Experimental[12]

The fluorinations were carried out in a 316 stainless steel autoclave employing a copper gasket. A rupture disk of 316 stainless steel was employed and changed after every fifth run. Hydrogen fluoride was generated *in situ* by the hydrolysis of sulfur tetrafluoride[3] ($SF_4 + H_2O \rightarrow SOF_2 + 2\ HF$). Sulfur tetrafluoride was measured by the pressure drop across a stainless steel reservoir of known volume on opening the reservoir to a frozen autoclave containing all other reactants. The fluorination procedure is illustrated by the preparation of 24,24,24-trifluoro-5β-cholan-3α-ol acetate. Other fluorinations were carried out under the same conditions.

24,24,24-Trifluoro-5β-cholan-3α-ol Acetate (Ib).—A mixture of 1.0 g. of lithocholic acid acetate, 20 ml. of methylene chloride, and 0.75 ml. of water was placed in a 100-ml. autoclave. The autoclave was sealed and frozen in a bath of Dry Ice and acetone before approximately 46 g. of sulfur tetrafluoride[13] was condensed into the autoclave. The autoclave was then agitated for 16 hr. at room temperature. The temperature of the cubicle used for high pressure reactions was 20°; several hours were required for the frozen autoclave to attain cubicle temperature. The autoclave was vented through caustic solution, evacuated to remove volatile materials, and finally opened. Its contents were taken up in 200 ml. of methylene chloride and washed with 10% potassium bicarbonate solution. The methylene chloride solution was dried over sodium sulfate and concentrated to dryness under reduced pressure leaving 1.20 g. of brown gum which was chromatographed on 60 g. of Florisil.[14] The column was developed with Skellysolve B[15] and methylene chloride–Skellysolve B mixtures containing an increasing concentration of methylene chloride. The Skellysolve B and 1% methylene chloride–Skellysolve B eluates contained a small amount of sulfur and trace amounts of a yellow gum lacking carbonyl absorption in the infrared. The eluates comprising 2 to 20% methylene chloride–Skellysolve B afforded crystalline fractions totaling 273 mg. Recrystallization from acetone–water afforded 2 crops totaling 268 mg. (25% yield) of crystalline solid, m.p. 147–149°. Recrystallization from acetone–water gave a sample $[\alpha]_D$ +44° (chloroform); ν_{mull} 1727 cm.$^{-1}$; m.p. 148–150°.

Anal. Calcd. for $C_{26}H_{41}O_2F_3$: C, 70.55; H, 9.34; F, 12.88. Found: C, 70.77; H, 9.49; F, 12.53.

3α-Hydroxy-5β-cholanyl Fluoride Acetate (Ia). Procedure A.—A mixture of 5.00 g. of lithocholic acid acetate, 20 ml. of methylene chloride, and 46 g. of sulfur tetrafluoride was agitated for 16 hr. at room temperature. The autoclave was vented and its contents taken up in methylene chloride, washed with 10% potassium bicarbonate, dried over sodium sulfate, and concentrated to dryness under reduced pressure leaving 5.00 g. of crystalline residue. Recrystallization from methylene chloride–Skellysolve B afforded 4.75 g. (95% yield), m.p. 157–158°. Three recrystallizations from the same solvents afforded a sample, m.p. 158–159°; ν 1838, 1733 cm.$^{-1}$; $[\alpha]_D$ +44°.

Anal. Calcd. for $C_{26}H_{41}FO_3$: C, 74.24; H, 9.83; F, 4.52. Found: C, 74.72; H, 9.89; F, 4.40.

Procedure B.—The fluorination procedure employed for 24,24,24-trifluoro-5β-cholan-3α-ol acetate, was followed except that 20 ml. of tetramethylene sulfone[16] replaced the methylene chloride. The crude product was diluted with methylene chloride, washed with 10% potassium bicarbonate and two portions of water, dried over sodium sulfate, and concentrated under reduced pressure leaving the product in approximately 8 ml. of tetramethylene sulfone. Dilution with water precipitated 0.82 g. crude Ia, m.p. 152–155°.

Acknowledgment.—The authors are indebted to M. A. Rebenstorf and D. T. Kloosterman who ran these autoclave reactions and to J. L. Johnson and W. A. Struck and associates for spectral and analytical determinations.

(12) Melting points are uncorrected. Rotations were observed at 26° on chloroform solutions. Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer from Nujol mulls. Ultraviolet spectra were taken on 95% ethanol solutions using a Cary Model 14.

(13) Obtained from the E. I. DuPont de Nemours Co., Wilmington, Del., and the Matheson Co., East Rutherford, N. J.

(14) A synthetic magnesia–silica gel manufactured by the Floridin Co., Warren, Pa.

(15) A saturated hydrocarbon fraction, b.p. 60–71°.

(16) Obtained from the Columbia Organic Chemicals Co., Columbia, South Carolina, and redistilled.

The Synthesis of Certain α-Cyano Keto Steroids

HENRY M. KISSMAN, ARLENE SMALL HOFFMAN, AND MARTIN J. WEISS

Lederle Laboratories Division, American Cyanamid Co., Pearl River, New York

Received March 8, 1962

The 2α-cyano derivatives of testosterone, progesterone, deoxycorticosterone, hydrocortisone, and cortisone were prepared by reaction of the corresponding 2-hydroxymethylene derivatives, having properly blocked side chains, with O,N-bis(trifluoroacetyl)hydroxylamine (II). The 16ξ-cyano derivatives of testosterone, estrone 3-methyl ether, and estradiol 3-methyl ether were prepared in the same manner from the corresponding 16-hydroxymethylene-17-keto precursors.

The introduction of halogen atoms or additional methyl or hydroxyl groups into the nucleus of steroid hormones in certain instances has had important effects on the biological activities of these hormones. It appears to us that with the present state of knowledge in this field, the discovery of other groups which would also favorably modify the biological activity of the parent hormones must largely stem from an empirical approach. As part of a continuing effort in our laboratory based on such an approach, we have prepared certain steroid hormones substituted at C-2 or C-16 with the cyano group.[1] These compounds are of interest *per se* and also as precursors for a variety of other steroid analogs.[2] Hitherto, cyano steroids have received little attention, but among those which have been

(1) For a preliminary communication see H. M. Kissman, A. S. Hoffman, and M. J. Weiss, *J. Org. Chem.*, **26**, 2610 (1961).

(2) Further transformations of these cyano steroids will be described in a forthcoming publication.

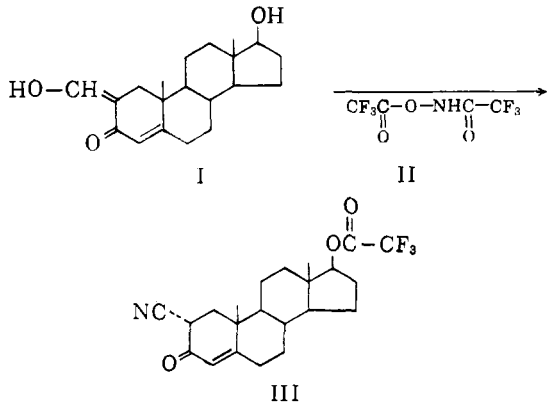
reported in the literature are 21-cyano-21-deoxycortisone,[3] 16α-cyanoprogesterone,[4] a variety of 6-cyano derivatives[5] and most recently, certain 2-cyano[6a] and 5-cyano[6b] derivatives.

A convenient method for the introduction of the cyano group into the steroid molecule seemed to be the reaction of a cyanogen halide with the sodium salts of alkoxalyl steroids.[9] Such a procedure appeared to have a reasonable chance of success in view of the reported[12] condensation of cyanogen chloride with ethyl benzoylacetate to give ethyl α-cyanobenzoylacetate in 70% yield. However, when tried with 3-hydroxy-2-methoxalyl-17α,20:20,21-bismethylenedioxy-2,4-pregnadien-11-one,[11c] as a readily available prototype, it soon became apparent that the reaction was inoperative under a variety of conditions and this approach had to be abandoned.

A new approach was suggested by the report of Pomeroy and Craig[13] wherein aldehydes were converted to nitriles by reaction with O,N-bis(trifluoroacetyl)hydroxylamine (II). It was obvious that successful application of this elegant procedure to hydroxymethylene steroids would afford a convenient synthesis of the desired cyano steroids. The method was first tried with 2-hydroxymethylenetestosterone (I) which was prepared from testosterone, ethyl formate, and sodium hydride according to Weisenborn, Remy, and Jacobs.[14] Treatment of compound I with one equivalent of the hydroxylamine derivative II in refluxing benzene containing an equivalent of pyridine afforded crystalline 2α-cyanotestosterone trifluoroacetate (III) in 30% yield.[15] By using two equivalents of II, it was possible to increase the yield of III to 70%.[16,17] For reasons which are discussed below it is our belief that the cyano group in III and in all the other 2-cyano-Δ⁴-3-ketones described in this paper is in the alpha (equatorial) configuration.

The synthesis of the 2-cyano derivatives of certain progestational, mineralocorticoid, glucocorticoid, and androgenic hormones, and of the 16-cyano derivatives of certain androgenic and estrogenic hormones now appeared possible and was undertaken. In order to prepare the requisite 2-hydroxymethylene-Δ⁴-3-ketone derivatives in the C-21 series it was necessary to use compounds which had suitably blocked side chains. Readily available starting materials for C-2 formylations were the 20-ethylene ketal derivatives of progesterone (IV),[18] deoxycorticosterone (V) and hydrocortisone (VI),[11a] and the 17α,20:20,21-bismethylenedioxy (BMD) derivative of cortisone (VII).[19]

Condensation of these compounds (IV–VII) with ethyl formate to give the corresponding hydroxymethylene derivatives (VIII–XI) was usually carried out with sodium hydride in benzene.[14] However, 2-hydroxymethylenehydrocortisone 20-ethylene ketal (X) was prepared with sodium methoxide and a large excess of ethyl formate as described in the patent literature.[20] In those preparations where sodium hydride was used, the reactions generally had to be primed by the addition of a few drops of ethanol.



(3) P. Borrevang, *Acta Chem. Scand.*, **9**, 587 (1955).

(4) J. Romo, *Tetrahedron*, **3**, 37 (1958); R. H. Mazur and J. A. Cella, *ibid.*, **7**, 130 (1959); B. Ellis, V. Petrow, and D. Wedlake, *J. Chem. Soc.*, 3748 (1958).

(5) A. Bowers, E. Denot, M. B. Sánchez, L. M. Sánchez-Hidalgo, and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 5233 (1959).

(6) (a) The preparation of 2α-cyanocortisone BMD[7] and 2α-cyanocholestan-3-one[8] *via* alkaline treatment of an appropriate isoxazole has been described. (b) A. Bowers, *J. Org. Chem.*, **26**, 2043 (1961); W. Nagata, S. Hirai, H. Itazaki, and K. Takeda, *ibid.*, **26**, 2413 (1961).

(7) J. A. Zderic, *et al.*, *Chem. Ind.* (London), 1625 (1960).

(8) F. Winternitz, Chr. Menou, and E. Arnal, *Bull. soc. chim.*, 505 (1960).

(9) Alkoxalyl steroids have been useful intermediates for the introduction of methyl[10] and fluorine[11] into the steroid nucleus.

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

(11) (a) H. M. Kissman, A. M. Small, and M. J. Weiss, *ibid.*, **82**, 2312 (1960); (b) H. M. Kissman, A. M. Small, and M. J. Weiss, *J. Org. Chem.*, **26**, 973 (1961); (c) C. E. Holmlund, L. I. Feldman, H. M. Kissman, and M. J. Weiss, *ibid.*, **27**, 2122 (1962).

(12) H. Rupe and B. Pieper, *Helv. Chim. Acta*, **12**, 637 (1929).

(13) J. H. Pomeroy and C. A. Craig, *J. Am. Chem. Soc.*, **81**, 6340 (1959).

(14) F. L. Weisenborn, D. C. Remy, and T. L. Jacobs, *ibid.*, **76**, 552 (1954).

(15) The conversion of an α-hydroxymethylenecyclohexanone derivative to an α-cyanocyclohexanone *via* base treatment of an intermediate isoxazole has been reported by W. S. Johnson and W. E. Shelberg [*ibid.*, **67**, 1745 (1945)], who noted its failure in the cyclopentanone series. More recently, however, K. Brückner, *et al.* [*Chem. Ber.*, **94**, 2897 (1961)], have prepared a 16-cyano-17-keto steroid by an adaptation of this general method. In any case, the Pomeroy-Craig[13] procedure is operative with 16-hydroxymethylene-17-keto steroids (see below). For examples of the application of the Johnson and Shelberg method to the synthesis of certain 2α-cyano steroids see ref. 7 and 8.

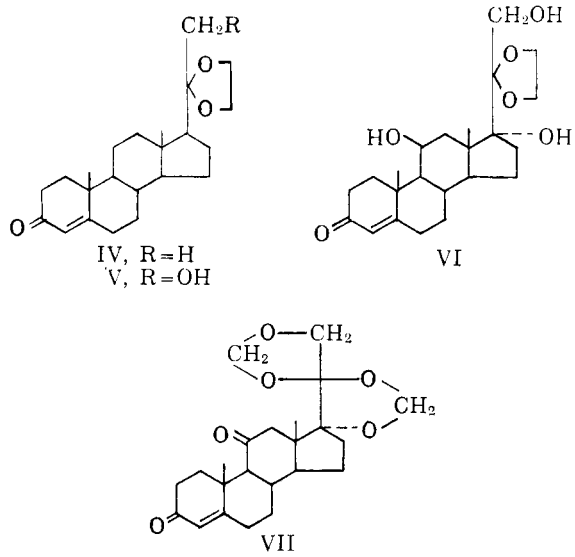
(16) In general it was found that under these conditions, O,N-bis-(trifluoroacetyl)hydroxylamine (II) will effect trifluoroacetylation of accessible primary and secondary hydroxy groups such as the 17β-hydroxy group in testosterone and the 21-hydroxy group in hydrocortisone 20-ethylene ketal (VI), but will not acylate hindered hydroxy groups such as the 11β- or the 17α-hydroxy groups of compound VI (see Experimental).

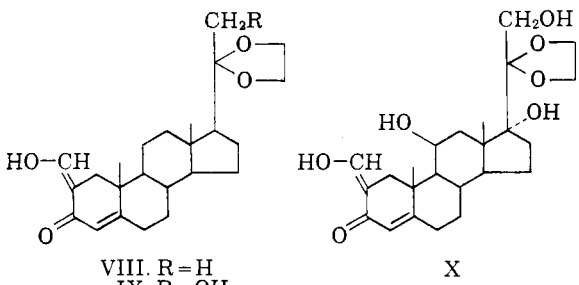
(17) Compound III could also be obtained in 57% yield by allowing the reaction to proceed at room temperature for 24 hr. However, these milder conditions were not effective with some of the other hydroxymethylene steroids and, therefore, were not used generally.

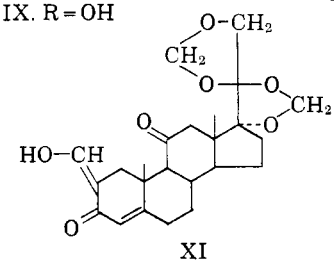
(18) M. Gut, *J. Org. Chem.*, **21**, 1327 (1956).

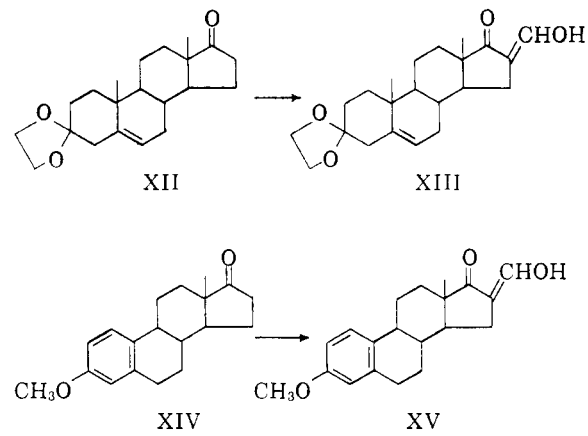
(19) R. E. Beyler, F. Hoffman, and L. H. Sarett, *J. Am. Chem. Soc.*, **82**, 178 (1960).

(20) Australian Patent Specification No. 23,672, April 12, 1956, assigned to Merck & Co., Inc.





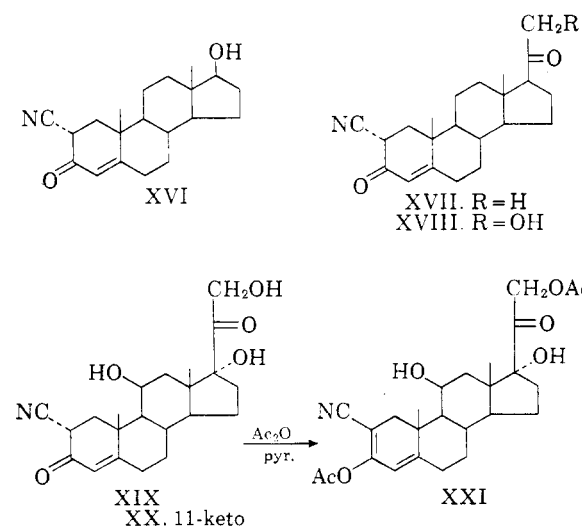




The required 16-hydroxymethylene derivatives in the C-19 series were obtained by formylation with sodium hydride of 5-androstene-3,17-dione 3-ethylene ketal (XII)[21] and of estrone 3-methyl ether (XIV).[22]

All the formylated derivatives prepared in this investigation were crystalline solids which gave strong ferric chloride tests and were in fact shown to be the hydroxymethylene tautomers by ultraviolet and infrared spectroscopy.[23]

Conversion of the various hydroxymethylene derivatives (VIII–XI, XIII, XV) to the corresponding nitriles was carried out under the conditions described above for the preparation of 2α-cyanotestosterone trifluoroacetate (III). An additional equivalent of the hydroxylamine derivative II was used for each "vulnerable" hydroxyl group present in the molecule.[16] Normally, the reaction proceeded smoothly and yields were in the range of 30 to 76%. With 2-hydroxymethylenecortisone-BMD (XI) a large amount of tar was formed during the reaction and a relatively poor yield (25%) was obtained.[24] Removal of the blocking groups was effected by standard procedures. Thus, the 20-ethylene ketal groups were hydrolyzed with a small amount of dilute sulfuric acid in refluxing methanol (one hour), and the BMD group was cleaved[19] with hot 60% aqueous formic acid (thirty minutes). De-O-acylation of 2α-cyano-17β-trifluoroacetyltestosterone (III) was carried out with 10% aqueous potassium carbonate solution in methanol for three hours. These hydrolytic conditions did not affect the cyano group. In this manner, there were obtained 2α-cyanotestosterone (XVI), 2α-cyanoprogesterone (XVII), 2α-cyanodeoxycorticosterone



(21) Compound XII was prepared through the preferential 3-ketalization of 4-androstene-3,17-dione with 2-methyl-2-ethyl-1,3-dioxolane according to Dauben and co-workers [*J. Am. Chem. Soc.*, **76**, 1359 (1954)]. In our hands this method gave a mixture of the 3-monoketal and the 3,17-bisketal, but only the former compound can undergo formylation to give a base-soluble 16-hydroxymethylene derivative.

(22) J. C. Bardhan, *J. Chem. Soc.*, 1848 (1936).

(23) W. Fulmor and G. O. Morton of these laboratories, unpublished work.

(24) It was thought that these poor results with XI might be due to attack by the hydroxylamine derivative II on the BMD group. However, cortisone-BMD (VII) was recovered unchanged when exposed to II in refluxing benzene for several hours.

TABLE I

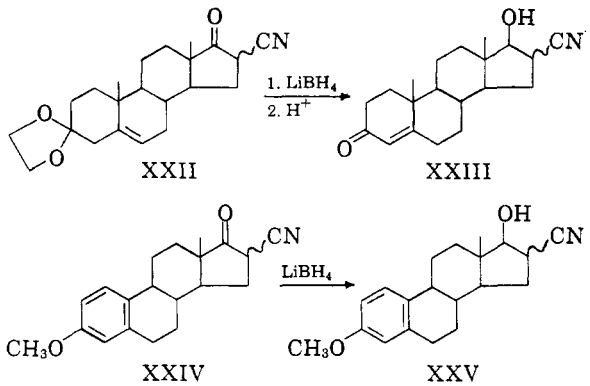
CHANGES IN POSITION OF INFRARED CARBONYL ABSORPTION BANDS AND OF MOLAR ROTATION VALUES RESULTING FROM THE INTRODUCTION OF THE α-CYANO GROUP

	2α-Cyano derivatives		Parent compounds		Differences	
	Infrared 3 C=O band, μ	MD[a]	Infrared 3-C=O band, μ	MD[a]	Δμ	ΔMD
2α-Cyanotestosterone (XVI)	5.91	+373	6.00	+337[b]	−0.09	+36
2α-Cyanoprogesterone 20-ethylene ketal	5.89	+441	6.01	+426[c]	−0.12	+15
2α-Cyanoprogesterone (XVII)	5.94 (5.84, CCl_4)	+720	6.01 (5.92, CCl_4)	+639[d]	−0.07 (−0.08)	+81
2α-Cyanodeoxycorticosterone (XVIII)	5.95	+630[e]	5.99	+587[f]	−0.04	+43
2α-Cyano-17α,20:20,21-bismethylenedioxy-4-pregnene-3,11-dione	5.94 (5.90, CH_3CN)	+389	5.98 (5.97, CH_3CN)	+330[g]	−0.04 (−0.07)	+59
2α-Cyanocortisone (XX)	5.90	+747[h]	5.97	+724[h]	−0.07	+23
2α-Cyanohydrocortisone 20-ethylene ketal 21-trifluoroacetate (XXVI)	5.91	+486	5.99	+437	−0.08	+49
2α-Cyanohydrocortisone (XIX)	5.95	+665[i]	6.02	+590[j]	−0.07	+75

[a] In chloroform at 23–26° unless stated otherwise. [b] S. A. Julia, Pl. A. Plattner, and H. Heusser, *Helv. Chim. Acta*, **35**, 665 (1952). [c] M. Gut, *J. Org. Chem.*, **21**, 1327 (1956). [d] A. Lardon, *Helv. Chim. Acta*, **32**, 1517 (1949). [e] In ethanol. [f] Ch. Meystre and K. Miescher, *Helv. Chim. Acta*, **34**, 2286 (1951), [in ethanol]. [g] R. E. Beyler, F. Hoffman and L. H. Sarett, *J. Am. Chem. Soc.*, **82**, 178 (1960). [h] In dioxane. [i] In methanol. [j] In methanol, N. L. Wendler, *et al.*, *J. Am. Chem. Soc.*, **74**, 3630 (1951).

(XVIII), 2α-cyanohydrocortisone (XIX) and 2α-cyanocortisone (XX).

16ξ-Cyanotestosterone (XXIII) was obtained from 16ξ-cyano-5-androstene-3,17-dione 3-ethylene ketal (XXII) *via* lithium borohydride reduction[25] followed by acid-catalyzed cleavage of the 3-ethylene ketal group. Finally, lithium borohydride reduction of *16ξ-cyanoestrone 3-methyl ether* (XXIV) afforded *16ξ-cyanoestradiol 3-methyl ether* (XXV).



The α-cyano keto steroids prepared in the course of this study have certain characteristics in common. Several of these compounds were shown to be soluble in base and recoverable upon acidification. It is reasonable to expect that all the α-cyano keto steroids reported here have this property. On the basis of ultraviolet and infrared spectroscopy, these compounds are not enolized in neutral solution,[23] but as expected from their base solubility they are completely enolized in alkaline solution as evidenced by the appearance of a new ultraviolet maximum at around 330 mμ. It is interesting to note that, in the one instance tried, treatment of a 2α-cyano-Δ⁴-3-ketone (XIX) with acetic anhydride in pyridine afforded the enol acetate XXI, which on preferential hydrolysis with base gave the 21-acetate of XIX.

We assign the α-configuration to the 2-cyano derivatives for the following reasons. (1) The products are most likely in the more stable configuration, since the transformation of the hydroxymethylene derivative to the cyano derivative involves heating in the presence of pyridine, a procedure which should be equilibrating. Furthermore, the deblocking procedures afford a second exposure to equilibrating conditions. The more stable configuration of Δ⁴-3-ketones having methyl[10] and halogen[11c,28a] substituents at C-2 is alpha. (2) The difference in molecular rotation between the 2-cyano compounds and the respective parent compounds is in the range of +15 to +81 (see Table I). These values are in general agreement with the effect on molecular rotation caused by substitution of halogen,[29] hydroxyl,[30] acetoxy,[30] and methyl[31] groups at the 2α-position. In this respect it may be noted that at C-6 a cyano group has an effect on the molecular rotation similar to that caused by the above-mentioned groups.[5]

It is of interest to note that introduction of the cyano group consistently results in a hypsochromic shift of the 3-carbonyl band in the infrared (see Table I). An analogous shift is observed on intro-

(25) Metal hydride reduction of C-16 substituted 17-keto steroids has been reported by several workers to afford the corresponding 17β-hydroxy derivatives.[26] However, in a few instances mixtures of the 17-epimeric alcohols have been obtained.[27]

(26) B. Ellis, D. Patel, and V. Petrow, *J. Chem. Soc.*, 800 (1958); J. Fajkoš and F. Šorm, *Coll. Czech. Chem. Comm.*, **24**, 766 (1959); J. Fajkoš, *J. Chem. Soc.*, 3966 (1959).

(27) C. W. Shoppe, R. H. Jenkins, and G. H. R. Summers, *J. Chem. Soc.* 3048 (1958); G. P. Mueller, W. F. Johns, D. L. Cook, and R. A. Edgren, *J. Am. Chem. Soc.*, **80**, 1769 (1958).

(28) (a) E. J. Corey, *ibid.*, **76**, 175 (1954); (b) R. N. Jones, D. A. Ramsay, F. Herling, and K. Dobriner, *ibid.*, **74**, 2828 (1952).

(29) B. Ellis and V. Petrow, *J. Chem. Soc.*, 1179 (1956).

(30) G. Rosenkranz, O. Mancera, and F. Sondheimer, *J. Am. Chem. Soc.*, **77**, 145 (1955).

(31) H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **21**, 1333 (1956).

duction of 2α-halo substituents in a Δ^4-3-ketone system.[32] However, such a shift is not observed with 2α-methyl-Δ^4-3-ketones.[33] The shift caused by 2α-halogen introduction has been attributed to electrostatic repulsion between the negatively charged halogen and the carbonyl oxygen atoms.[28] A similar repulsion is conceivable between the cyano nitrogen and the carbonyl oxygen. The presence of the 2-cyano group has little effect on the position of the Δ^4-3-ketone chromophore in the ultraviolet. 2α-Halogen substitution also causes little shifting of this chromophore, but 2β-bromo or chloro substitution has a bathochromic effect.[29]

It is most probable that the C-16 cyano derivatives are also in the more stable configuration. However, since it is uncertain which configuration is the more stable at this position,[26,27] we are unable to make a definite assignment.

Experimental

General.—Melting points were taken on a Kofler micro hot stage and are corrected. Ultraviolet spectra were determined in methanol on a Cary recording spectrophotometer. Aliquots were diluted 1:10 with 0.1 *N* aqueous hydrochloric acid for the acid spectrum and 1:10 with 0.1 *N* aqueous sodium hydroxide for the base spectrum. Infrared spectra were determined in KBr disks on a Perkin-Elmer spectrophotometer (Model 21). Polarimetric data were obtained in chloroform solution unless stated otherwise. Solutions were dried over magnesium sulfate and evaporations were carried out *in vacuo*. An ethanolic solution of ferric chloride was used for the enol test. The sodium hydride–oil dispersion (50%) was obtained from Metal Hydrides Inc., Beverly, Massachusetts. Duolite A-4 is the trademark of the Chemical Process Co., Redwood City, California, for a weakly basic anion exchange resin. Nitrogen analysis on the cyano steroids was carried out by the Kjeldahl method, since the Dumas method gave erroneous and unrepeatable results. Water analyses were carried out when possible by the Karl Fischer method.

2α-Cyanotestosterone Trifluoroacetate (2α-Cyano-17β-trifluoroacetyl-4-androsten-3-one, III).—A solution of 1.28 g. (4.05 mmoles) of 2-hydroxymethylene-17β-hydroxy-4-androsten-3-one (I)[14] and 1.82 g. (8.1 mmoles) of O,N-bis-(trifluoroacetyl)hydroxylamine (II)[13] in 50 cc. of benzene and 2.42 cc. of pyridine was allowed to reflux with stirring for 2 hr. The cooled solution was washed with two 10-cc. portions of water, and the benzene phase was dried and evaporated. The residue was triturated with ether to afford 1.16 g. (70%) of a crystalline solid with m.p. 212–216°. Recrystallization from methylene chloride–ether gave a sample with m.p. 212–217°; $[\alpha]^{25}D$ +83.3° (*c* 0.91); λ_{max} 4.43 μ (w), 5.61 μ (s), 5.91 μ (s), 6.15 μ (w); λ_{max} 249 mμ (ε 14,720) in acid, 242 mμ (ε 16,400) in methanol, 330 mμ (ε 6250) in base.

Anal. Calcd. for $C_{22}H_{26}O_3F_3N$: C, 64.50; H, 6.40; F, 13.91; N, 3.42. Found: C, 64.85; H, 6.75; F, 14.20; N, 3.24.

The conversion of 2-hydroxymethylene-17β-hydroxy-4-androsten-3-one (I) to the 2-cyano derivative III could also be effected by stirring the reactants at room temperature for 24 hr. After the usual work-up compound III was isolated in 57% yield.

2-Hydroxymethyleneprogesterone 20-Ethylene Ketal (VIII).—A mixture of progesterone 20-ethylene ketal[18] (IV, 7.16 g., 20 mmoles), 3.4 g. of sodium hydride–oil dispersion, 6 cc. of ethyl formate, and 130 cc. of dry benzene was stirred under nitrogen. The reaction was started by the addition of a few drops of absolute ethanol and stirring was continued for 18 hr. Benzene (150 cc.) was added to the dark brown suspension and then a few drops of ethanol to destroy excess sodium hydride. The mixture was extracted three times with water and then with several portions of cold 1% aqueous potassium hydroxide solution until the extracts no longer gave a positive enol test. The combined extracts were neutralized through the addition of 30% aqueous sodium dihydrogen phosphate solution, and the mixture was extracted with several portions of chloroform. The combined chloroform solutions were washed with a little water, dried, and evaporated. The residue was crystallized with ether to afford 2.8 g. (36%) of a yellow solid with m.p. 145–152°. A sample of this compound obtained in a similar experiment was recrystallized twice from ether; m.p. 160–164°; $[\alpha]^{25}D$ +42.4°, (*c* 1.03); λ_{max} 6.06 μ (s) broad band, 6.32 μ (m); λ_{max} 252 mμ (ε 14,900) and 305 mμ (ε 4050) in acid, 249 mμ (ε 13,550) and 305 mμ (ε 5030) in methanol, 245 mμ (ε 15,670), and 356 mμ (ε 12,220) in base.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.56; H, 8.98.

Deoxycorticosterone 20-Ethylene Ketal (20-Ethylenedioxy-21-hydroxy-4-pregnen-3-one, V).—Deoxycorticosterone acetate 20-ethylene ketal[34] (12.4 g., 29.8 mmoles) was deacetylated in 350 cc. of methanol and 25 cc. of 1 *N* methanolic sodium methoxide solution under nitrogen at room temperature for 45 min. After neutralization with 1.5 cc. of glacial acetic acid, the mixture was evaporated and the residue distributed between chloroform and water. The chloroform phase was dried and evaporated to afford a crystalline residue which was recrystallized from ether–hexane; 10.08 g. (90%), m.p. 156–158°. A sample recrystallized twice from ether showed m.p. 163–165°; $[\alpha]^{25}D$ +100° (*c* 1.30); λ_{max} 6.02 μ (s); λ_{max} 242 mμ (ε 16,840).

Anal. Calcd. for $C_{23}H_{34}O_4 \cdot {}^1/_4H_2O$: C, 72.88; H, 9.18; H_2O, 1.19. Found: C, 72.99; H, 9.22; H_2O, 1.26.

2-Hydroxymethylenedeoxycorticosterone 20-Ethylene Ketal (20-Ethylenedioxy-21-hydroxy-2-hydroxymethylene-4-pregnen-3-one, IX).—A mixture of 1.87 g. (5 mmoles) of deoxycorticosterone 20-ethylene ketal (V), 2 cc. of ethyl formate, 1 g. of sodium hydride–oil suspension, and 100 cc. of benzene was stirred under nitrogen for 16 hr. Reaction was started by the addition of a few drops of ethanol. The mixture was worked up by extraction with water and neutralization with sodium dihydrogen phosphate as described for the preparation of IX above. There was obtained a crystalline solid which was recrystallized from methylene chloride–ether to afford 1.27 g. (60%) of a light yellow product with m.p. 184–190° The analytical sample was recrystallized from a large volume of ether; m.p. 191–192°; positive enol test; $[\alpha]^{25}D$ + 41.2° (*c*, 1.12); λ_{max} 6.07 μ (s) broad band, 6.36 μ (m); λ_{max} 252 mμ (ε 11,880) and 307 mμ (ε 3,625) in acid, 252 mμ (ε 11,880) and 306 mμ (ε 5,230) in methanol, 244 mμ (ε 14,500) and 357 mμ (ε 11,070) in base.

Anal. Calcd. for $C_{24}H_{34}O_5 \cdot {}^1/_4H_2O$: C, 70.82; H, 8.54. Found: C, 70.74; H, 8.67.

2-Hydroxymethylenehydrocortisone 20-Ethylene Ketal (20-Ethylenedioxy-2-hydroxymethylene-11β,17α,21-trihydroxy-4-pregnen-3-one, X).—Sodium (276 mg., 12 mg.-atoms) was dissolved in 50 cc. of absolute methanol and the solvent was removed under reduced pressure in a 100° bath. To the residual sodium methoxide was added 25 cc. of dry benzene, 18 cc. of purified ethyl formate, and 1.2 g. (2.95 mmoles) of hydrocortisone 20-ethylene ketal (20-ethylenedioxy-11β,17α,21-trihydroxy-4-pregnen-3-one, VI).[11a] The mixture was stirred at room temperature under nitrogen for

(32) M. Fieser, M. A. Romero, and L. F. Fieser, *J. Am. Chem. Soc.*, **77**, 3305 (1955); E. G. Cummins and J. E. Page, *J. Chem. Soc.*, 3847 (1957).

(33) S. Bernstein, M. Heller, R. Littell, S. M. Stolar, R. H. Lenhard, W. S. Allen, and I. Ringler, [*J. Am. Chem. Soc.*, **81**, 1696 (1959)] have reported λ_{max}^{KBr} 6.02 μ for a 2α-methyl-Δ^4-3-keto steroid.

(34) F. Sondheimer and Y. Klibansky, *Tetrahedron*, **5**, 15 (1959).

18 hr. Chloroform and cold 30% aqueous sodium dihydrogen phosphate solution were added and the layers were separated. The aqueous phase was extracted several times with chloroform, and the combined extracts were washed with water, dried, and evaporated. The residue was dissolved in methylene chloride, and the solution was extracted with portions of cold 1% potassium hydroxide solution until these extracts no longer gave a positive ferric chloride test. The combined extracts were neutralized with sodium dihydrogen phosphate solution, and the mixture was extracted with methylene chloride. These methylene chloride extracts were combined, washed with a little water, dried, and evaporated to afford 830 mg. of yellow glass. Crystallization from hot ethyl acetate gave 462 mg. (37%) with m.p. 224–231°. A sample was recrystallized several times from this solvent; m.p. 233–236°; $[\alpha]^{25}D$ +47.1 (*c* 0.66); λ_{max} 6.06 μ (s), 6.21 μ (m) shoulder; λ_{max} 252 mμ (ε 13,600) and 307 mμ (ε 2,810) in acid, 250 mμ (ε 12,200) and 308 mμ (ε 4,460) in methanol, 247 mμ (ε 13,802) and 356 mμ (ε 11,400) in base.

Anal. Calcd. for $C_{24}H_{34}O_7 \cdot {}^1/_4H_2O$: C, 65.66; H, 8.55; H_2O, 0.97. Found: C, 65.88; H, 8.15; H_2O, 1.19.

2-Hydroxymethylene-17α,20:20,21-bismethylenedioxypregnene-3,11-dione (XI).[7]—A mixture of 4.02 g. (10 mmoles) of 17α,20:20,21-bismethylenedioxy-4-pregnene-3,11-dione (VII),[19] 2.0 g. of sodium hydride–oil suspension, 4 cc. of ethyl formate and 200 cc. of dry benzene was stirred under nitrogen for 16 hr. and was then worked up as described for the preparation of VIII. There was obtained a crude residue which was crystallized from methylene chloride–ether to afford a light yellow solid, 3.46 g. (81%), m.p. 205–211°. For analysis, material obtained in a similar experiment was recrystallized from the same solvent mixture; m.p. 206–209°; $[\alpha]^{25}D$ +9.2° (*c*, 0.875); λ_{max} 5.89 μ (s), 6.06 μ (s), 6.29 μ (m); λ_{max} 248 mμ (ε 10,980) and 305 mμ (ε 3,830) in acid, 248 mμ (ε 9,920) and 305 mμ (ε 4,950) in methanol, 243 mμ (ε 12,660) and 362 mμ (ε 12,000) in base. Certain of these constants are not in good agreement with those reported in the literature,[7] which are as follows: m.p. 244–250°, $[\alpha]D$ +40°.

Anal. Calcd. for $C_{24}H_{30}O_7 \cdot {}^1/_4H_2O$: C, 66.26; H, 7.07. Found: C, 65.98; H, 7.07.

3-Ethylenedioxy-16-hydroxymethylene-5-androsten-17-one (XIII).—To a solution of 1.12 g. (3.4 mmoles) of 3-ethylenedioxy-5-androsten-17-one (XII)[21] in 70 cc. of anhydrous benzene was added 1 cc. of freshly distilled ethyl formate and 0.6 g. of a sodium hydride–oil suspension. The reaction was started by the addition of a few drops of dry ethanol, and the mixture was stirred under nitrogen for 20 hr. The dark brown suspension was treated with a little methanol to destroy excess sodium hydride and then with 25 cc. of water. The layers were separated and the benzene phase was washed with three portions of water. The combined water extracts were washed once with ether and were then neutralized by the addition of 30% aqueous sodium dihydrogen phosphate solution. The mixture was extracted with several portions of chloroform, and the combined extracts were washed with water, dried, and evaporated. The dry residue was crystallized from ether and recrystallized from methylene chloride–ether to afford 711 mg. of a white solid melting at 203–206°; positive enol test; $[\alpha]^{25}D$ +26.8° (*c* 2.01); λ_{max} 5.92 μ (s), 6.10 μ (m) [no absorption at 5.77 μ (17-one region)]; λ_{max} 265 mμ (ε 7430) in acid, 265 mμ (ε 8,920) and 305 mμ (ε 4530) in methanol, 304 mμ (ε 23,680) in base.

Anal. Calcd. for $C_{22}H_{30}O_4 \cdot {}^1/_4 H_2O$: C, 72.79; H, 8.47. Found: C, 73.03; H, 8.62.

2α-Cyanotestosterone (2α-Cyano-17β-hydroxy-4-androsten-3-one, XVI).—A suspension of 124 mg. (0.3 mmole) of III in 5 cc. of methanol containing 0.6 cc. of 10% aqueous potassium carbonate solution was stirred under nitrogen for 3 hr. Most of the original solid went into solution during this period and another solid precipitated. After neutralization with a few drops of acetic acid, the mixture was evaporated. The residue was distributed between water and methylene chloride, and the organic phase was washed with a little water and was dried and evaporated. The yellow residue was decolorized with activated charcoal in ether and was then crystallized and recrystallized from ether–hexane; 61 mg. (64%), m.p. 155–156°; $[\alpha]^{25}D$ +119° (*c* 0.54); λ_{max} 2.82 μ (m), 4.43 μ (w), 5.91 μ (s) broad peak, 6.16 μ (m); λ_{max} 248 mμ (ε 17,970) in acid, 242 mμ (ε 15,600) in methanol 332 mμ (ε 6710) in base.

Anal. Calcd. for $C_{20}H_{27}O_2N$: C, 76.64; H, 8.63; N, 4.47. Found: C, 76.27; H, 8.83; N, 4.22.

2α-Cyano-20-ethylenedioxy-4-pregnen-3-one.—The reaction of 386 mg. (1 mmole) of 20-ethylenedioxy-2-hydroxymethylene-4-pregnen-3-one (VIII) with 225 mg. (1 mmole) of II in 10 cc. of benzene and 0.3 cc. of pyridine was carried out as described for III. The crystalline residue was collected and washed with ether; 290 mg. (76%), m.p. 258–260°. A sample recrystallized from methylene chloride–ether showed m.p. 261–263°; $[\alpha]^{25}D$ +115° (*c* 0.97); λ_{max} 4.43 μ (w), 5.89 μ (s), 6.14 μ (m); λ_{max} 249 mμ (ε 17,200) in acid, 242 mμ (ε 17,270) in methanol, 330 mμ (ε 6440) in base.

Anal. Calcd. for $C_{24}H_{33}O_3N$: C, 75.16; H, 8.67; N, 3.65. Found: C, 74.89; H, 8.76; N, 3.70.

2α-Cyanoprogesterone (2α-Cyano-4-pregnene-3,20-dione, XVII).—Crude 2α-cyano-20-ethylenedioxy-4-pregnen-3-one was prepared from 700 mg. (1.83 mmoles) of VIII as described in the preceding experiment. The crystalline product was dissolved partially without drying in 10 cc. of water, 10 cc. of acetic acid, and 3 cc. of ethanol. The mixture was heated on the steam bath for 1 hr. and was then evaporated. The residue was dissolved in methylene chloride and water, and the organic phase was dried and evaporated. The residue was crystallized with ether and recrystallized (with activated charcoal) from methylene chloride–ether, 331 mg. (54% over-all from VIII), m.p. 191–195°. For analysis, the material was recrystallized with activated charcoal from a large volume of ether to give material with m.p. 193–195° (some earlier sintering); $[\alpha]^{25}D$ +212° (*c* 0.95); λ_{max} 4.44 μ (s); 5.89–5.94 μ (s), 6.14 μ (m), no absorption at 9.5 μ (ketal region); λ_{max} 250 mμ (ε 16,300) in acid, 242 mμ (ε 16,300) in methanol, 330 mμ (ε 6450) in base.

Anal. Calcd. for $C_{22}H_{29}O_2 \cdot {}^1/_4H_2O$: C, 76.81, H, 8.63; N, 4.07. Found: C, 77.20; H, 8.74; N, 3.64.

2α-Cyanodeoxycorticosterone (2α-Cyano-21-hydroxy-4-pregnene-3,20-dione, XVIII).—The reaction of 2-hydroxymethylenedeoxycorticosterone 20-ethylene ketal (IX) (402 mg., 1 mmole) with 450 mg. (2 mmoles) of II and 0.7 cc. of pyridine in 15 cc. of benzene was carried out as described for the preparation of III. The crude product which was isolated as a glass (470 mg.) and could be obtained crystalline from methanol, was not further characterized. It was dissolved with warming in 20 cc. of methanol, aqueous potassium carbonate solution (10%, 1 cc.) was added, and the mixture was stirred under nitrogen for 1 hr. There was then added 20 cc. of methanol and 1 cc. of 8% aqueous sulfuric acid, and the mixture was heated under reflux for 1 hr. The acid was neutralized by stirring with Duolite A-4 anion exchange resin (OH^- form), and the solution, obtained after filtration and washing of the resin with methanol, was evaporated. The residue was dissolved in ethyl acetate and water and the organic phase was separated, washed with a little water, dried, and evaporated. The residue was crystallized from methylene chloride–ether, 184 mg. (52%), m.p. 174–176°. The analytical sample was recrystallized with activated charcoal from a large volume of ether; m.p. 183–184°; $[\alpha]^{25}D$ +175° (*c* 0.84, in EtOH), +208° (*c* 0.41); λ_{max} 2.86 μ (m), 4.43 μ (w), 5.85–5.95 μ (s), 6.16 μ (m); λ_{max} 248 mμ (ε 15,200) in acid, 242 mμ (ε 15,280) in methanol, 334 mμ (ε 3325) in base.

Anal. Calcd. for $C_{22}H_{29}O_3N \cdot {}^1/_2H_2O$: C, 72.49; H, 8.07; N, 3.85; H_2O, 2.47. Found: C, 72.17; H, 8.39; N, 3.85; H_2O, 2.46.

2α-Cyanohydrocortisone 20-Ethylene Ketal 21-Trifluoroacetate (2α-Cyano-20-ethylenedioxy-11β,17α-dihydroxy-21-trifluoroacetoxy-4-pregnen-3-one, XXVI).—The reaction of

250 mg. (0.5 mmole) of 2-hydroxymethylenehydrocortisone 20-ethylene ketal (X) with 225 mg. (1 mmole) of II and 0.3 cc. of pyridine in 10 cc. of benzene was carried out as described under the preparation of III. The product was crystallized from ether–hexane to afford 87 mg. (30%) with m.p. 197–207°. A sample recrystallized from ether with activated charcoal showed m.p. 225–227°; $[\alpha]^{25}D$ +92.2° (*c* 0.93); λ_{max} 2.82 μ (m), 4.44 μ (w), 5.57 μ (s), 5.91 μ (s) broad peak, 6.15 μ (m); λ_{max} 248 mμ (ϵ 16,100) in acid, 242 mμ (ϵ 15,300) in methanol, 331 mμ (ϵ 6320) in base.

Anal. Calcd. for $C_{26}H_{32}O_7F_3N$: C, 59.19; H, 6.11; N, 2.66; F, 10.82. Found: C, 59.23; H, 6.23; N, 2.35; F, 10.57.

Hydrocortisone 20-Ethylene Ketal 21-Trifluoroacetate. Reaction of Hydrocortisone 20-Ethylene Ketal (VI) with II.—A solution of 1.6 g. (4 mmoles) of VI, 2.7 g. (12 mmoles) of II and 3.6 cc. of pyridine in 80 cc. of dry benzene was stirred under reflux for 2 hr. The cooled solution was washed several times with water, and the benzene phase was dried and evaporated. The residue was triturated with ether to yield 1.3 g. (66%) of solid with m.p. 180–188°. Recrystallization from ether–methylene chloride gave 1.1 g. with m.p. 186–189° (hydrocortisone 20-ethylene ketal 21-trifluoroacetate). The analytical sample obtained in another experiment had m.p. 190–192°; $[\alpha]^{25}D$ +87° (*c* 0.84); λ_{max} 2.90 μ (m), 5.60 μ (s), 6.02 μ (s), λ_{max} 242 mμ (ϵ 18,100). The same product was formed when the reactants were kept at room temperature for 22 hr. or when 1 molar equivalent of II was allowed to react with 1 equivalent of the steroid VI at the reflux temperature.

Anal. Calcd. for $C_{25}H_{33}O_7F_3$: C, 59.75; H, 6.62; F, 11.35. Found: C, 59.95; H, 6.77; F, 11.18.

2α-Cyanohydrocortisone (2α-Cyano-11β,17α,21-trihydroxy-4-pregnene-3,20-dione, XIX).—The blocked compound XXVI (200 mg., 0.38 mmole) in 7 cc. of methanol and 0.7 cc. of a 10% aqueous potassium carbonate solution was stirred under nitrogen for 1 hr. There was then added 18 cc. of methanol and 1 cc. of an 8% aqueous sulfuric acid solution, and the mixture was heated under reflux with stirring for 1 hr. After neutralization with Duolite A-4 anion exchange resin (OH^- form), the filtrate and washings were evaporated. The residue was dissolved in a mixture of ethyl acetate and water, and the water layer was washed with several portions of ethyl acetate. The combined organic layers were washed with a little water, dried, and evaporated to afford a residue which was crystallized from a small amount of hot ethyl acetate; 72 mg. (49%), m.p. 220–222°. A sample recrystallized twice from ethyl acetate with activated charcoal showed m.p. 235–237°; $[\alpha]^{25}D$ +172° (*c* 0.262 in methanol); λ_{max} 2.90 μ (s) broad peak, 4.45 μ (w), 5.84 μ (m), 5.95 μ (s) 6.17 μ (m); λ_{max} 249 mμ (ϵ 14,900) in acid, 243 mμ (ϵ 14,330) in methanol, 330 mμ (ϵ 5035) in base.

Anal. Calcd. for $C_{22}H_{29}O_5N \cdot {}^1/_4H_2O$: C, 67.40; H, 7.58; N, 3.57; H_2O, 1.15. Found: C, 67.45, H, 7.62; N, 3.67; H_2O, 2.37.

3,21-Diacetoxy-2-cyano-11β,17α-dihydroxy-2,4-pregnadien-20-one (XXI).—To a chilled solution of 329 mg. (0.88 mmole) of 2α-cyanohydrocortisone (XIX) in 5 cc. of pyridine was added 1 cc. of acetic anhydride. The mixture was allowed to come to room temperature, stand for 16 hr., and was added dropwise to 100 cc. of ice water. The solid which formed was collected, washed with water, dissolved in chloroform, and the chloroform solution was washed with water, dried, and evaporated. The residue was triturated with ether to afford 354 mg. (85%) of XXI with m.p. 215–224°. The analytical sample waas recrystallized three times from methylene chloride–ether; m.p. 218–228°; $[\alpha]^{25}D$ +149° (*c* 0.53); λ_{max} 2.80 μ (m), 4.54 μ (m), 5.65 μ (s) shoulder, 5.70 μ (s), 5.76 μ (s), 6.05 μ (w), 6.27 μ (m), 8.13 μ (s), 8.44 μ (s) broad peak; λ_{max} 303 mμ (ϵ 10,800) in acid, 300 mμ (ϵ 10,430) in methanol, 218 mμ (ϵ 21,200) and 333 mμ (ϵ 6600) in base.

Anal. Calcd. for $C_{26}H_{33}O_7N$: C, 66.22; H, 7.05; N, 2.97. Found: C, 66.14; H, 7.26; N, 2.92.

21-Acetoxy-2α-cyano-11β,17α-dihydroxy-4-pregnene-3,20-dione.—A mixture of 125 mg. (0.27 mmole) of XXI, 8 cc. of methanol, and 0.05 cc. of 10% aqueous sodium hydroxide solution was stirred at room temperature for 5 min. and was then neutralized with acetic acid. Solvent was removed *in vacuo*, and the residue was partitioned between chloroform–water. The organic phase was washed with water and saline solution, and was dried and evaporated to residue which on trituration with ether yielded 88 mg. (77%) of white crystals, m.p. 220–228°. The analytical sample was recrystallized twice from methylene chloride–ether; m.p. 233–238°; $[\alpha]^{25}D$ +173° (*c*, 0.53); λ_{max} 2.90 μ (m), 4.44 μ, (w), 5.71 μ (s), 5.80 μ (s) shoulder, 6.02 μ (s), 6.18 μ (m), 8.13 μ (s) broad peak; λ_{max} 249 mμ (ϵ 15,700) in acid, 242 mμ (ϵ 15,400) in methanol, 215 mμ (ϵ 14,600) and 333 mμ (ϵ 6200) in base.

Anal. Calcd. for $C_{24}H_{31}O_6N$: C, 67.11; H, 7.28; N, 3.26. Found: C, 66.72; H, 7.63; N, 2.39.

2α-Cyano-17α,20:20,21-bismethylenedioxy-4-pregnene-3,11-dione.[7]—A mixture of 430 mg. (1 mmole) of 2-hydroxmethylene - 17α,20:20,21 - bismethylenedioxycortisone (XI) and 225 mg. (1 mmole) of II was heated in 10 cc. of benzene and 0.3 cc. of pyridine for 1 hr. The mixture which had become quite dark during this period was diluted with 10 cc. of benzene and was washed with several small portions of water. Evaporation of the dried benzene phase left a dark gum which was purified by solution in acetone–hexane and decantation from a black oil. Treatment of the supernatant with activated charcoal and partial evaporation with the addition of hexane gave a white crystalline product, 107 mg. (25%), m.p. 223–228°. Several recrystallizations from ether–methylene chloride afforded an analytical sample with m.p. 232–233°; $[\alpha]^{25}D$ +91.2° (*c* 0.428); λ_{max} 4.42 μ (w), 5.80 μ (s), 5.94 μ (s), 6.15 μ (m); λ_{max} 243 mμ (ϵ 15,900) in acid, 238 mμ (ϵ 14,350) in methanol, 332 mμ (ϵ 6200) in base [lit.,[7] m.p. 235–239°; $[\alpha]D$ +94°; λ_{max}^{EtOH} 238 mμ (log ϵ 4.05)].

Anal. Calcd. for $C_{24}H_{29}O_6N$: C, 67.43; H, 6.84; N, 3.24. Found: C, 67.21; H, 7.16; N, 2.84.

2α-Cyanocortisone (2α-Cyano-17α,21-dihydroxy-4-pregnene-3,11,20-trione, XX).—2α-Cyano-17α,20:20,21-bismethylenedioxy-4-pregnene-3,11-dione (120 mg., 0.28 mmole) was heated with 5 cc. of 60% formic acid on the steam bath for 30 min. The solution was evaporated and water was added to the residue. The suspension was extracted with several portions of ethyl acetate and the combined extracts were dried and evaporated. The residue was crystallized from ethyl acetate; 53 mg. (50%), m.p. 240–243°. Two recrystallizations from that solvent with activated charcoal gave a sample with m.p. 246–247°; $[\alpha]^{25}D$ +194° (*c* 0.638 in dioxane); λ_{max} 2.86 μ (m), 4.45 μ (w), 5.90 μ (s) broad peak, 6.15 μ (m); λ_{max} 242 mμ (ϵ 18,500) in acid, 235 mμ (ϵ 18,500) in methanol, 331 mμ (ϵ 4930) in base.

Anal. Calcd. for $C_{22}H_{27}N \cdot {}^1/_2H_2O$: C, 66.98; H, 7.16; N, 3.56. Found: C, 67.20; H, 7.40; N, 3.46.

16ξ-Cyano-3-ethylenedioxy-5-androsten-17-one (XXII).—To a solution of 358 mg. (1 mmole) of 3-ethylenedioxy-16-hydroxymethylene-5-androsten-17-one (XIII) in 10 cc. of dry benzene was added 225 mg. (1 mmole) of II and 0.3 cc. of dry pyridine. After 2 hr. reflux the mixture was worked up as described in the preparation of III. The crystalline residue was recrystallized from ether; 248 mg. (69%), m.p. 236–238°. For analysis, a sample was crystallized once more from methylene chloride–ether, m.p. 240–242°; $[\alpha]^{25}D$ +4.3° (±21°) (*c* 0.234); λ_{max} 4.46 μ (w), 5.68 μ (s); λ_{max} 268 mμ (ϵ 12,980) in base.

Anal. Calcd. for $C_{22}H_{29}O_3N$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.37; H, 8.44; N, 4.21.

16ξ-Cyanotestosterone (16ξ-Cyano-17β-hydroxy-4-androsten-3-one, XXIII).—Solvent (5 cc.) was distilled out of a solution of XXII (204 mg., 0.58 mmole) in 40 cc. of peroxide-free tetrahydrofuran. The solution was cooled to 0° and 150 mg. of lithium borohydride was added. The mixture was stirred at room temperature for 3 hr., and excess

hydride was then destroyed by the addition of about 2 cc. of acetic acid followed by water until gas evolution ceased. The mixture was evaporated in a 50° bath, and the wet residue was distributed between methylene chloride and water. The organic phase was washed with water and saturated saline solution and was dried and evaporated. The residue was dissolved partially in 10 cc. of 50% acetic acid, and the stirred mixture was heated on the steam bath for 30 min. when all of the solid had dissolved. The solution was evaporated and the residue was dissolved in methylene chloride and water. The organic phase was washed with a little water and was dried and evaporated. The residue was crystallized from ethyl acetate; 88 mg. (49%), m.p. 190–192°. One recrystallization from ethyl acetate gave a sample with m.p. 218–219°; $[\alpha]^{25}D$ +88.5° (*c* 0.521); λ_{max} 2.87 μ (m), 4.44 μ (w), 5.96 μ (s) broad band, 6.16 μ (m); λ_{max} 240 mμ (ϵ 16,170) in methanol, 247 mμ (ϵ 15,680) in base.

Anal. Calcd. for $C_{20}H_{27}O_2N$: C, 76.64; H, 8.63; N, 4.43. Found: C, 76.18; H, 8.80; N, 4.44.

16ξ-Cyanoestrone 3-Methyl Ether (XXIV).—The reaction of 1.7 g. (5.45 mmoles) of 16-hydroxymethyleneestrone 3-methyl ether (XV)[22] with 1.22 g. of II in 54 cc. of benzene and 1.63 cc. of pyridine was carried out as described for the preparation of III. The product was crystallized from ether to afford 1.16 g. (69%), m.p. 149–153°. Several recrystallizations from methylene chloride–ether gave material with m.p. 138–148°; $[\alpha]^{25}D$ +189° (*c* 0.99); λ_{max} 4.43 μ (w), 5.68 μ (s), 6.17 μ (m), 6.32 μ (w).

Anal. Calcd. for $C_{20}H_{23}O_2N \cdot {}^1/_4H_2O$: C, 76.53; H, 7.54; N, 4.46. Found: C, 76.64; H, 7.90; N, 4.90.

16ξ-Cyanoestradiol 3-Methyl Ether (XXV).—A solution of 1.56 g. (5.05 mmoles) of XXIV in 150 cc. of tetrahydrofuran was reduced with 360 mg. of lithium borohydride for 3 hr. at room temperature. Acetic acid was added carefully and then water until the solution was homogeneous. Removal of most of the solvents under reduced pressure left a residue which was triturated with water and filtered. The precipitate was washed with water and was dissolved in methylene chloride. The solution was washed with a little water and was dried and evaporated to afford 1.5 g. of product which was recrystallized from methylene chloride–ether; 1.17 g. (74%), m.p. 194–200°. For analysis, a sample was recrystallized from ethyl acetate, m.p. 197–200°; $[\alpha]^{25}D$ +54° (*c* 1.39); λ_{max} 2.86 μ (s), 4.47 μ (m), no absorption in the carbonyl region.

Anal. Calcd. for $C_{20}H_{25}O_2N \cdot {}^1/_4H_2O$: C, 76.01; H, 8.14; N, 4.43; H_2O, 1.43. Found: C, 76.08; H, 8.30; N, 4.06; H_2O, 1.10.

Acknowledgment.—The authors wish to thank Mr. W. Fulmor and staff for spectrophotometric and polarimetric data, Mr. L. Brancone and staff for microanalyses and Dr. H. Arlt, Jr., and staff of the Chemical Preparations Laboratory for the large-scale preparation of certain intermediates.

Steroidal Aldosterone Antagonists. VI[1]

LEONARD N. NYSTED AND ROBERT R. BURTNER

Division of Chemical Research, G. D. Searle & Co., Chicago 80, Illinois

Received March 5, 1962

The synthesis of several steroidal 17-spirolactams analogous to physiologically active spirolactones is described.

There are numerous examples of physiologically important compounds which contain a lactam moiety. Our experience with the steroidal spirolactones as aldosterone antagonists[2] suggested the investigation of the corresponding spiro-γ-lactams.[3] The conventional method for converting γ-lactones to γ-lactams by treatment with an appropriate amine was unsuccessful in our hands. Thus, the treatment of 3-methoxy-17α-(2-carboxyethyl)-17β-hydroxy-1,3,5(10)-estratriene lactone[2] with ammonia, methylamine, or aniline under forcing conditions yielded only the corresponding amides. We therefore chose the sequence of reactions shown on the following page.

Smilagenin was degraded to 3β-acetoxy-16-pregnen-20-one by the procedure of Mueller.[4] The reduced product was converted to the oxime which was subjected sequentially to Beckmann rearrangement and saponification to yield 3β-hydroxy-17β-amino-5β-androstane (Ib).[5] Selective monoacetylation and oxidation afforded the 17-nitro compound which condensed smoothly with methyl acrylate in the presence of tetramethylguanidine. It should be noted that when either Triton B or sodium alkoxide was used the yield was only 10%.

The configuration of the Michael adduct is based upon the following:

(1) Oxidation of the 17β-amino group under *acidic* conditions should produce the 17β-nitro derivative. (2) Because of the flatness of the *aci*-nitro anion, approach from the rear by an entering group should be favored. Only one adduct was found. (3) The o.r.d. curves are similar and positive for the 17β-nitro compound (IIb) and the Michael adduct (IIIb). This would not be true had inversion occurred during addition.

Catalytic hydrogenation afforded the spirolactam (IVb) which was saponified and oxidized to the ketone (VIb). Bromination followed by dehydrobromination with the lithium bromide–dimethylformamide method gave the desired 17α-(2-

(1) Paper V, R. C. Tweit, F. B. Colton, N. L. McNiven, and W. Klyne, *J. Org. Chem.*, **27**, 3325 (1962).

(2) J. A. Cella, E. A. Brown, and R. R. Burtner, *ibid.*, **24**, 743 (1959).

(3) The lactams and certain intermediates described herein are the subject of U.S. Patent 3,001,986 issued September 26, 1961, to R. R. Burtner and Leonard Nysted.

(4) G. P. Mueller, *Nature*, **181**, 771 (1958).

(5) German Patent 871,010 (1953); *Chem. Zentr.*, 6938 (1953); J. Schmidt-Thomé, *Ber.*, **88**, 895 (1955).