137°. Recrystallization from the same solvent pair gave white crystals, m.p. 136–137°; $[\alpha]_D^{25}$ +112° (±5·90); λ_{max} 230 mμ (ε 2,500) and 331 mμ (ε 6,900); $\lambda_{max}^{0\cdot1N\ HCl}$ 230 mμ (ε 2,500) and 337 mμ (ε 6,000); $\lambda_{max}^{0\cdot1N\ NaOH}$ 230 mμ (ε 4,950) and 338 mμ (ε 11,800); $\lambda_{max}^{CH_3CN}$ 2·83, 5·76, 6·40μ. (Found: C, 67·86; H, 9·13; N, 4·46; Calc. for $C_{19}H_{29}NO_4$ (353·43): C, 68·03; H, 8·71; N, 4·18%).

17β-Hydroxy-4-nitro-5α-androstan-3-one (XIV). A solution of testosterone (3·0 g) in 30 ml purified tetrahydrofuran was added to a stirred solution containing 219 mg lithium in about 500 ml anhydrous liquid ammonia (dried by prior addition of the minimum amount of lithium required to retain the blue color). Toward the end of the addition the blue color gradually disappeared until at the end of the addition the color was completely discharged, resulting in a milky-white solution. A solution containing 10 g amyl nitrate in 10 ml tetrahydrofuran was added and the resulting solution was stirred for about 18 hr. Ammonium chloride (5 g) was added, followed by 200 ml water and 200 ml ether. A crystalline material separated and was collected by filtration. This material (655 mg) did not contain nitrogen according to combustion analysis, and it was set aside. This compound apparently is a dimer and we hope to report on its structure in a subsequent publication. The mother liquor was evaporated to dryness to give an intractable syrup, which was dissolved in 20 ml benzene and chromatographed on 10 g silica gel. The column was washed with 250 ml benzene, 250 ml 5% ether-in-benzene, and 250 ml 10% ether-in-benzene and these washings were discarded. Elution with 100 ml 15% ether-in-benzene and evaporation of the eluate gave 703 mg intractable syrup. This material was subjected to partition chromatography on Celite diatomaceous earth using the system heptane–methanol.[84] The column was packed with 550 g Celite diatomaceous earth. The first 2750 ml effluent contained a negligible amount of material; the next 1 l. effluent contained the major peak which on evaporation afforded 414 mg (12%) product; $[\alpha]_D^{25}$ +9·7°; $\lambda_{max}^{0\cdot1N\ NaOH}$ 232 mμ (ε 9,700); $\lambda_{max}^{0\cdot1N\ NaOCH_3}$ 239 mμ (ε 6,220); $\lambda_{max}^{0\cdot1N\ KOt\text{-}bu}$ 224 mμ (ε 4,550), no significant uv absorption in t-butanol or methanol solution; $\lambda_{max}^{CHCl_3}$ 5·80, 6·44, 7·25 μ. (Found: C, 67·33; H, 9·98; N, 3·43; H_2O, 0·97; Calc. for $C_{19}H_{29}NO_4 \cdot \frac{1}{2} H_2O$: C, 67·46; H, 8·79; N, 4·14; H_2O, 0·67%).

17β-Hydroxy-4β-nitro-5β-androstan-3-one (XV). Treatment of 17β-hydroxy-5β-androstan-3-one (4 g) dissolved in 120 ml tetrahydrofuran containing 3·24 g potassium t-butoxide and 3 ml t-butanol with a solution of amyl nitrate (2·02 g) in 12 ml tetrahydrofuran preparation of 20-ethylenedioxy-2α-nitropregn-4-en-3-one) gave 5 g intractable material. This material was dissolved in 50 ml benzene and chromatographed on 200 g silica gel. The column was washed with 500 ml benzene, 500 ml 5% ether-in-benzene, 500 ml 10% ether-in-benzene, 500 ml 15% ether-in-benzene and 500 ml 20% ether-in-benzene and these washings were discarded. Elution with 750 ml 25% ether-in-benzene, followed by evaporation of the eluate and recrystallization of the residue from acetone–pet. ether furnished 1·504 g (32%) product, m.p. 190–191°; $[\alpha]_D^{25}$ +66°, no significant UV absorption discernable in methanol or 0·1N HCl; $\lambda_{max}^{0\cdot1N\ NaOH}$ 235 mμ (ε 11,900) and 338 mμ (ε 503); $\lambda_{max}^{0\cdot1N\ NaOCH_3}$ 239 mμ (ε 8·950) and 347 mμ (ε 588): $\lambda_{max}^{0\cdot1N\ KOt\text{-}bu}$ 348 mμ (ε 6,030); [for 1-nitrobutane: $\lambda_{max}^{0\cdot1N\ NaOH}$ 233 mμ (ε 9,900). no significant absorption in methanol or 0·1N HCl]; $\lambda_{max}^{CH_3CN}$ 2·82, 5·73, 6·09, 6·37 μ; λ_{max}^{KBr} 2·81, 5·78, 6·43, 7·28 μ; NMR: 47 (C_{18}–CH_3), 70(C_{19}—CH_3), multiplet centered at 225 (17–H), 345·5 c.p.s. (center of doublet, J = 13 c.p.s., integration indicates one proton, H—C—NO_2). (Found: C, 67·71; H, 8·76; N, 4·08; Calc. for $C_{19}H_{29}NO_4$: C, 68·03; H, 8·71; N, 4·18%).

Treatment of 17β-hydroxy-4β-nitro-5β-androstan-3-one (XV) *with potassium t-butoxide followed by acidification.* A solution containing 100 mg XV in 2 ml purified tetrahydrofuran was added to 70 mg sublimed potassium t-butoxide (2·1 equiv.) dissolved in 5 ml tetrahydrofuran, and 1 ml t-butanol. The resulting mixture was allowed to stand 5 min and then acidified (2N HCl). After 10 min, the solution was diluted with water and extracted twice with methylene chloride. The combined extracts were washed with water, dried ($MgSO_4$) and evaporated to dryness. The resulting material was recrystallized to give 90 mg solid, m.p. 189–190°, with IR spectrum identical to that of XV.

Treatment of 17β-hydroxy-4β-nitro-5β-androstan-3-one (XV) *with sodium methoxide, followed by*

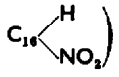
[87] Duolite A-4 is the trademark of Chemical Process Co. for a weakly basic anion exchange resin.

acidification. A solution containing 80 mg XV and 35 ml 0·1N methanolic $NaOCH_3$ in 35 ml methanol was allowed to stand at room temp for 20 min and then was acidified (2 N HCl). After concentration to a small volume *in vacuo* (bath temp 35°), the mixture was extracted twice with methylene chloride. The combined extracts were washed with water, dried ($MgSO_4$) and evaporated to dryness to give 85 mg syrup. This material was combined with product from an identical experiment to give 170 mg which was subjected to partition chromatography on Celite diatomaceous earth. The system n-heptane:ethyl acetate:methanol:water (60:40:12:8) was used and the column was packed with 160 g of Celite. The first two peaks gave 12 mg and 2 mg respectively of amorphous apparently non-steroidal material which was rejected. The next peak gave 14 mg amorphous material with the following characteristics: $\lambda_{max}^{0\cdot1N\ NaOH}$ 282 mμ ($E_{1\ cm.}^{1\%}$ 80); $\lambda_{max}^{CHBr_3}$ 3·577 (s), 6·45 (s), 7·25 (m), 8·60 (s) μ; NMR: 45(C_{18}—CH_3), 64(C_{19}—CH_3), 224 c.p.s. (+shoulder at 223) (—OCH_3 + C_{17}—H), approximate integral ratio of 45 c.p.s. peak to 224 c.p.s. peak 3·6:3. The next peak afforded 42 mg amorphous material which had no significant UV absorption at 20γ/ml in 0·1N NaOH; $\lambda_{max}^{CHBr_3}$ 3·577 (s), 6·45 (w), 7·26 (m), 8·60 (s) μ; NMR: 46(C_{18}—CH_3), 61 (+shoulder at 59), (C_{19}—CH_3), 223 c.p.s. (—OCH_3 + C_{17}—H). The final peak gave 17 mg amorphous material; $\lambda_{max}^{CHBr_3}$ 3·568 (w), 5·78 (s), 6·47 (w), 7·27 (m), 8·60 (s) μ; NMR: 44(C_{18}—CH_3), 58(C_{19}—CH_3), 222 c.p.s. (—OCH_3).

It is worth noting that the NMR position of the C_{19}—CH_3 group for each of the above three substances was shifted considerably from that observed with XV.

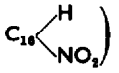
3-Ethylenedioxy-16α- and 16β- nitroandrost-5-en-17-one (XVI). Treatment of a solution of 3-ethylenedioxyandrost-5-en-17-one[28] (2 g) in a tetrahydrofuran solution (30 ml) containing 1·31 g sublimed potassium t-butoxide with a solution of amyl nitrate (4·4 ml) in 10 ml tetrahydrofuran (prep. of 20-ethylenedioxy-2α-nitropregn-4-en-3-one) afforded 1·27 g (56%) XVI, m.p. 192–195° dec.

In a pilot run, the yield was 460 mg (60%), m.p. 186–188° dec. Several recrystallizations from methylene chloride–ether gave white crystals, m.p. 192–195° dec.; $[\alpha]_D^{26}$ +3·3° (1·23%); λ_{max} 230 (ϵ 4,130), 240 (shoulder) (ϵ 3,750) and 335 mμ (ϵ 5,500); $\lambda_{max}^{CHCl_3}$ 300 mμ (ϵ 486); $\lambda_{max}^{(CH_3)_2SO}$ 345 mμ (ϵ 6,580); $\lambda_{max}^{0\cdot1N\ HCl}$ 230 (ϵ 3,680) and 240 mμ (ϵ 3,680); $\lambda_{max}^{0\cdot1N\ NaOH}$ 230 (ϵ 6,300), 235 (ϵ 5,650) and 325 mμ (ϵ 15,000); $\lambda_{max}^{CHCl_3}$ 5·69 (s), 5·98 (w), 6·45, 7·40 μ, no bands below 3·4 μ; NMR: 68,66 (+shoulder at 65), 61 c.p.s. (presumably 66 + 65 represents C_{19} methyl and 68 + 61 the epimeric C_{18} methyls, 68 and 61 are about equal in intensity and total 3 protons; the parent 3-ethylenedioxy-androst-5-en-17-one has methyl peaks at 64 and 53 c.p.s.), 307 c.p.s. (center of complex multiplet,



no significant absorption from 340 to 1000 c.p.s. Note that the presence of two peaks (66 and 65) for the C_{19}-methyl group is indicative of two epimers rather than two conformers resulting from restricted rotation of the C_{18}-methyl group in the 16β-nitro epimer. (Found: C, 67·36; H, 7·98; N, 3·86; Calc. for $C_{21}H_{29}NO_5$ (375·45): C, 67·18; H, 7·79; N, 3·73%).

16α- and 16β-Nitroestrone 3-methyl ether (*3-methoxy-16α- and 16β-nitroestra-1,3,5(10)-trien-17-one*, XVII). Treatment of a solution of estrone 3-methyl ether (2 g) in 50 ml purified tetrahydrofuran containing 1·3 g sublimed potassium t-butoxide with a solution of amyl nitrate (40 ml) in 6 ml tetrahydrofuran (prep of 20-ethylenedioxy-2α-nitropregn-4-en-3-one) gave, after recrystallization of the residue from methylene chloride–ether, 1·82 g (79%) XVII, m.p. 180–183° dec. Further recrystallization from the same solvent pair did not alter the m.p.; $[\alpha]_D^{25}$ +72·3°; λ_{max} 280 (ϵ 2,800), 288 (ϵ 3,130) and 335 mμ (ϵ 6,260); $\lambda_{max}^{(CH_3)_2SO}$ 280 (ϵ 2,820), 288 (ϵ 2,790) and 343 mμ (ϵ 5,740); no significant absorption in chloroform from 295 mμ to 400 mμ; $\lambda_{max}^{0\cdot1N\ HCl}$ 280 (ϵ 2,300) and 286 mμ (ϵ 2,100); $\lambda_{max}^{0\cdot1N\ NaOH}$ 288 (shoulder) (ϵ 4,900) and 325 mμ (ϵ 14,800); $\lambda_{max}^{CHCl_3}$ 5·67, 6·20, 6·42, 6·69, 6·81, 6·86, 7·38 μ, no absorption maxima below 3·30 μ; NMR: 61, 68 c.p.s. (epimeric C_{18} methyl peaks, total intensity equal to 3 protons about equally divided; C_{18} methyl peak in parent estrone 3-methyl ether occurs at 56 c.p.s.), 307 c.p.s. (center of complex 1 proton multiplet,



no significant absorption between 450 c.p.s. and 1000 c.p.s. (Found: C, 69·17; H, 7·19; N, 4·19; Calc. for $C_{19}H_{23}NO_4$ (329·38): C, 69·28; H, 7·04; N, 4·25%).

[28] H. M. Kissman, A. S. Hoffman, and M. J. Weiss, *J. Org. Chem.* **26**, 973 (1961).

16ξ-*Nitroestradiol* 3-*methyl ether.* (17β-*hydroxy*-3-*methoxy*-16ξ-*nitroestra*-1,3,5(10)-*triene*). A suspension of 300 mg 16-nitroestrone 3-methyl ether and 100 mg $LiBH_4$ in 25 ml purified tetrahydrofuran was stirred at room temp for 20 hr. Excess hydride was then destroyed (2 ml acetic acid followed by ice water until gas evolution ceased). The mixture was concentrated to a small volume on a 50° bath and the resulting solution was extracted several times with methylene chloride. The combined extracts were washed with water, dried and evaporated to dryness. The residue (160 mg) was subjected to partition chromatography on Celite diatomaceous earth. The system n-heptane–methanol was used. The column was packed with 80 g Celite and the recording spectrophotometer was set at 280 mμ. The first 400 ml effluent contained a negligible amount of material; the next 260 ml effluent contained the major peak which on evaporation afforded 76 mg crude material. Two recrystallizations from acetone–petroleum ether gave 52 mg product, m.p. 102–104°; $[\alpha]_D^{26}$ +80°; λ_{max} 279 (ε 3,200) and 287 mμ (ε 2,150); λ_{max}^{KBr} 2·78, 2·91, 6·18, 6·45, 7·23, 9·65 μ. (Found: C, 68·15; H, 8·27; N, 4·02; H_2O(K–F), 0·5; Calc. for $C_{19}H_{25}NO_4$ (·5% H_2O): C, 68·52; H, 7·56; N, 4·21%).

Acknowledgements—We wish to acknowledge with thanks several helpful discussions with Professor Howard Zimmerman. We also wish to thank the staff of the spectroscopy laboratory for the spectrophotometric, most of the NMR, and the polarimetric data, Dr. J. Lancaster of the Stamford Laboratories of the American Cyanamid Company for certain of the NMR data, Mr. L. Brancone and staff for the microanalytical data and Mr. C. Pidacks and staff for the partition chromatographic work.