monohydrate in 45 ml. of xylene was heated under reflux for 4.5 hr. The reaction mixture was poured onto a column of 30 g. of silica gel. The material obtained by elution with 9:1 and 3:1 benzene–ethyl acetate mixtures was dissolved in benzene and placed on 25 g. of alumina. The fractions eluted with 1:1 benzene–petroleum ether and with benzene were combined, evaporated to dryness *in vacuo*, and the residue recrystallized from petroleum ether giving 0.275 g. of *8a*, m.p. 158–161.5°, identical with the material prepared in A above.

6α,16α-Dimethyl-4-pregnen-6β-ol-3,20-dione (6β-Hydroxy-6α,16α-dimethylprogesterone) (*19*).—To a degassed solution of 0.5 g. of 6α,16α-dimethylpregnane-5α,6β-diol-3,20-dione (*16*) in 100 ml. of absolute ethanol was added 4.0 ml. of 0.1 *N* aqueous sodium hydroxide which had also been degassed. The mixture was allowed to stand at room temperature for 3 days and then evaporated *in vacuo* to a small volume. Water was added and the organic material extracted with a mixture of ethyl acetate and ether. The extracts were washed once with water and then with saturated salt solution. Evaporation afforded 0.41 g. of a solid product which was recrystallized from acetone–petroleum ether to give 0.30 g. (63%), m.p. 248–255°. A further recrystallization from acetone–petroleum ether provided the sample for analysis, m.p. 256–260°, $[\alpha]^{24}D$ +77.3°, λ_{max} 239 mμ (13,300), λ_{max}^{KBr} 5.83, 5.93, 6.22, and 11.37 μ.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.92; H, 9.53.

6α,16α-Dimethyl-1,4-pregnadiene-3,20-dione (Δ¹-Dehydro-6α,16α-dimethylprogesterone) (*7c*).—A mixture of 3.0 g. of 6α,16α-dimethylprogesterone (*7b*), 3.0 g. of selenium dioxide, and 3.0 ml. of glacial acetic acid in 300 ml. of *t*-butyl alcohol was heated under reflux for 16 hr. The suspension was then filtered through Celite and the filtrate evaporated to a red oil. The oil was taken up in 250 ml. of ethyl acetate and washed with 5% aqueous sodium bicarbonate solution, water, 10% ammonium polysulfide solution, 10% ammonium hydroxide, and finally with saturated salt solution. Evaporation of the ethyl acetate solution *in vacuo* gave 2.5 g. of a yellow foam which was dissolved in benzene, diluted with petroleum ether and placed on 120 g. of alumina. The material obtained with the first 250 ml. of the 49:1 benzene–ether eluates was recrystallized from acetone–petroleum ether to give 0.334 g. (11%), m.p. 140–143°, $[\alpha]^{26}D$ +71.0°, λ_{max} 245 mμ (15,760), $\lambda_{max}^{CCl_4}$ 5.84, 5.98, 6.12, 6.21, and 11.22 μ.

Anal. Calcd. for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47. Found: C, 80.79; H, 9.30.

6,16α-Dimethyl-1,4,6-pregnatriene-3,20-dione (Δ¹,⁶-Bisdehydro-6,16α-dimethylprogesterone) (*8b*).—Following the same procedure as described in the preparation of *7c*, 2.13 g. of Δ⁶-dehydro-6,16α-dimethylprogesterone (*8a*) was oxidized with 0.65 g. of selenium dioxide. After chromatography and recrystallization from acetone–petroleum ether, 0.626 g. (28%) of the trienedione was obtained as prisms, m.p. 139–141°, $[\alpha]^{30}D$ +65.2°, λ_{max} 228 mμ (13,400), 255 mμ (9060), 305 mμ (11,960), $\lambda_{max}^{CCl_4}$ 5.84, 6.00, 6.17, and 11.21 μ.

Anal. Calcd. for $C_{23}H_{30}O_2$: C, 81.61; H, 8.93. Found: C, 81.78, 81.63; H, 8.81, 8.62.

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Preparation and Reactions of Steroidal α-Aminonitriles

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The 17α-aminonitriles of estrone and dehydroepiandrosterone were prepared by the addition of cyanide to the appropriate ternary imminium salt. The reaction of the nitriles with methyl and ethynyl Grignard reagents was found to lead to the 17-methyl- and 17-ethynyl-17-dimethylamino compounds. Evidence is presented which indicates that the Grignard reagent enters the molecule on the same side as the departing cyano group.

In the continuing search for compounds which may show useful "splits" in their hormonal activities considerable attention has been devoted to steroids modified by the replacement of oxygen by nitrogen. While a sizeable number of 3-[1] and 17-[2] aminoandrostanes are known, relatively few reports of interesting properties have appeared. Since most of the compounds of this class contained a nitrogen fragment attached to a secondary center, the possibility was considered that facile metabolism at this site might account for the apparent lack of hormonal properties. We therefore undertook the preparation of some 17-alkyl-17-dimethylamino steroids incorporating nitrogen at the tertiary carbon atom of a series of compounds whose oxygenated parents are known to be potent hormonal agents.

The versatility of α-aminonitriles as intermediates in the preparation of highly substituted amines has been demonstrated previously.[3] These nitrogen analogs of cyanohydrins are readily obtained from aldehydes and simple ketones by reaction of the carbonyl compound with an amine salt and cyanide ion.[4] Though dehydroepiandrosterone (I) undergoes the cyanohydrin reaction,[5] this

(1) V. Prelog, L. Ruzicka, P. Meister, and P. Wieland, *Helv. Chim. Acta*, **27**, 618 (1944); D. P. Dodgson and R. D. Haworth, *J. Chem. Soc.*, **67**, 1952; J. Joska and F. Sorm, *Chem. Listy*, **49**, 1687 (1955).

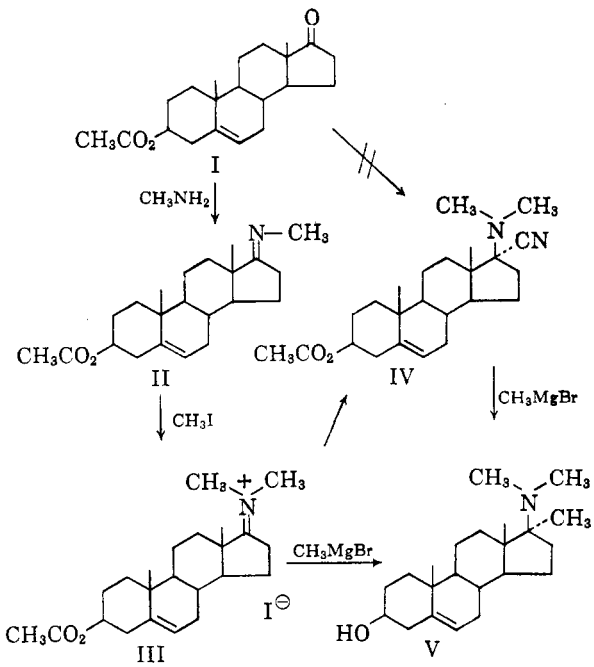
(2) R. E. Marker, *J. Am. Chem. Soc.*, **58**, 480 (1936); P. L. Julian, E. W. Meyer, J. W. Cole, and A. Magnani, U.S. Patent 2,566,336 (1951); J. Schmidt-Thome, *Ber.*, **88**, 895 (1955).

(3) N. J. Leonard and F. Hauck, Jr., *J. Am. Chem. Soc.*, **79**, 5279 (1957); N. J. Leonard and A. S. Hay, *ibid.*, **78**, 1986 (1956); L. H. Goodson and H. Christopher, *ibid.*, **72**, 358 (1950).

(4) V. Migrdichian, "The Chemistry of Organic Cyanogen Compounds," ACS Monograph No. 105, p. 205, N. Y. (1947).

compound failed to form the aminonitrile on treatment with potassium cyanide and dimethylamine hydrochloride.

The failure of this straightforward approach led us to the more circuitous route which has been successfully employed for the preparation of the α-aminonitriles of aromatic ketones.[6]



The imine (II) was obtained by passing a stream of methylamine through a melt of the steroid for six hours. Treatment with methyl iodide converted the crude base to the ternary iminium salt (III), which was then precipitated with ether. (Neither the imines nor their ternary salts need be and in fact were not purified.) The addition of a solution of III in acetonitrile to aqueous potassium cyanide afforded the α-aminonitrile almost immediately as a crystalline precipitate. The assignment of the α-configuration to the nitrile at C-17 rests on the observed stereospecificity of the cyanide addition and the known tendency for the attack of reagents at C-17 to occur from the α-side.[7,8]

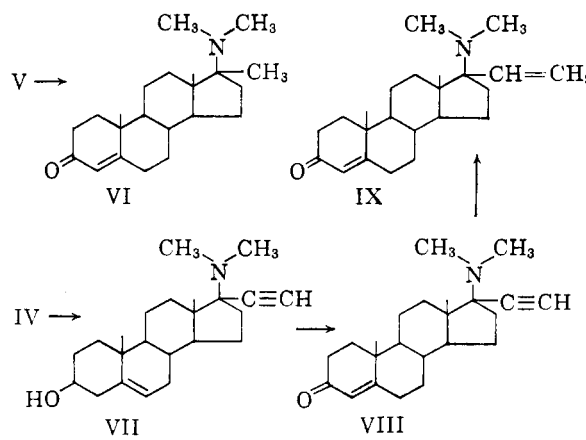
The reaction of IV with an excess of methylmagnesium bromide afforded the amine (V). The reaction of aminonitriles with Grignard reagents to afford the product of a formal replacement of cyanide is a characteristic reaction of this class of compounds,[9] though little is known of the stereochemical course of this transformation.

It has been known for some time that ternary iminium salts in themselves will undergo Grignard addition[10]; the α-aminonitrile is however in most cases a more convenient substrate in that it presents a greater solubility in the common solvents used for that reaction. The C=N system of the ternary iminium salt is co-planar with the D ring of the steroid and is thus isosteric with the carbonyl function of a 17-keto steroid. Since the latter compounds are known to form 17β-hydroxy-17α-alkyl compounds almost exclusively with Grignard reagents,[11] there is little reason to expect the nitrogen analog to behave differently.

The ternary iminium salt (III) reacted smoothly with methylmagnesium bromide to afford a basic product identical to that obtained from the Grignard reaction of the α-aminonitrile (IV). The same steric result was observed in the estrone series (see below). The transformation III→V allows the assignment of the α-configuration to the new methyl group.

Since both the Grignard reagent and the cyanide ion attack C-17 from the same side, it follows that in the course of the Grignard reaction the cyanide ion leaves from the same side as the entering methyl group. Because of the abundance of nitrogen atoms surrounding the reaction site, it seems likely that a magnesium—N complex is involved in this reaction. It is interesting to note that an attempt to effect reaction of the ternary iminium salt with methyl lithium led largely to unchanged starting material.[12]

The α-aminonitrile (IV) was also found to react smoothly with ethinylmagnesium bromide to yield (VII), formulated as shown in view of the above discussion. The 3-alcohols were oxidized in the usual manner to the unsaturated ketones and finally VIII was selectively reduced to the corresponding vinyl compound (IX).



(5) P. DeRuggieri and C. Ferrari, *J. Am. Chem. Soc.*, **81**, 5725 (1959).

(6) C. R. Hauser and D. Lednicer, *J. Org. Chem.*, **24**, 46 (1959).

(7) See L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., N. Y., (1959).

(8) In contrast to this result, cyanhydrin formation at C-17 is known[5] to afford both isomers. The latter reaction is however carried out under conditions where equilibration is possible, whereas the aminonitrile precipitates from the reaction medium.

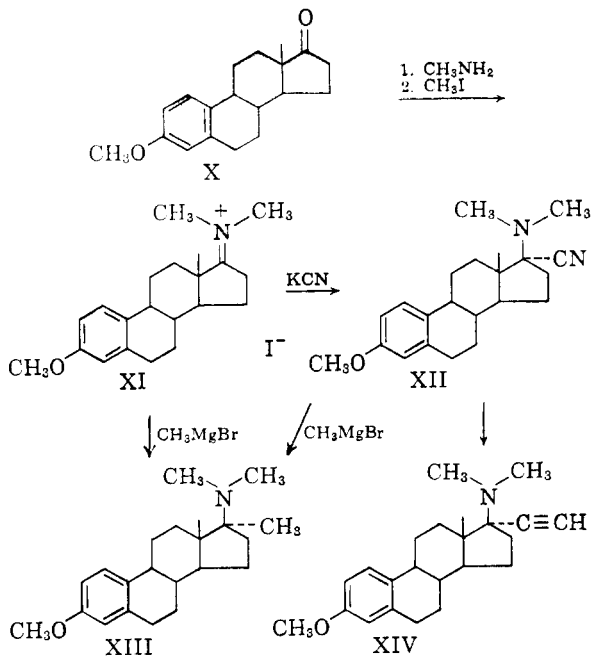
(9) T. S. Stevens and T. Thomsen, *J. Chem. Soc.*, 2607 (1932).

(10) M. Sommelet, *Compt. rend.*, **183**, 302 (1926).

(11) L. Ruzicka, M. W. Goldberg, and H. R. Rosenberg, *Helv., Chim. Acta*, **18**, 1487 (1935).

(12) From XI, isolated as estrone methyl ether (X). This result cast some doubt as to the applicability of these findings to other series since the diaryl α-aminonitriles undergo ready displacement reactions with carbanions.[4]

A similar sequence of reactions was carried out using estrone 3-methyl ether as the starting material:



The findings in this series were substantially the same as those in the androstene series. It will be noted that the observations regarding the steric course of the Grignard reaction with α-aminonitriles were fully substantiated in this series, XI and XII both giving XIII.

Compound XIII, exhibits estrogenic activity. Neither VI nor VII exhibited androgenic or anabolic properties.

Experimental[13]

17β-*N*,*N*-Dimethylamino-17-cyanoandrost-5-en-3-ol Acetate (IV). — A stream of methylamine was bubbled through a melt of 10.0 g. of dehydroepiandrosterone acetate in a bath at 195–200° for 6 hr. The melt was allowed to cool under a blanket of nitrogen, taken up in methylene chloride and washed with water. The solid which remained when the solvent was removed possessed infrared absorption bands at 1723 and 1675 cm.$^{-1}$.

A solution of the methylimine in 50 ml. of methylene chloride was treated with 60 ml. of methyl iodide, and allowed to stand for 3.5 hr. The semisolid ternary iminium salt which was obtained when the solution was poured into ether was quickly dissolved in 100 ml. of acetonitrile. The solution was then added to 6 g. of potassium cyanide in 60 ml. of water with good stirring. At the end of 40 min. the suspension was diluted with 800 ml. of water and the product collected on a filter. There was obtained 5.36 g. of IV m.p. 146–152°.

A small sample was recrystallized twice from hexane (cooling to −20°) to yield the analytical sample, m.p. 145.5–150°; λ_{max} 2780, 2210, 1732–1735, 1670 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{36}N_2O_2$: C, 74.96; H, 9.44; N, 7.29. Found: C, 74.84; H, 9.44; N, 7.37.

(13) The authors are indebted to J. L. Johnson, W. A. Struck, and R. W. Rinehart and associates for the analyses, ultraviolet and infrared spectra. All melting points are uncorrected and were determined on a Thomas-Hoover capillary melting point apparatus.

17β-*N*,*N*-Dimethylamino-17-methylandrost-5-en-3-ol. (A) **From IV.**—A solution of 1.0 g. (0.0026 mole) of aminonitrile in 30 ml. of tetrahydrofuran (THF) was added to 10 ml. of 3 *M* methylmagnesium bromide in ether. After 2 hr. of heating under reflux the excess reagent was destroyed with water. Additional water, as well as ether and methylene chloride, was added to the reaction mixture. The organic layer was washed well with brine, dried by percolation through magnesium sulfate and the solvent removed. The glassy solid which remained was recrystallized from aqueous methanol to give 0.55 g. of fine plates, m.p. 149–152°.

One further crystallization from the same solvent afforded a sample m.p. 149–151.5°; λ_{max}, 3400, 3320–3100, 2750, 1663 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{37}NO \cdot 1/4H_2O$: C, 78.44; H, 11.25; N, 4.17. Found: C, 78.26; H, 11.28; N, 4.25.

(B) **From III.**—A solution of 0.50 g. of the tertiary iminium salt in 30 ml. of THF was added to 7.5 ml. of 3 *M* methylmagnesium bromide. After 3 hr. of heating the excess reagent was decomposed with water and the product worked up as above. The crude product was recrystallized from aqueous methanol to afford 0.20 g. (59%) of the amine m.p. 148–149.5°. The m.p. of this was not depressed on admixture with a sample obtained by route A.

17β-*N*,*N*-Dimethyl-17-methylandrost-4-en-3-one (VI).—About 4 ml. of solvent was removed by distillation from a solution of 1.0 g. of V in 8.5 ml. of cyclohexanone and 50 ml. of toluene. Aluminum isopropoxide (0.55 g.) in 10 ml. of toluene was then added and the solution stirred under reflux for 2 hr. A small amount of water was then added and the solution concentrated *in vacuo*. The residue was washed with ether–methylene chloride and this extract washed with brine followed by 100 ml. of 2.5 *N* hydrochloric acid. The crude product which was obtained when the extract was made alkaline was recrystallized from aqueous methanol to yield 0.17 g. of ketone, m.p. 140–143.5°.

Two further crystallizations afforded a sample m.p. 140.5–144°; λ_{max}, 2780, 1675, 1617 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{35}NO$: C, 80.19; H, 10.17; N, 4.25. Found: C, 80.54; H, 11.22; N, 4.51.

17β-*N*,*N*-Dimethylamino-17-ethynylandrost-5-en-3-ol (VII).—A stream of acetylene was bubbled through an ether-free solution of 0.19 mole of methylmagnesium bromide in 30 ml. of THF. At the end of this time 6.12 g. of the aminonitrile IV was added in 12 ml. of THF. The reaction mixture was heated under reflux for 16 hr. and allowed to cool. Water, methylene chloride, and ether were added, and the organic layer separated. The latter was washed thoroughly with brine and then extracted with 100 ml. of 0.5 *N* hydrochloric acid. The crude amine which was obtained on making the acid solution alkaline was recrystallized from aqueous methanol to yield 3.5 g. of VII, m.p. 200–203°.

A sample was recrystallized to a constant m.p. 206–208°; infrared shows evidence of hydration.

Anal. Calcd. for $C_{23}H_{35}NO \cdot 1/4H_2O$: C, 80.06; H, 10.37; N, 4.06. Found: C, 80.33; H, 10.24; N, 4.42.

17β-*N*,*N*-Dimethylamino-17-ethynylandrost-4-en-3-one (VIII).—Solvent was distilled from a solution of 3.0 g. of VII in 25.5 ml. of cyclohexanone and 150 ml. of toluene until no more water came over. Aluminum isopropoxide (1.65 g.) was added in toluene and the reaction mixture maintained at reflux temperature for 3 hr. Water was then added and the major portion of the solvent removed *in vacuo*. The residue was taken up in ether, washed with water, and the organic layer washed with 0.5 *N* hydrochloric acid. On making the acid extracts basic there was obtained 2.37 g. of crude ketone. Three recrystallizations from aqueous methanol afforded 1.29 g. of XVIII, m.p. 158–161°; λ_{max}, 3240, 2790, 1680, 1613 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{33}NO$: C, 81.36; H, 9.80; N, 4.13. Found: C, 81.06; H, 10.02; N, 4.48.

17β-*N*,*N*-Dimethylamino-17-vinylandrost-4-en-3-one

(IX).—A suspension of 0.30 g. of 5% palladium on charcoal in 200 ml. of pyridine was shaken in an atmosphere of hydrogen for 45 min. There was then added 1.50 g. of the ethynyl compound VIII. Within 4 hr. the theoretical hydrogen uptake had been observed. The catalyst was removed by filtration and the solution concentrated to 5–10 ml. *in vacuo*. The solid which was obtained on dilution of the residue with water was recrystallized from aqueous methanol to yield 0.77 g. of product m.p. 154–156°; ν_{max} 3030, 2750, 1670, 1637, 1615 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{35}NO$: C, 80.88; H, 10.33; N, 4.10. Found: C, 81.14; H, 10.29; N, 4.18.

17β-*N*,*N*-Dimethylamino-17-cyano-3-methoxyestra-1,3,5-triene (XII).—Methylamine was bubbled through a melt of 5 g. of estrone methyl ether heated to 195° for 7 hr. The solid which was obtained on cooling was taken up in methylene chloride, and this solution washed with water and taken to dryness.

A solution of the crude product from above in 50 ml. of methylene chloride was allowed to stand for 2 hr. with 15 ml. of iodomethane. The solid which was obtained when the mixture was poured into ether (500 ml.) was dissolved in 120 ml. of acetonitrile and added to 50 ml. of 10% aqueous potassium cyanide. Following 1 hour standing the solution was diluted with water. The solid thus obtained (4.80 g.; m.p. 140–147°), was recrystallized from ethyl acetate–hexane to yield 4.15 g. of XII, m.p. 148–150°.

A sample was recrystallized once again from the same solvent; m.p. 148–150°.

Anal. Calcd. for $C_{22}H_{30}N_2O$: C, 78.06; H, 8.93; N, 8.28. Found: C, 78.27; H, 9.13; N, 8.26.

17β-*N*,*N*-Dimethyalmino-17-methyl-3-methoxyestra-1,3,5-triene (XIII). (A) **From XII.**—A solution of 1.50 g. of aminonitrile XII in 25 ml. of THF was added to 10 ml. of 3 *M* methylmagnesium bromide in ether. After 3 hr. of heating under reflux the reaction mixture was worked up in the same manner as XV to give 1.20 g. of product m.p. 104–108°. A single crystallization from aqueous methanol gave 1.10 g. of fine long needles of XIII, m.p. 110.5–112°.

The analytical sample, m.p. 110.5–111.5°, was obtained by crystallization from the same solvent.

Anal. Calcd. for $C_{22}H_{30}N_2O$: C, 80.68; H, 10.16; N, 4.68. Found: C, 80.77; H, 10.40; N, 4.52.

(B) **From XI.**—A solution of 0.021 mole of methylmagnesium bromide in 131 ml. of ether was added to a suspension of 0.88 g. of the salt XI in 30 ml. of THF. The resulting solution was heated at reflux for 2 hr. After cooling, the reaction mixture was worked up as above to give 0.30 g. of basic material, m.p. 96–110°. Two crystallizations from aqueous methanol gave 0.21 g. of XIV m.p. 104–108; mixture m.p. with XIV obtained from aminonitrile: 105–109°.

17β-Dimethylamino-17-ethynyl-3-methoxyestra-1,3,5-triene (XIV).—A solution of 1.5 g. of the intermediate XII in 25 ml. of THF was added to 0.03 mole of ethynylmagnesium bromide in 20 ml. of ether-free THF. The mixture was heated at reflux for 3 hr., allowed to cool, and worked up in the same manner as above. The crude products were recrystallized twice from chloroform hexane to afford 0.60 g. of XIV, m.p. 198–200°.

The analytical sample showed m.p. 199.5–201°.

Anal. Calcd. for $C_{23}H_{31}NO$: C, 81.85; H, 9.26; N, 4.15. Found: C, 81.94; H, 9.68; N, 4.61.

C-6 Hydroxylated Steroids. II. Preparation of 6α- and 6β-Hydroxyhydrocortisone and 6α-Hydroxyprednisolone[1]

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The preparation of 6α- and 6β-hydroxyhydrocortisone from the 5α,6α-epoxide of hydrocortisone bisethylene ketal *via* the intermediate, 5α,6β,11β,17α,21-pentahydroxypregnane-3,20-dione is described. 6α-Hydroxyprednisolone was obtained by selenium dioxide dehydrogenation of 6α-hydroxyhydrocortisone 6,21-diacetate followed by saponification.

The biochemical importance of C-6 oxygenated steroids, especially 6β-hydroxyhydrocortisone (IIIa), is now well established. Numerous publications have appeared on C-6 hydroxylation under *in vitro* conditions.[2] *Inter alia*, it has been demonstrated by incubation studies that the human adrenal contains a C-6 β-hydroxylase as this gland is capable of producing 6β-hydroxyhydrocortisone (IIIa).[2g]

6β-Hydroxyhydrocortisone (IIIa) has been isolated as an urinary metabolite in both the normal guinea pig[3] and normal human after the oral administration of hydrocortisone, and from late human pregnancy urine.[4,5] Moreover in the third trimester of normal pregnancy and in toxemia a rise in the excretion of 6β-hydroxyhydrocortisone (IIIa)[5] has been observed. This compound appears also to be the principal unconjugated urinary metabolite in the newborn human,[6] and a major urinary excretory product in human adrenal hyper-

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