by gas chromatography on column A. Samples were taken directly from the reaction flask and injected into the gas chromatograph. The resulting chromatograms were then analyzed by measuring the peak areas by triangulation. Checks of the triangulation method were performed by cutting the peaks from the chromatogram and weighing the peaks. It was found that the two methods of analysis agreed to within 1%. Percentages were rounded off to the nearest per cent since the molar responses of the three isomers were not determined but were assumed to be equal. The ranges were determined from reanalyses and from analyses of duplicate experiments.

Hydrogenation of 5-Methylenenorbornene.—Palladium-on-charcoal catalyst (100 mg., 10%) was weighed into a hydrogenation flask and 15 ml. of 95% ethanol was added. The flask was shaken on the hydrogenator for 10–15 min. With 25 ml. of ethanol, 0.108 g. (1.02 mmoles) of XI was added to the hydrogenation flask. The calculated hydrogen uptake for one double bond at 25.5° and 635 mm. was 29.9 ml.; it was found to be 26.0 ml. after 30 min.

The palladium-on-charcoal catalyst was removed by filtration and then the ethanol was removed by distillation. The n.m.r. spectrum of the resulting colorless liquid indicated complete reaction of the endocyclic double bond as no resonance at τ 4.1, characteristic of the norbornene olefinic protons, was present. Also, the two singlets at τ 5.1 and 5.4, due to the exocyclic double bond protons of XI, were still present in the hydrogenated adduct.

When the n.m.r. sample was added to 25 ml. of ethanol containing 50 mg. of platinum oxide and subjected to hydrogenation, 32 ml. of hydrogen was taken up within 15 min. The n.m.r. spectrum of this sample showed no resonances due to olefinic protons.

Analytical.—All gas chromatographic analyses were performed on one of two columns. Column A was a 3-m., $^3/_8$-in. copper column packed with 20M Carbowax (25%) on Chromosorb P, 35/80 mesh. Column temperature was approximately 170° and helium flow rate was about 80 ml./min. Column B was a 1-m., $^1/_4$-in. copper column packed with PDEAS (25%) on Chromosorb P, 35/80 mesh. Column temperature was approximately 180° and helium flow rate was about 50 ml./min. Infrared spectra were obtained from a Beckman IR-5 recording spectrometer. Nuclear magnetic resonance spectra were obtained using a Varian Associates Model A-60 spectrometer. Mass spectra samples were collected from gas chromatography and the spectra were obtained on a Consolidated Electrodynamics Corp. Model 21-103C spectrometer.

Acknowledgment.—The authors are indebted to the National Science Foundation, the Shell Development Company, and the donors of the Petroleum Research Fund of the American Chemical Society for support of this work. 5-Methylenenorbornene was also obtained through the generosity of the Dow Chemical Company.

The Synthesis, Properties, and Some Reactions of Steroidal D-Homo α-Amino Ketones

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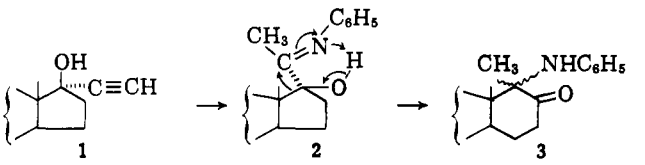
Several steroidal D-ring tertiary α-ketols were heated with methylamine and with ammonia, affording rearranged D-homo α-amino ketones. The products were shown to be derivatives of 17aβ-methyl-17aα-amino- (or methylamino-) D-homoandrostan-17-one, 17aα-methyl-17aβ-amino- (or methylamino-) D-homoandrostan-17-one, and 17β-methyl-17α-methylamino-D-homoandrostan-17a-one, depending upon the starting ketol employed. Some of the chemical transformations of these compounds are discussed and their physical and spectral properties are tabulated. It is shown that the sign of the Cotton effect of an α-axial aminocyclohexanone is not necessarily the same as that of the corresponding α-axial hydroxycyclohexanone. The mechanism of the rearrangement reaction leading to these α-amino ketones is discussed.

It has been shown that substituents on the D-ring of steroid hormones can markedly affect their physiological properties. In particular, groups attached to the 17α-position have been shown to influence anabolic, progestational, glucocorticoid, and electrolyte-regulating activities.[1] There have been few reported examples of the introduction of an amino group adjacent to a carbonyl function on the D-ring of a steroid,[2] and the pharmacological activity of steroids substituted in this manner has not been investigated. The synthesis of such a series of D-homo steroidal α-amino ketones is the subject of this paper.[3]

The aniline–mercuric chloride catalyzed hydration of a 17α-ethinyl-17β-hydroxy steroid (1) has been shown to give, in addition to the expected 17β-hydroxy-17α-pregnan-20-one, a nitrogenous by-product.[4] The structure of this compound was postulated by Shoppee and Prins to be a 17aξ-anilino-17aξ-methyl-17-keto-D-homo steroid (3).[4c,d] The formation of this anilino steroid presumably involved a 1,2-migration of the C-13 tertiary alkyl group of the intermediate α-hydroxy anil (2) from C-17 to C-20.[4c,d] Additional examples of this type of rearrangement in which aliphatic amines were prepared have been recently reported in simpler systems.[5] The driving force for this type of rearrangement is presumably the 35 kcal./mole of free energy released in the formation of the thermodynamically more stable amino ketone system from the less



1 2 3

(1) N. Applezweig, "Steroid Drugs," McGraw-Hill Book Co., Inc., New York, N. Y., 1962.

(2) (a) D. F. Morrow and M. E. Butler, *J. Heterocyclic Chem.*, **1**, 53 (1964); (b) F. Winternitz and C. R. Engel, Abstracts, Second International Symposium on the Chemistry of Natural Products, Prague, Czechoslovakia, Aug.-Sept. 1962, p. 130; (c) J. A. Moore, W. F. Holton, and E. L. Wittle, *J. Am. Chem. Soc.*, **84**, 390 (1962); (d) C. L. Hewett, U. S. Patent 3,026,318 (1962).

(3) A preliminary account of this work appeared in *Chem. Ind.* (London), 1655 (1962).

(4) (a) H. E. Stavely, *J. Am. Chem. Soc.*, **62**, 489 (1940); (b) M. W. Goldberg and R. Aeschbacher, *Helv. Chim. Acta*, **22**, 1188 (1939); (c) C. W. Shoppee and D. A. Prins, *ibid.*, **26**, 185 (1943); (d) *ibid*, **26**, 201 (1943).

(5) (a) B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **73**, 2196 (1951); (b) I. Elphimoff-Felkin, *Bull. soc. chim. France*, 653 (1962); (c) C. L. Stevens, R. D. Elliott, and B. L. Winch, *J. Am. Chem. Soc.*, **85**, 1464 (1963).

favored hydroxylimine system.[6] On this basis it should be possible to convert any tertiary α-ketol into a rearranged α-amino ketone by formation and pyrolysis of the intermediate α-hydroxylimine, at least in those cases in which no other large energy factors would be opposed. (In the steroid example discussed above, the additional free energy gained in the formation of the more stable C–D *trans*-decalin system (**3**) from the strained C–D *trans*-hydrindane system (**1**) would also favor the rearrangement.)

The facile and, in most cases, reversible interconvertibility of the various D-homo-17,17a-tertiary ketols (**4** and **9**) and their relationships with the isomeric 17-hydroxy-20-ketopregnanes (**6** and **7**) have been elucidated by Wendler, *et al.*[7] The application of the rearrangement reaction to these readily available ketols of known stereochemical configuration would afford an opportunity both to prepare steroids substituted in a new manner and to investigate the steric course of the rearrangement of α-hydroxylimines to α-amino ketones.

The ketols were heated with methylamine or ammonia at about 200° for 10 hr., either neat or with methanol or 1,2-dimethoxyethane as a cosolvent. Acid hydrolysis of the resulting α-aminoimines afforded the crystalline hydrochloride salts of the desired α-amino ketones in a fairly pure state. The various products obtained from the different ketols are listed in Table I.

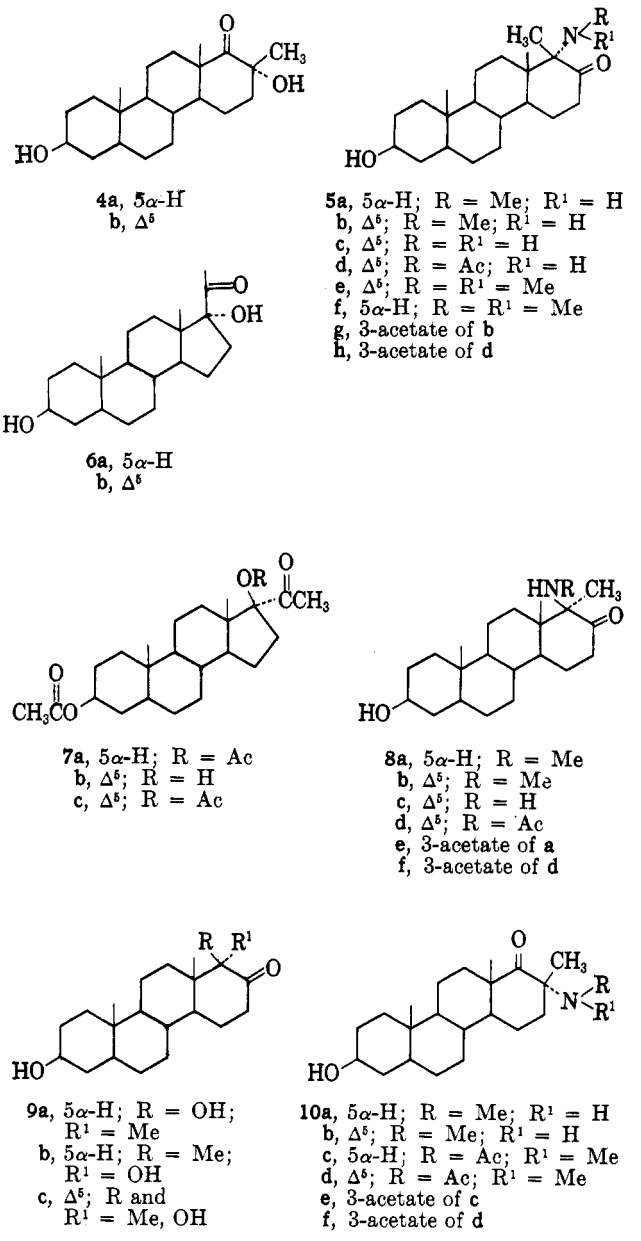
TABLE I
PREPARATION OF AMINO KETONES FROM α-HYDROXY KETONES

Ketol	Amine	Solvent	Product(s)	Yield, %[a]
4a	$MeNH_2$	...	**5a**	39
4b	$MeNH_2$	...	**5b**	35
4b	$MeNH_2$	MeOH	**5b**	34
4b	NH_3	MeOH	**5c**	29
6a	$MeNH_2$	...	**5a**	79
6b	$MeNH_2$	...	**5b**	84
6b	$MeNH_2$	MeOH	**5b**	39
6b	NH_3	...	**5c**	26
			8c	27
6b	NH_3	DME[b]	**5c**	62
7a	$MeNH_2$	...	**8a**	63
7a	$MeNH_2$	MeOH	**5a**	4
			10a	2
7b	$MeNH_2$	...	**8b**	35
7c	$MeNH_2$	...	**5b**	16
			10b	3
7c	$MeNH_2$	MeOH	**5b**	3
			10b	21
7c	NH_3	...	**8c**	29
9a	$MeNH_2$	...	**10a**	54
9b	$MeNH_2$	...	**10a**	70
9c	$MeNH_2$	...	**10b**	64
9c	$MeNH_2$	MeOH	**10b**	63

[a] The yields reported are for purified material isolated. In the cases of the known mixtures, at least, the true yields are probably much higher. [b] 1,2-Dimethoxyethane.

The major product of the reaction of 3β,17α-dihydroxy-17β-methyl-D-homoandrostan-17a-one[8] (**4a**) with methylamine was shown to be 3β-hydroxy-17aα-methylamino-17aβ-methyl-D-homoandrostan-17-one (**5a**). This methylamino steroid was also prepared from 3β,-17α-dihydroxy-5α-pregnan-20-one[9] (**6a**) by treatment with methylamine. The corresponding Δ⁵-analog **5b** could be synthesized from the Δ⁵-ketol **6b**,[10] or, alternatively, from the D-homo ketol **4b**, which in turn was prepared from **6b** by treatment with boron trifluoride etherate in acetic acid[11] and subsequent saponification of the acetate groups. The product obtained from the reaction of 3β,17aβ-dihydroxy-17aα-methyl-D-homoandrostan-17-one (**9a**)[4d] and methylamine was postulated to be 3β-hydroxy-17α-methylamino-17β-methyl-D-homoandrostan-17a-one (**10a**). This same product was obtained in somewhat higher yield from the 17a-epimeric ketol, 3β,17aα-dihydroxy-17aβ-methyl-D-homoandrostan-17-one (**9b**).[4c] The Δ⁵-analog of this methylamino steroid (**10b**) was prepared from an ap-

CHART I



(6) C=N + C—O → C=O + C—N; ΔH = −35 kcal; S. Glasstone, "Textbook of Physical Chemistry," 2nd Ed., MacMillan and Co. Ltd., London, 1955, p. 590.

(7) N. L. Wendler, D. Taub, and R. W. Walker, *Tetrahedron*, **11**, 163 (1960).

(8) D. K. Fukushima, S. Dobriner, M. S. Heffler, T. H. Kritchevsky, F. Herling, and G. Roberts, *J. Am. Chem. Soc.*, **77**, 6585 (1955).

(9) T. H. Kritchevsky and T. F. Gallagher, *ibid.*, **73**, 184 (1951).

(10) P. L. Julian, E. W. Meyer, and I. Ryden, *ibid.*, **72**, 367 (1950).

(11) R. B. Turner, *ibid.*, **75**, 3484 (1953).

proximately 1:1 mixture of the two corresponding 17a-epimeric ketols (**9c**).[4d] A third isomeric methylamino steroid, 3β-hydroxy-17aβ-methylamino-17aα-methyl-D-homoandrostan-17-one (**8a**), was obtained from the reaction of 3β,17β-diacetoxy-5α,17α-pregnan-20-one (**7a**)[4c] with methylamine. The Δ⁵-derivative **8b** was prepared similarly from the 3-acetate of 3β,17β-dihydroxy-17α-pregn-5-en-20-one (**7b**).[4d] However, when either ketol acetate **7a** or **7c**[4d] was heated with methylamine in methanol, a mixture of the isomeric 17aα-methylamino-17aβ-methyl-17-keto- and 17α-methylamino-17β-methyl-17a-keto-D-homo steroids (**5a** and **10a**, and **5b** and **10b**, respectively) was obtained. The same mixture (**5b** and **10b**) was obtained when the Δ⁵-ketol acetate (**7c**) was heated with methylamine alone. (See Chart I.)

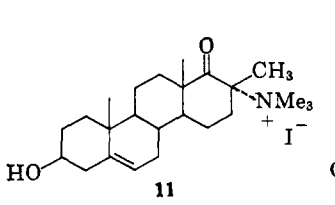
The use of ammonia in place of methylamine afforded the corresponding primary amino ketones. From 3β,17α-dihydroxy-17β-methyl-D-homoandrost-5-en-17a-one (**4b**) was obtained 3β-hydroxy-17aα-amino-17aβ-methyl-D-homoandrost-5-en-17-one (**5c**), while the diacetate of 3β,17β-dihydroxy-17α-pregn-5-en-20-one (**7c**) yielded 3β-hydroxy-17aβ-amino-17aα-methyl-D-homoandrost-5-en-17-one (**8c**). An approximately 1:1 mixture of these two amino steroids (**5c** and **8c**) was obtained in 70% yield when 3β,17α-dihydroxypregn-5-en-20-one (**6b**) was heated with ammonia alone. It is interesting to note, however, that the use of 1,2-dimethoxyethane as a cosolvent afforded 3β-hydroxy-17aα-amino-17aβ-methyl-D-homoandrost-5-en-17-one (**5c**) in 62% yield, and no appreciable amounts of the isomer **8c** were detected. No crystalline products other than those described were obtained from the mother liquors of any of these reactions (see Experimental).

The optimum conditions for the rearrangement, when run in the pure amine, were found to be 10 hr. at about 195°. From reactions run below 180° or for less than 7 hr., only very poor yields or in some cases none of the desired product could be isolated. Reactions run above 215° or for more than 15 hr. gave dark mixtures which seldom yielded any crystalline material. However, when a cosolvent such as methanol or 1,2-dimethoxyethane was used, good yields of product were obtained after 8 hr. at 180°. The addition of small amounts of *p*-toluenesulfonic acid did not affect the rate or the yield of the reaction appreciably.

The amino groups of both the 17aα- and 17aβ-methylamino steroids were very hindered, as would be expected for α,α-disubstituted neopentylamines. Treatment of 3β-hydroxy-17aα-methylamino-17aβ-methyl-D-homoandrost-5-en-17-one (**5b**) with excess acetic anhydride in either dioxane or pyridine at room temperature, or with acetyl chloride and triethylamine in ether at 0°, afforded only the 3-acetate of the starting material (**5g**) and none of the expected amide. Similar treatment of 3β-hydroxy-17aβ-methylamino-17aα-methyl-D-homoandrostan-17-one (**8a**) also gave only the 3-acetate of the methylamino steroid (**8e**). The latter compound failed to react with ketene in ether solution at room temperature. Attempts were made to N-acylate the 17aα-methylamino compound **5b** using more vigorous reaction conditions. Only unchanged starting material **5b** was recovered from an attempt to form the N-formyl derivative with chloral in refluxing chloroform.[12] However, treatment of **5b** with either refluxing acetic anhydride or acetic anhydride and pyridine at 100° produced an unexpected mixture of compounds which exhibited ultraviolet absorption bands at 293 mμ (ε 8600) and 265 mμ (ε 8500) and infrared absorption at 1727, 1607, and 1543 cm.⁻¹. Hydrolysis of this crude product with either dilute acid or base afforded a solid which exhibited ultraviolet absorption at 242 mμ (ε 8600) and infrared absorption at 1675 and 1611 cm.⁻¹. Because of difficulties in purifying these compounds, they were not investigated further. The infrared spectrum of the crude gum obtained from the reaction of **5b** with ketene in ether at room temperature exhibited peaks at 1699 and 1638 cm.⁻¹ which could be attributed to the desired ketoamide. However, extensive decomposition occured during even the mildest attempts at purification.

Both the 17aα- and the 17aβ-amino compounds (**5c** and **8c**) as well as the 17α-methylamino isomers (**10a** and **b**) were less hindered and formed amides (**5d**, **8d**, and **10c**, and **d**) with acetic anhydride or ketene under the usual mild conditions. The reaction of either the 17aα-amino- or the 17aα-methylamino-17-keto steroids (**5a–c**) with methyl iodide and potassium carbonate in refluxing acetonitrile gave the corresponding 17aα-dimethylamino derivatives (**5e** and **f**). There was no evidence of the formation of any quaternary salt. However, a stable quaternary iodide (**11**) was formed from the less hindered 17α-methylamino-17a-keto steroid **10b** under these conditions.

These three series of D-homo α-amino ketones did not rearrange with aluminum isopropoxide or with base, in contrast with their α-hydroxyketo analogs (**4** and **9**), which are readily equilibrated under these conditions.[7] Very high recoveries of pure starting materials were obtained after treatment of either **5b** or **8b** with aluminum isopropoxide in refluxing toluene. The formation of more than one amino ketone in some of the reactions must involve multiple pathways from a common intermediate rather than the equilibration of a single amino ketone product, for the isomeric amino ketones were shown not to equilibrate under the conditions in which they were formed. [This again contrasts with the formally similar rearrangements of the D-homo ketols (**4** and **9**), most of which readily equilibrate under the conditions in which they are formed.] Although some



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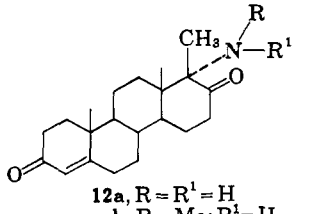
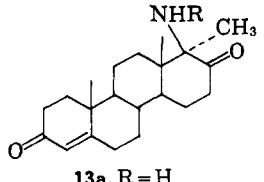
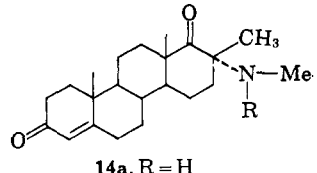


12a, R = R¹ = H
b, R = Me; R¹ = H
c, R = R¹ = Me
d, R = Ac; R¹ = H
e, Δ⁶; R = Ac; R¹ = H



13a, R = H
b, R = Ac



14a, R = H
b, R = Ac

(12) F. F. Blicke and C.-J. Lu, *J. Am. Chem. Soc.*, **74**, 3933 (1952).

TABLE II

N.M.R. SPECTRA OF AMINO KETONES

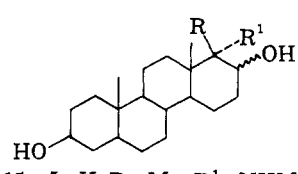
Compd.	No.	Methyls, c.p.s.[a] C-19	C-18	C-17a (or 17)	N
3β,17aα-Dihydroxy-17aβ-methyl-D-homoandrostan-17-one	**9b**	46	41	69	
3β-Hydroxy-17aα-amino-17aβ-methyl-D-homoandrost-5-en-17-one	**5c**	59	46	65	
3β-Hydroxy-17aα-methylamino-17aβ-methyl-D-homoandrost-5-en-17-one	**5b**	59	46	62	131
3β-Hydroxy-17aα-dimethylamino-17aβ-methyl-D-homoandrost-5-en-17-one	**5e**	59	42	56	132
3β,17aβ-Dihydroxy-17aα-methyl-D-homoandrostan-17-one	**9a**	47	43	80	
3β-Hydroxy-17aβ-amino-17aα-methyl-D-homoandrost-5-en-17-one	**8c**	60	46	77	
3β-Hydroxy-17aβ-methylamino-17aα-methyl-D-homoandrostan-17-one	**8a**	47	42	80	140
3β-Hydroxy-17aβ-methylamino-17aα-methyl-D-homoandrost-5-en-17-one	**8b**	59	43	78	140
3β,17α-Dihydroxy-17β-methyl-D-homoandrost-5-en-17a-one	**4b**	61	69	86	
3β,17β-Dihydroxy-17α-methyl-D-homoandrostan-17a-one[b]		48	68	79	
3α,17β-Dihydroxy-17α-methyl-D-homo-5β-androstane-11,17a-dione 3-acetate[c]		71 or 73	71 or 73	82	
3β-Hydroxy-17α-methyl-D-homoandrostan-17a-one	**20a**	60	67	59	
3β-Hydroxy-17α-methylamino-17β-methyl-D-homoandrostan-17a-one	**10a**	47	67 or 69	67 or 69	130
3β-Hydroxy-17α-amino-17β-methyl-D-homoandrost-5-en-17a-one[d]		61	71 or 74	71 or 74	

[a] Run in deuteriochloroform solvent on a Varian A-60 instrument (60 Mc.); shifts expressed as c.p.s. downfield from tetramethylsilane used as an internal standard. [b] The authors are grateful to Dr. D. K. Fukushima of the Sloan-Kettering Institute for Cancer Research for a sample of this compound. [c] The authors are indebted to Dr. N. L. Wendler of Merck Sharp and Dohme for the n.m.r. spectrum of this compound. [d] D. F. Morrow, M. E. Butler, and E. C. Y. Huang, *J. Org. Chem.*, to be published.

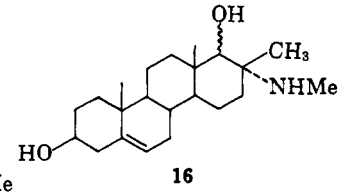
decomposition occurred, the pure amino ketones **5c**, **8c**, and **10b** were recovered in pure form in about 80% yield when heated at 200° for 10 hr. under an atmosphere of nitrogen. Treatment of **5b** with methylamine at 200° for 10 hr. and subsequent acid hydrolysis afforded the pure starting material in 85% yield.

All of the Δ^5-amino, methylamino, and dimethylamino compounds underwent Oppenauer oxidations in good yields to the corresponding Δ^4-3-keto derivatives (**12a–c**, **13a**, and **14a**), which were very stable as the free bases. Jones oxidations[13] of the Δ^5-17a-amides (**5d** and **8d**) afforded in high yields the same Δ^4-3-keto-amides (**12d** and **13b**) that were prepared from the corresponding Oppenauer oxidation products **12a** and **13a** by treatment with acetic anhydride. Chloranil oxidation[14] of N-(17aβ-methyl-D-homoandrost-4-ene-3,17-dion-17aα-yl)acetamide (**12d**) gave the corresponding 4,6-diene (**12e**), but only starting material was recovered from a similar reaction with the dimethylamino steroid **12c**.

Reduction of the 17aα-amino (**5c**), 17aα-methylamino (**5a**), and 17aβ-methylamino (**8a**) ketones with metal hydrides or by catalytic reduction gave the corresponding amino alcohols, none of which was readily cleaved by periodate. Starting material was recovered in 84% yield from the 17aα-methylamino derivative **15a** after 24 hr. at 65° with 0.08 *M* periodic acid at pH 8, and 63% of the starting material was recovered unchanged when the 17aα-amino steroid **15b** was treated with 0.12 *M* periodic acid at pH 6 for 5 days at room temperature. This lack of reactivity may be due either to excessive steric hindrance about the amine group or to unfavorable *trans* conformations of the amino alcohols.



15a, 5α-H; R = Me; R¹ = NHMe
b, 5α-H; R = Me; R¹ = NH₂
c, Δ⁵; R = NH₂; R¹ = Me



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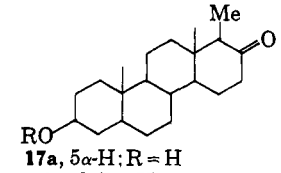
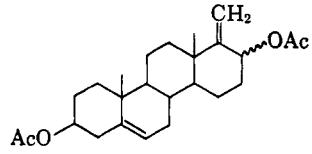


17a, 5α-H; R = H
b, Δ⁵; R = H
c, Δ⁵; R = Ac



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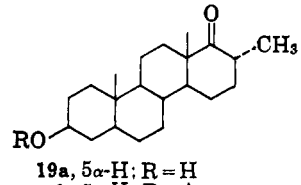


19a, 5α-H; R = H
b, 5α-H; R = Ac
c, Δ⁵; R = H

The structures of the two series of epimeric 17a-amino ketones (**5** and **8**) were assigned primarily on the basis of their n.m.r. spectra. Comparison of the spectra of the amino steroids with the spectra of the corresponding known D homo α-ketols (**9a** and **b**) showed definite correlations which determined the stereochemical configurations of these compounds[15] (see Table II). The C-19 angular methyl peaks at 60 ± 1 c.p.s. for the Δ^5-series and at 47 ± 1 c.p.s. for the 5α-series were

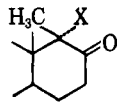
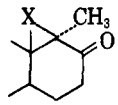
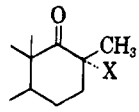
(13) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(14) E. J. Agnello and G. D. Laubach, *J. Am. Chem. Soc.*, **82**, 4293 (1960).

(15) The authors are deeply indebted to Dr. James N. Shoolery of Varian Associates for determining some of these n.m.r. spectra and especially for his very helpful interpretation of them. The spectra were run at 60 Mc. using deuteriochloroform as the solvent. The shifts are reported as cycles per second relative to tetramethylsilane used as an internal standard.

TABLE III

ULTRAVIOLET SPECTRA OF AMINO KETONES

X	λ_{max}, mμ	ε	Δ_{OH}
			
H	276	269	−20
OH	296	56	0
NH_2	303	77	+7
NH_3^+	294	26	−2
NHMe	311	65	+15
NH_2Me^+	294	37	−2
NMe_2	290[a]		
$NHMe_2^+$	296	27	0
NHAc	284	53	−12
			
OH	281	40	0
NH_2	285	46	+4
NH_3^+	281	37	0
NHMe	292	53	+11
NH_2Me^+	281	36	0
NHAc	280	41	−1
			
OH	290	46	0
NH_2[b]	305	58	+15
NH_3^+[b]	291	48	+1
NHMe	316	71	+26
NH_2Me^+	289	36	−1
NHAc[b]	296	56	+6

[a] Shoulder; no maximum evident. [b] D. F. Morrow, M. E. Butler, E. C. Y. Huang, *J. Org. Chem.*, to be published.

easily assigned, as were the N-methyl peaks at 135 ± 5 c.p.s. The lack of any peak attributable to a methyl ketone and the high-field absorption of the 18-methyl group indicated that both series **5** and **8** were 17-keto-D-homo steroids.[16] The 17a-methyl peaks at 77–80 c.p.s. in the 17aβ-amino series (**8**) corresponded well with the 80-c.p.s. peak for the 17aα-methyl in the known ketol **9a**, and the 62- and 65-c.p.s. peaks for the 17aβ-methyls of the epimeric series (**5**) agreed fairly well with the 69-c.p.s. peak for the 17aβ-methyl of the known ketol **9b**.

The position of the keto function in these two series at C-17 was corroborated by the Zimmermann test for α-methylene ketones. Both amino ketones **5c** and **8c** gave strong positive reactions with the same intensity and time of formation as their hydroxy analogs **9a** and **9b**. The stereochemical assignments were corroborated by the ultraviolet spectra of the amino ketones (see Table III).

It is well known that an α-axial hydroxyl group causes a bathochromic shift of the absorption maximum of a cyclohexanone, whereas an α-equatorial hydroxyl group causes a hypsochromic shift.[17] A similar effect would be expected for an α-amino cyclohexanone. As can be seen in Table III, in every case the keto group in compounds of series **5** absorbed at a higher wave length than the corresponding compound in series **8**. Furthermore, acetylation of the axial amino group produced a greater hypsochromic shift (−19 mμ) than acetylation of the equatorial amine (−5 mμ), which roughly parallels the ketol case.[17a] In both series, the amine hydrochlorides absorbed at nearly the same wave length as the hydroxy analog, whereas the free bases absorbed at higher wave lengths. No maximum was discernable for the axial dimethylamino compound **5e**.

These configurational assignments are also supported by the relative base strengths of these two series of compounds (See Table IV). The axial amines of series **5** are much less basic than their equatorial counterparts of series **8**. Bird and Cookson have shown that equatorial amines in general are more basic than the corresponding axial amines, owing to greater steric hindrance to solvation of the axial cation.[18] In series **8**, a greater degree of hydrogen bonding is possible between the protonated amine function and the 17-oxygen atom than in series **5**, and this also contributes to the greater basicity of the equatorial amines.[19] The high degree of steric hindrance about the nitrogen atom in compounds of series **5** is reflected by the unusual inversion of the relative basicities of the primary and secondary amines of this series, which indicates that the hindrance to solvation provided by the bulk of an additional methyl group is more than sufficient to overcome the inductive effect of this group.

Chemical confirmation of the structure of the 17aα-amino series (**5**) was provided by the reduction of the hydrochloride salt of 3β-hydroxy-17aα-dimethylamino-17aβ-methyl-D-homoandrost-5-en-17-one (**5e**) to 3β-hydroxy-17aβ-methyl-D-homoandrost-5-en-17-one (**17b**)[20] with zinc and acetic acid in 63% yield.[21] Attempts to reduce either the 17aα-amino compound (**5c**) or its amide (**5d**) in a similar manner were unsuccessful. The great degree of steric strain present in the dimethylamino compound apparently provides a large portion of the driving force for this reductive cleavage.

A chemical degradation of series **8** was also successful in eliminating the amine group. Sodium borohydride reduction of the amino ketone **8c** afforded the two epimeric amino alcohols (**15c**), and repeated fractional crystallization of the mixture afforded one epimer in a pure state and concentrated the other in the mother liquors. Treatment of both epimers with methyl iodide and potassium carbonate in refluxing acetonitrile afforded the corresponding quaternary salts, which decomposed spontaneously to the corresponding epimeric 17a-methylene 17-alcohols, isolated as the diacetates (**18**). The structures were easily assigned on the basis of their n.m.r. and infrared spectra and microanalytical data. Because the conformation of the D-ring of these compounds is uncertain, no attempt was was made to assign the stereochemistry at C-17 of the

(16) N. R. Trenner, B. H. Arison, D. Taub, and N. L. Wendler, *Proc. Chem. Soc.*, 214 (1961).

(17) (a) R. C. Cookson and S. H. Dandegaonker, *J. Chem. Soc.*, 352 (1955); (b) G. Baumgartner and C. Tamm, *Helv. Chim. Acta*, **38**, 441 (1955).

(18) C. W. Bird and R. C. Cookson, *J. Chem. Soc.*, 2343 (1960).

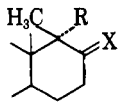
(19) J. F. King, "Technique of Organic Chemistry," Vol. XI, part 1, K. W. Bentley, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p. 344.

(20) (a) K. Miescher and H. Kägi, *Helv. Chim. Acta*, **22**, 184 (1939); (b) L. Ruzicka and H. Meldahl, *ibid.*, **22**, 421 (1939).

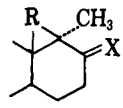
(21) A similar reductive cleavage of a γ-(N-piperidino)-α,β-unsaturated ketone was reported by H. Pines and H. E. Eschinazi, *J. Am. Chem. Soc.*, **77**, 6314 (1955).

TABLE IV

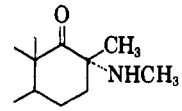
BASIC STRENGTHS OF THE AMINO STEROIDS[a]



R	X	Compd.	pK_a
NH_2	O	**5c**	6.2
NH_2	O	**12a**	6.3
NHMe	O	**5b**	6.0
NHMe	O	**5g**	5.8
NMe_2	O	**5e**	5.6
NH_2	OH	**15b**	8.8



R	X	Compd.	pK_a
NH_2	O	**13a**	7.4
NHMe	O	**8a**	8.0
NHMe	O	**8b**	8.0
NH_2	OH	**15c**	9.1



Compd.	pK_a
10b	7.6

[a] Determined in 2:1 dimethylformamide–water.

two epimers. A small amount of ketone, presumably the desired 3β-hydroxy-17aβ-methyl-D-homoandrost-5-en-17-one (**17b**) was evident in the infrared spectra of the crude products, but an attempt at chromatographic separation was unsuccessful.

The third isomeric series (**10**) was shown to have a 17a-keto D-homo structure on the basis of its n.m.r. spectra[16] (see Table II) and a negative Zimmermann test. However, a definite assignment of the stereochemistry at C-17 was not possible. The C-17 methyl peaks at 70 ± 3 c.p.s. in the n.m.r. spectra of this series did not correspond well with the C-17 methyl peaks of either of the known epimeric 17-hydroxy-17-methyl 17a-ketones (86 and ~80 c.p.s.). This may well be due to a slight twist about the C-17–C-17a bond of the somewhat flexible boat form[22] of these compounds as a result of either hydrogen bonding or steric repulsion. The ultraviolet spectra of this series of amino steroids exhibited a large bathochromic shift relative to the corresponding ketol **4**, similar to that of the series of known α-axial amino ketones **5** (Table III). Although an analogy drawn by comparison of boat and chair forms of cyclohexanones cannot be strictly valid, the spectral data for this series is suggestive of the presence of a 17α-(pseudo-axial)amine function in the boat form of ring D. This stereochemistry might also be expected for this series on the basis of the stability and the ease of formation of the corresponding ketols.[7]

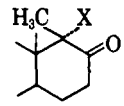
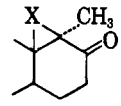
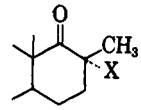
Chemical verification of this structure was obtained by treatment of the methylamino alcohol **16**, obtained by borohydride reduction of the ketone **10b**, with methyl iodide and potassium carbonate in refluxing acetonitrile. The product was shown to be 3β-hydroxy-17α-methyl-D-homoandrost-5-en-17a-one (**19c**) by catalytic reduction to the known 5α-dihydro derivative (**19a**).[22f,23] The pinacol-like rearrangement of this α-hydroxy pseudo-axial quaternary salt contrasts with the Hofmann elimination of the two epimeric α-hydroxy equatorial quaternary salts (from **15c**). A pinacol type of rearrangement in the latter cases is less favored, because neither of the two epimeric C-17 protons can assume a *trans*-coplanar relationship with the departing trimethylamine group in either a chair or boat conformation of the D-ring.

(22) (a) M. Uskoković, M. Gut, E. N. Trachtenberg, W. Klyne, and R. I. Dorfman, *J. Am. Chem. Soc.*, **82**, 4965 (1960); (b) N. L. Wendler, *Chem. Ind.* (London), 1662 (1958); (c) N. L. Wendler, *Tetrahedron*, **11**, 213 (1960); (d) D. K. Fukushima, S. Dobriner, and R. S. Rosenfeld, *J. Org. Chem.*, **26**, 5025 (1961); (e) M. Heller, S. M. Stolar, and S. Bernstein, *ibid.*, **26**, 5036 (1961); (f) R. S. Rosenfeld, *J. Am. Chem. Soc.*, **79**, 5540 (1957).

(23) (a) R. E. Marker and E. Rohrmann, *ibid.*, **61**, 2719 (1939); (b) D. A. Prins and C. W. Shoppee, *J. Chem. Soc.*, 494 (1946); (c) W. Klyne, *Nature*, **166**, 559 (1950).

TABLE V[a]

OPTICAL ROTATORY DISPERSION CURVES OF AMINO KETONES

X	λ_1[b]	$[\alpha_1]$[b]	λ_2[c]	$[\alpha_2]$[c]
				
OH (5α)	318	−820	277	+650
OH (5α)[d]	320	−1000	280	+1070
NH_2	327	+800	283	−2080
NH_3^+	319	−1920	276	+840
NHMe	332	+1600	289	−2820
NH_2Me^+ (5α)	321	−820	278	+780
NMe_2 (5α)	309	−1180	271	+460
$NHMe_2^+$	322	−1060	281	+105
NHAc	305	−2020	...	...
				
OH (5α)	301	−760	266	+220
OH (5β)[d]	302	−670	267.5	+470
NH_2	304	−1130	275	+280
NH_3^+	298	−770	...	...
NHMe (5α)	317	−1120	275	+1380
NH_2Me^+ (5α)	307	−380	...	...
NHAc	299	−1120	...	...
				
OH[e]	325	+650	269	−2180
OH (3-0Ac,5α)[d]	322.5	+1000	272.5	−1340
NH_2[f]	325	+970	281	−1920
NH_3^+[f]	324	+1031	276	−1650
NHMe (5α)	335	+1610	291	−1700
NH_2Me^+ (5α)	324	+860	280	−1480
NMe_3^+	342	+200	292	−750
NHAc[f]	319	+70	...	...
NMeAc	313	−135 (max)	...	...

[a] The authors are indebted to Dr. M. L. Wolfrom of Ohio State University for allowing us the use of his Rudolph automatic recording spectropolarimeter. The samples were run as 0.2% solutions in methanol in a 1.0-cm. tube at 28°. The constants reported are for the Δ5-3β-hydroxy compounds unless otherwise noted. [b] Wave length (in mμ) and amplitude (in degrees) of first extremum. [c] Wave length (in mμ) and amplitude (in degrees) of second extremum. [d] See ref. 24. [e] The epimeric 3β,17β-dihydroxy-17α-methyl-D-homoandrostan-17a-one exhibited λ_1 331 mμ, [α] +520°. No minimum was observed above 270 mμ. The authors are indebted to Dr. D. K. Fukushima of the Sloan-Kettering Institute for Cancer Research for furnishing us a sample of this compound. [f] D. F. Morrow, M. E. Butler, and E. C. Y. Huang, *J. Org. Chem.*, to be published.

TABLE VI

PHYSICAL PROPERTIES OF COMPOUNDS

Compd.	No.	Method of prepn.	Yield, %	M.p., °C.	Solvent[a]	$[\alpha]^{25}D$[b]	Formula	Calcd., % C	H	N	Cl	Found, % C	H	N	Cl
3β-Hydroxy-17aα-methylamino-17aβ-methyl-D-homoandrostan-17-one	**5a**	A	*c*	217–219	Me–W	+36	$C_{22}H_{37}NO_2$	76.03	10.73	4.03		75.81	10.74	4.08	
hydrochloride salt				280–285 dec.	Me	−47	$C_{22}H_{38}ClNO_2$	68.81	9.98	3.65	9.23	68.66	10.04	3.65	9.21
3β-Hydroxy-17aα-methylamino-17aβ-methyl-D-homoandrost-5-en-17-one	**5b**	A, B	*c*	218–220	Me	−15	$C_{22}H_{35}NO_2$	76.47	10.21	4.05		76.58	10.17	3.98	
hydrochloride salt				285–287 dec.	Me	−96	$C_{22}H_{36}ClNO_2$	69.17	9.50	3.67	9.28	69.01	9.59	3.53	9.20
3β-Hydroxy-17aα-amino-17aβ-methyl-D-homoandrost-5-en-17-one	**5c**	A, B	*c*	259–260	Et	−63	$C_{21}H_{33}NO_2$	76.09	10.03	4.23		76.06	10.01	4.20	
hydrochloride salt				268–270 dec.	Me	−106	$C_{21}H_{34}ClNO_2$	68.68	9.32	3.81	9.64	68.59	9.29	3.58	9.54
N-(3β-Hydroxy-17aβ-methyl-D-homoandrost-5-en-17-on-17aα-yl)acetamide	**5d**	C	62	311–312	Ac	−145[d]	$C_{23}H_{35}NO_3$	73.95	9.45	3.75		74.05	9.32	3.72	
N-(3β-Acetoxy-17aβ-methyl-D-homoandrost-5-en-17-on-17aα-yl)acetamide	**5h**	D	61	202–204	Me–W	−147[d]	$C_{25}H_{37}NO_4$	72.25	8.98	3.37		71.98	9.07	3.45	
3β-Hydroxy-17aα-dimethylamino-17aβ-methyl-D-homoandrost-5-en-17-one	**5e**	E	83	107–109 163–165	E–PE	−114	$C_{23}H_{37}NO_2$	76.83	10.37	3.90		76.75	10.25	4.13	
hydrochloride salt				222–223	IP	−130	$C_{23}H_{38}ClNO_2$	69.76	9.67	3.54	8.95	69.50	9.64	3.47	8.65
3β-Hydroxy-17aα-dimethylamino-17aβ-methyl-D-homoandrostan-17-one	**5f**	E	74	146–148	IP–W	−64	$C_{23}H_{39}NO_2$	76.40	10.87	3.87		76.19	10.45	3.83	
hydrochloride salt				202–204	Me	−89	$C_{23}H_{40}ClNO_2 \cdot 0.5CH_3OH$	68.13	10.15	3.38	8.55	68.17	10.26	3.42	8.60
3β-Acetoxy-17aα-methylamino-17aβ-methyl-D-homoandrost-5-en-17-one	**5g**	F	67	214–215	Me–W	−62[d]	$C_{24}H_{37}NO_3$	74.38	9.62	3.61		74.22	9.80	3.69	
3β-Hydroxy-17aβ-methylamino-17aα-methyl-D-homoandrostan-17-one	**8a**	A	*c*	177–179	Et–W	−10	$C_{22}H_{37}NO_2$	76.03	10.73	4.03		75.95	10.64	3.89	
hydrochloride salt				263–266 dec.	Et–EA	±0	$C_{22}H_{38}ClNO_2$	68.81	9.98	3.65	9.23	69.14	10.19	3.41	8.98
3β-hydroxy-17aβ-methylamino-17aα-methyl-D-homoandrost-5-en-17-one	**8b**	A	*c*	178–179	Me	−83	$C_{22}H_{35}NO_2 \cdot 0.5CH_3OH$	74.75	10.32	3.87		74.85	10.11	4.02	
hydrochloride salt				273–275 dec.	IP	−67	$C_{22}H_{36}ClNO_2$	69.17	9.50	3.67	9.28	69.06	9.42	3.62	9.23
3β-Hydroxy-17aβ-amino-17aα-methyl-D-homoandrost-5-en-17-one	**8c**	A	*c*	199–200	Et	−111	$C_{21}H_{33}NO_2$	76.09	10.03	4.23		76.10	10.26	4.24	
hydrochloride salt				295–296 dec.	IP	−69	$C_{21}H_{34}ClNO_2$	68.68	9.32	3.81	9.64	68.59	9.29	3.79	9.48
N-(3β-Hydroxy-17aα-methyl-D-homoandrost-5-en-17-on-17aβ-yl)acetamide	**8d**	C	69	300–302	Ac	−179[d]	$C_{23}H_{35}NO_3$	73.95	9.45	3.75		74.08	9.47	3.59	
N-(3β-Acetoxy-17aα-methyl-D-homoandrost-5-en-17-on-17aβ-yl)acetamide	**8f**	F	27	217–218	Me	−160[d]	$C_{25}H_{37}NO_4$	72.25	8.98	3.37		72.50	9.07	3.35	
3β-Acetoxy-17aβ-methylamino-17aα-methyl-D-homoandrostan-17-one	**8e**	D	50	199–202	Me–W	−17[d]	$C_{24}H_{39}NO_3$	73.99	10.09	3.60		73.88	10.24	3.62	
3β-Hydroxy-17α-methylamino-17β-methyl-D-homoandrostan-17a-one	**10a**	A	*c*	209–211	Me	+65[d]	$C_{22}H_{37}NO_2$	76.03	10.73	4.03		75.77	10.81	3.98	
hydrochloride salt				287–289	IP		$C_{22}H_{38}ClNO_2$	68.81	9.98	3.65	9.23	68.89	10.03	3.67	8.93
3β-Hydroxy-17α-methylamino-17β-methyl-D-homoandrost-5-en-17a-one	**10b**	A, B	*c*	205–207	Me	−17	$C_{22}H_{35}NO_2$	76.47	10.21	4.05		76.28	10.12	4.21	
hydrochloride salt				>310	Me–EA	−23	$C_{22}H_{36}ClNO_2$	69.17	9.50	3.67	9.28	69.02	9.57	3.65	8.91

N-(3β-Hydroxy-17β-methyl-D-homoandrostan-17a-on-17α-yl)-N-methylacetamide	**10c**	G	80	242–247	EA	−93[d]	$C_{24}H_{39}NO_3$	73.99	10.09	3.60		74.17	10.02	3.79	
N-(3β-Acetoxy-17β-methyl-D-homoandrostan-17a-on-17α-yl)-N-methylacetamide	**10e**	D	57	192–194	EA–H	−23[d]	$C_{26}H_{41}NO_4$	72.35	9.58	3.25		72.24	9.73	3.35	
N-(3β-Hydroxy-17β-methyl-D-homoandrost-5-en-17a-on-17α-yl)-N-methylacetamide	**10d**	G	86	243–245	Me	−93	$C_{24}H_{37}NO_3$	74.38	9.62	3.61		74.36	9.72	3.40	
N-(3β-Acetoxy-17β-methyl-D-homoandrost-5-en-17a-on-17α-yl)-N-methylacetamide	**10f**	D	78	194–196	Ac–PE	−86[d]	$C_{26}H_{39}NO_4$	72.69	9.15	3.26		72.70	9.08	3.28	
(3β-Hydroxy-17β-methyl-D-homoandrost-5-en-17a-on-17α-yl)trimethylammonium iodide	**11**	E	60	240–242	Me	−21	$C_{24}H_{40}INO_2$	57.46	7.91	2.75	24.91[e]	57.10	7.93	2.85	24.91[e]
17aα-Amino-17aβ-methyl-D-homoandrost-4-ene-3,17-dione[f]	**12a**	H	73	213–214	Et	+67	$C_{21}H_{31}NO_2$	76.55	9.48	4.25		76.32	9.60	4.24	
17aα-Methylamino-17aβ-methyl-D-homoandrost-4-ene-3,17-dione[g] hydrochloride salt[h]	**12b**	H	93	157–161	Me–IE	+100	$C_{22}H_{33}NO_2$	76.92	9.68	4.08		77.00	9.90	4.16	
				227–231 dec.	IP	+13	$C_{22}H_{34}ClNO_2$	69.54	9.02	3.69	9.53	69.51	9.08	3.64	8.88
17aα-Dimethylamino-17aβ-methyl-D-homoandrost-4-ene-3,17-dione[i] hydrochloride salt[j]	**12c**	H	60	189–191	EA–H	+18	$C_{23}H_{35}NO_2$	77.26	9.87	3.92		77.19	9.99	3.96	
		E	93												
				204–207	IP	−37	$C_{23}H_{36}ClNO_2$	70.11	9.21	3.56	9.00	70.30	9.11	3.60	8.74
N-(17aβ-Methyl-D-homoandrost-4-ene-3,17-dion-17aα-yl)acetamide[k]	**12d**	D	87	290–292	Ac	−45[d]	$C_{23}H_{33}NO_3$	74.36	8.95	3.77		74.50	9.10	3.97	
		I	49												
N-(17aβ-Methyl-D-homoandrosta-4,6-diene-3,17-dion-17aα-yl)acetamide[l]	**12e**	J	48	302–305	Me–EA	−142[d]	$C_{23}H_{31}NO_3$	74.76	8.46			74.33	8.56		
17aβ Amino-17aα-methyl-D-homoandrost-4-ene-3,17-dione, hydrochloride salt[m]	**13a**	H	50	217–220 dec.	Me–EA	+10	$C_{21}H_{34}ClNO_2 \cdot CH_3OH$	66.39	9.12	3.52	8.91	66.32	9.03	3.59	8.87
N-(17aα-Methyl-D-homoandrost-4-ene-3,17-dion-17aβ-yl)acetamide[n]	**13b**	I	50	235–238	Me–W	−58[d]	$C_{23}H_{33}NO_3$	74.36	8.95			74.23	8.89		
17α-Methylamino-17β-methyl-D-homoandrost-4-ene-3,17a-dione[o] hydrochloride salt[p]	**14a**	H	84	195–197	IP	+124	$C_{22}H_{33}NO_2$	76.92	9.68	4.08		76.81	9.69	4.03	
				267–272 dec.	IP	+94	$C_{22}H_{34}ClNO_2$	69.54	9.02	3.69	9.33	69.13	9.09	3.62	8.95
N-(17β-Methyl-D-homoandrost-4-ene-3,17a-dion-17α-yl)acetamide[q]	**14b**	D	92	208–210	Me	+46	$C_{24}H_{35}NO_3$	74.70	9.15	3.63		74.26	9.20	3.87	
3β,17-Dihydroxy-17aα-amino-17aβ-methyl-D-homoandrostane, hydrochloride salt	**15b**	K	97	283–288	Me		$C_{21}H_{38}ClNO_2 \cdot H_2O$	64.67	10.34	3.59	9.09	64.84	10.28	3.54	8.80
3β,17-Dihydroxy-17aβ-amino-17aα-methyl-D-homoandrost-5-ene	**15c**	L	45	261–263	Me	−53	$C_{21}H_{35}NO_2$	75.63	10.58	4.20		75.45	10.60	4.35	
3β,17a-Dihydroxy-17α-methylamino-17β-methyl-D-homoandrost-5-ene hydrochloride salt	**16**	L	57	>300	IP	−40	$C_{22}H_{38}ClNO_2$	68.81	9.98	3.65	9.23	68.67	9.95	3.62	9.36

[a] Ac = acetone, E = ether, EA = ethyl acetate, Et = ethanol, H = heptane, IE = isopropyl ether, IP = isopropyl alcohol, Me = methanol, PE = petroleum ether, W = water. [b] Run as approximately 1% solutions in methanol unless otherwise noted. [c] The yields of these compounds, which varied with the starting ketol and reaction conditions employed, can be found in Table I. [d] Run as approximately 0.5% solutions in chloroform. [e] These figures are for per cent iodine rather than chlorine. [f] λ_{max} 241 mμ (ε 16,300). [g] λ_{max} 240 mμ (ε 14,500). [h] λ_{max} 240 mμ (ε 16,700). This salt crystallized with 0.5 mole of isopropyl alcohol of crystallization. The anhydrous salt was prepared by prolonged heating of the alcoholate at 110° and 0.1 mm. [i] λ_{max} 240 mμ (ε 16,800). [j] λ_{max} 240 mμ (ε 16,200). [k] λ_{max} 240 mμ (ε 16,600). [l] λ_{max} 283 mμ (ε 26,800). [m] λ_{max} 239 mμ (ε 14,800). [n] λ_{max} 240 mμ (ε 14,100). [o] λ_{max} 236 mμ (ε 16,600). [p] λ_{max} 240 mμ (ε 16,700). [q] λ_{max} 240 mμ (ε 16,200).

The optical rotatory dispersion (O.R.D.) curves of these D-homo amino ketones were obtained and compared with the O.R.D. curves of the corresponding ketols[24] (see Table V). Good correlation was evident in both the 17aα-methyl-17-keto (**8** and **9a**) and the 17β-methyl-17a-keto series (**4** and **10**).[25] However, some anomalous curves were obtained in the 17aβ-methyl-17-keto series (**5** and **9b**). Although the Cotton effects of the amide, the dimethylamino compound, and all the salts possessed the same sign as that of the ketol **9b**, the amino and methylamino compounds exhibited Cotton effects of the opposite sign. The reason for this is not entirely clear. However, since the atomic refractivity[26] of the nitrogen atom of aliphatic amines (2.5–3.0) lies between that of carbon (2.4) and that of chlorine (6.0), whereas that of hydroxyl (1.5) is lower than that of carbon, an axial amine function, like an axial halogen,[27] in close proximity to a ketone should have a much more pronounced effect upon the O.R.D. curve than a corresponding axial hydroxyl group.[28] In series **5** a substituent in the 17aα-position should tend to cause a positive Cotton effect. If this substituent is an amine function, the magnitude of this effect may be sufficient to override the effect of the remainder of the steroid molecule, which produces a weak negative Cotton effect.[29] On this basis it is possible to rationalize the positive Cotton effects of **5b** and **5c**. The "anomalous" negative Cotton effect of the dimethylamino derivative **5e** may be due to a deformation of the D-ring into a boat form due to steric crowding between the C-12α and C-16α protons and the large dimethylamino group, resulting in a pseudo-equatorial disposition of the latter. The ultraviolet spectrum of this compound was also anomalous (Table III), showing no maximum but only a shoulder at about 290 mμ, corresponding approximately to the wave length due to an equatorial α-amino ketone. The change in the sign of the Cotton effects of *Lycopodium* alkaloids in going from the free base to the salt form has led Ayer, *et al.*, to postulate that a positively charged nitrogen atom has a *negative* specific rotativity.[30] The negative Cotton effects of the salts of **5b** and **5c** can be explained on this basis.

In series **8** and **9a**, the hydroxyl and amino groups are equatorial and should have little effect upon the O.R.D. curve of the ketone. In these series, then, the parallel Cotton effects of the amino compounds and of the ketol would be expected. In series **10**, the effect of the axial amine group in a negative octant may not be sufficient to overcome the effect of the remainder of the steroid molecule, which, in contrast to series **5** and **9b**, lies almost exclusively in a positive octant.[31] However, a clearer understanding of these anomalous O.R.D. curves must await further investigation of the O.R.D. spectra of simpler models of epimeric α-aminocyclohexanones.

The stereochemical and conformational effects which control the mechanism of the formation of these amino ketones cannot be fully understood until all the basic products from these reactions are identified. However, in most cases, the major product isolated corresponded to the ketol (NHR replacing OH) obtained from the same starting material by treatment with a Lewis acid.[7] This indicates that, of the two mechanisms proposed by Stevens[5c] for this reaction, the intramolecular cyclic mechanism, in which the imine and hydroxyl groups are in an *s-cis* relationship, is more likely than the alternate mechanism involving abstraction of the hydroxyl proton by an amine molecule at high temperatures. If the latter mechanism prevailed, the dipole of the imine should orient itself away from the anion, yielding amino ketones whose stereochemistry corresponded to the ketols obtained by isomerization of the starting materials with strong base.[11] The stereochemistry of the formation of **5a–c** from **6a** and **b** is again that to be expected from an *s-cis* cyclic mechanism. However, in this case, in contrast to the Lewis acid catalyzed rearrangement of **6a** and **b**, the tertiary C-13 atom migrated rather than the secondary C-16 atom. The reason for this difference in migratory aptitude of these two carbon atoms in these two very similar reactions is not at all clear. However, the explanation advanced by Elphimoff-Felkin[32] and Wendler, *et al.*,[33] to explain the migration of the electronically less favored C-16 atom in the Lewis acid catalyzed ketol rearrangement based on the conformation of the transition state should be re-examined in light of the finding that 17,17-disubstituted 17a-ketones such as **4** and **10** exist in the boat form.[22] Other examples in which the relative migratory aptitudes of these two carbon atoms seem to reverse are known.[34] The formation of **10a** from **9a** is puzzling, for the starting ketol **9a** is stable to Lewis acids,[7] and there is no simple mechanism to account for the migration of the methyl group from the α- to the β-face of the steroid molecule. The possibility that **9a** is first isomerized to **9b** under the basic conditions of the reaction is unlikely, for the ketol **6b**, which is more easily isomerized by base than **9a**,[7] was recovered unchanged after treatment with trimethylamine at 200° for 10 hr. An alternate explanation is conversion of **9a** to the presumably unstable (by analogy with the ketol series[7]) 17β-methylamino-17α-methyl-17a ketone imine, which under the influence of heat is isomerized to the product **10a**, probably proceeding through an intermediate 17-amino-20-iminopregnane derivative. An analogous mechanism has been proposed for the base-catalyzed equilibration of **9a** and **9b**.[7]

(24) C. Djerassi, O. Halpern, V. Halpern, O. Schindler, and C. Tamm, *Helv. Chim. Acta*, **41**, 250 (1958).

(25) Although in the latter series (**4** and **10**) both the hydroxy and amino ketones possessed a positive Cotton effect, the analogous 17,17-dimethyl 17a-ketone has been shown to have a negative Cotton effect.[23a] The boat conformation of the D-ring of these compounds is very flexible, and these anomalies must be due to the various degrees of twisting of this ring.

(26) N. A. Lange, "Handbook of Chemistry," 8th Ed., Handbook Publishers, Inc., Sandusky, Ohio, 1952, p. 1421.

(27) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, pp. 120–128.

(28) W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961), footnote 11.

(29) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956).

(30) W. A. Ayer, J. A. Berezowsky, and D. A. Law, *Can. J. Chem.*, **41**, 649 (1963).

(31) It has been shown that the A- and B-rings alone of a D-homo 17a-ketone produce a strong positive Cotton effect: W. Klyne, "Advances in Organic Chemistry: Methods and Results," Vol. 1, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p. 332.

(32) I. Elphimoff-Felkin, *Bull. soc. chim. France*, 1845 (1956).

(33) N. L. Wendler, D. Taub, and R. Firestone, *Experientia*, **15**, 237 (1959).

(34) (a) N. L. Wendler, D. Taub, and H. L. Slates, *J. Am. Chem. Soc.*, **77**, 3559 (1955); (b) F. Ramirez and S. Stafiej, *ibid.*, **78**, 644 (1956).

The effect of varying the solvent and the reagent on the structure of the products obtained from series **7** may be attributed in part to a change in the rate of imine formation, which, in turn, may be caused by a difference in the rate of hydrolysis (or aminolysis) of the 17β-acetate.[35] If removal of the 17-acetate occurs only at elevated temperature, the liberated heat-sensitive ketol **7b** (or 5α-H) may rearrange to the D-homo-17-keto ketol **9a** (or Δ^5) prior to imine formation. The latter ketol would then undergo imine formation and rearrangement to yield compounds of series **10**. There is at this time no single simple mechanistic explanation which can account for the formation of all the various products of this rearrangement reaction (*e.g.*, **5** from **7**, and **8c** from **6b**). For the physical properties of the compounds, see Table VI.

Experimental[36]

Procedure A. Preparation of Amino Ketones.—The hydroxy ketone was treated with 15 ml. of liquid methylamine (or ammonia)/gram of steroid and heated under pressure at 195 ± 5° for 10 hr. The reaction mixture was cooled, the excess methylamine (or ammonia) was vented, and the residue was dissolved in methanol. This solution was concentrated to dryness under reduced pressure to remove any residual volatile base. The residue was dissolved in 10 ml. of isopropyl alcohol and 1 ml. of 12 *N* hydrochloric acid/gram of starting steroid; the mixture was heated on a steam bath for 1 hr. and then was cooled and filtered, affording the hydrochloride salt of the α-methylamino (or α-amino) keto steroid. Further crops of product were obtained by concentration of the filtrate.

Several of the very dark mother liquors from the acid hydrolyses were separated into neutral and basic fractions. Small amounts of starting material were recovered from some of the neutral fractions. The basic nitrogenous fractions were usually dark and gummy, and all attempts to isolate any of the isomeric amino or methylamino ketones which may have accompanied the major product(s) were unsuccessful. The only exceptions to this were the reactions of the 17β-hydroxy-17α-pregn-20-ones **7a** and **7c** which yielded the mixtures of **5a** and **10a** or **5b** and **10b**. The basic fractions from the mother liquors of these reactions were dark but crystalline mixtures containing two or more methylamino steroid ketones (by infrared), presumably additional quantities of the original two isomers. The hydrochloride salts of both the 17a-epimeric 17a-amino 17-ketones **5c** and **8c** formed from 3β,17α-hydroxypregn-5-en-20-one (**6b**) by treatment with pure ammonia crystallized directly from the hydrolysis mixture and were separated by fractional crystallization of the free bases. The basic fraction from this hydrolysis mixture was also a dark gum, from which no additional crystalline material could be obtained.

Procedure B. Preparation of Amino Ketones.—The hydroxy ketone was treated with 15 ml. of liquid methylamine (or ammonia) and 15 ml. of methanol/gram of steroid and was heated under pressure at 180 ± 5° for 8 hr. The reaction mixture was treated in the same manner as in procedure A.

Procedure C. Preparation of Amides.—A solution of the amino ketone in a minimum amount of methanol was treated with four times its weight of acetic anhydride and kept at room temperature for 24 hr. The solution was concentrated to dryness under reduced pressure, affording the crude amide.

Procedure D. Preparation of Amides.—A suspension of 1.0 g. of the amino steroid in 35 ml. of acetic anhydride was stirred at room temperature for 72 hr. The solution was poured into water, neutralized carefully with sodium bicarbonate, and filtered to yield the crude amide.

Procedure E. Methylation of Amines.—A solution of 1.0 g. of the amino steroid in 80 ml. of dry acetonitrile was treated with 1.0 g. of potassium carbonate and 10 ml. of methyl iodide, and the mixture was stirred and refluxed for 24 hr. The mixture was then cooled, concentrated to a small volume under reduced pressure, and poured into water. The solid was separated by filtration, giving the crude tertiary amine or quaternary iodide.

Procedure F. Preparation of 3-Acetates.—A solution of 0.50 g. of the amino steroid in 100 ml. of ether (in some cases a little benzene or dioxane was added to improve solubility) was cooled to 5° and treated with 5 ml. of triethylamine and 2.5 ml. of acetyl chloride. The mixture was kept at 5° for 24 hr. and then washed with water, dilute sodium hydroxide solution, and water again. The solution was dried over magnesium sulfate and concentrated to dryness on a steam bath, affording the crude 3-acetate.

Procedure G. Preparation of Amides.—Ketene was bubbled into a solution of 0.20 g. of the amino steroid in 20 ml. of benzene and 5 ml. of acetone for 15 min., and the solution was allowed to stand at room temperature for 1 hr. The benzene solution was then washed with water, dilute hydrochloric acid, and water again, and was dried over magnesium sulfate. The solution was concentrated to dryness on a steam bath to give the crude amide.

Procedure H. Oppenauer Oxidation to Δ^4-3-Ketones.—A solution of 6.5 g. of the Δ^5-3β-hydroxyamino steroid in 200 ml. of toluene was treated with 10 g. of aluminum isopropoxide and 80 ml. of cyclohexanone, and the mixture was stirred and refluxed for 40 min. The mixture was then cooled, washed well with an aqueous solution of potassium sodium tartrate and with water, and dried over magnesium sulfate. The dried solution was concentrated to an oil under reduced pressure. The oil was dissolved in anhydrous ether and treated with an ether solution of anhydrous hydrogen chloride. The precipitate was filtered and washed well with ether, affording the hydrochloride salt of the Δ^4-3-ketoamino steroid.

Procedure I. Jones Oxidation to Δ^4-3-Ketones.—A solution of 1.0 g. of the Δ^5-3β-hydroxyamide in 175 ml. of purified acetone was cooled to 5°, covered with an atmosphere of nitrogen, and treated with 1.1 equiv. of Jones reagent.[13] After 7 min. at 5°, the solution was poured into water. Potassium carbonate was added and the suspension was extracted with chloroform. The chloroform layer was washed well with water, dried over magnesium sulfate, and concentrated to dryness on a steam bath to give the Δ^4-3-ketoamide.

Procedure J. Chloranil Oxidation to $\Delta^{4,6}$-3-Ketones.—A solution of 0.50 g. of the Δ^4-3-ketoamide in 35 ml. of *t*-butyl alcohol was treated with 1.72 g. of chloranil, and the mixture was stirred and refluxed for 3 hr. The mixture was then cooled and filtered, and the residue was washed with *t*-butyl alcohol. The combined filtrate and washings were concentrated to dryness under reduced pressure. The residue was dissolved in chloroform, washed well with water, dilute sodium hydroxide solution, and water, and dried over magnesium sulfate. Concentration of the solution under reduced pressure yielded the crude $\Delta^{4,6}$-dienonamide.

Procedure K. Catalytic Reduction of Amino Ketones.—A solution of 1.0 g. of the hydrochloride salt of the Δ^5-amino ketone in 50 ml. of acetic acid and 200 ml. of methanol was treated with 0.2 g. of platinum oxide and reduced at 50 p.s.i. until hydrogen uptake ceased (2.0 equiv.). The mixture was filtered and concentrated to dryness under reduced pressure to give the crude 5α-amino alcohol hydrochloride.

Procedure L. Hydride Reduction of Amino Ketones.—A solution of 1.0 g. of amino ketone in 100 ml. of absolute ethanol was treated with 1.0 g. of sodium borohydride and left at room temperature 2.5 hr. The solution was poured into concentrated aqueous potassium carbonate solution and filtered to yield the crude amino alcohol.

3β,17α-Dihydroxy-17β-methyl-D-homoandrost-5-en-17a-one (**4b**).—A solution of 4.84 g. of 3β,17α-dihydroxypregn-5-en-20-one[10] in 400 ml. of glacial acetic acid was treated with 14 ml. of acetic anhydride and 12 ml. of boron trifluoride etherate and left at room temperature overnight. The solution was poured into water and extracted with ether. The ether solution was washed well with water, dilute sodium hydroxide solution, and water again, and then dried over magnesium sulfate. The ether was evaporated on a steam bath, and the residue was recrystallized from methanol to give 4.59 g. (76%) of **3β,17α-diacetoxy-17β-methyl-D-homoandrost-5-en-17a-one**, m.p. 250–252°.

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.14; H, 8.92.

A solution of 4.40 g. of the diacetate in 125 ml. of methanol was treated with 3.5 g. of potassium hydroxide dissolved in 5 ml.

(35) It has been shown that 17β-hydroxy-17-iso-20-ketopregnanes readily form oximes, whereas their 17β-acetate derivatives are quite resistant to oxime formation.[34b]

(36) Melting points were determined on a Fisher-Johns block and are corrected. The ultraviolet spectra were run in methanol. All compounds had infrared spectra which agreed with their assigned structures.

of water, and the resulting solution was refluxed for 1 hr. and then poured into water. The organic material was extracted with dichloromethane. This solution was dried over magnesium sulfate, concentrated to a small volume, diluted with heptane, cooled, and filtered. The crude product, 3.08 g. (91%), m.p. 186–188°, was recrystallized from ethyl acetate–heptane for analysis, m.p. 187–189°, $[\alpha]^{25}D$ −9° (*c* 1.0, MeOH).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.70; H, 9.68.

Zinc Reduction of the Hydrochloride Salt of 3β-Hydroxy-17aα-dimethylamino-17aβ-methyl-D-homoandrost-5-en-17-one (5e).—A solution of 1.04 g. of the hydrochloride salt of **5e** in 150 ml. of acetic acid was treated with 4.0 g. of zinc dust, and the mixture was stirred and heated on a steam bath for 2.25 hr. The solution was cooled, decanted from the zinc, and concentrated to dryness under reduced pressure. The residue was dissolved in ether and water, and the ether layer was washed with dilute hydrochloric acid and with water. The ether solution was then dried over magnesium sulfate and concentrated to dryness. The crude product, which contained some 3-acetate, was dissolved in 70 ml. of methanol and treated with 1.0 g. of sodium hydroxide dissolved in 2 ml. of water. After 1 hr. at room temperature, the solution was poured into water and filtered. The product was recrystallized from methanol, affording 0.52 g. (63%) of 3β-hydroxy-17aβ-methyl-D-homoandrost-5-en-17-one (**17b**): m.p. 222–224°, $[\alpha]^{25}D$ −128° (*c* 1.0, EtOH); lit. m.p. 223–224°, $[\alpha]^{20}D$ −124° (*c* 1.0, EtOH)[20a]; m.p. 220–222°, $[\alpha]^{20}D$ −125° (*c* 1.0, EtOH).[20b]

A solution of 200 mg. of 3β-hydroxy-17aβ-methyl-D-homoandrost-5-en-17-one in 40 ml. of acetic anhydride was refluxed 1 hr., cooled, treated with 50 ml. of methanol, and refluxed an additional 0.5 hr. The solution was cooled and concentrated to dryness under reduced pressure. The residue was recrystallized from heptane to yield 128 mg. (57%) of 3β-acetoxy-17aβ-methyl-D-homoandrost-5-en-17-one (**17c**): m.p. 177–178°, $[\alpha]^{25}D$ −116° (*c* 1.0, EtOH); lit. m.p. 178–179°, $[\alpha]^{20}D$ −114° (*c* 1.0, EtOH)[20a]; m.p. 179–180°, $[\alpha]^{20}D$ −117° (*c* 1.0, EtOH).[20b]

Similar treatment of the hydrochloride salt of 3β-hydroxy-17aα-dimethylamino-17aβ-methyl-D-homoandrostan-17-one (**5f**) afforded 3β-hydroxy-17aβ-methyl-D-homoandrostan-17-one (**17a**) in 42% yield: m.p. 206–209°, $[\alpha]^{25}D$ −48° (*c* 1.0, $CHCl_3$); lit.[34b] m.p. 210–212°, $[\alpha]^{25}D$ −54° (*c* 1.0, $CHCl_3$).

3β,17-Diacetoxy-17a-methylene-D-homoandrost-5-enes (18).—A solution of 490 mg. of purified 3β,17-dihydroxy-17aβ-amino-17aα-methyl-D-homoandrost-5-ene (**15c**), m.p. 261–263°, in 100 ml. of dry acetonitrile was treated with 500 mg. of potassium carbonate and 15 ml. of methyl iodide, and the mixture was stirred and refluxed for 24 hr. The mixture was then cooled and concentrated to dryness under reduced pressure. The residue was extracted well with ether. Evaporation of the ether yielded an oil, which was dissolved in 20 ml. of pyridine, treated with 10 ml. of acetic anhydride, and left overnight at room temperature. The solution was poured into dilute hydrochloric acid and filtered. An infrared spectrum of this crude material showed a weak carbonyl band at 1708 cm.$^{-1}$. Recrystallization from methanol afforded 234 mg. (41%) of epimer A of 3β,17-diacetoxy-17a-methylene-D-homoandrost-5-ene (**18**), m.p. 136–137°, $[\alpha]^{25}D$ −118° (*c* 0.7, $CHCl_3$). The n.m.r. spectrum of this compound exhibited resonances at 62 (19-Me), 66 (18-Me), 121 (acetate Me groups), 136 and 144 (7-H atoms), 276 (3α-H), 299 and 305 (2 sets of doublets, J = 1 c.p.s., for the two protons of the methylene group at 17a), and 325 (6-H and 17-H) c.p.s. The infrared spectrum showed absorption at 3110, 1741, 1640, 1420, and 880 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.64; H, 9.23.

The mother liquors from the purification of the above starting amino alcohol were concentrated to dryness (600 mg.) and treated in the same manner. Recrystallization of the crude product from methanol afforded 241 mg. (35%) of epimer B of 3β,17-diacetoxy-17a-methylene-D-homoandrost-5-ene (**18**), m.p. 170–171°, $[\alpha]^{25}D$ −137° (*c* 1.0, $CHCl_3$). The n.m.r. spectrum of this compound exhibited resonances at 62 (18 and 19 Me), 122 (3β-acetate), 127 (17-acetate), 135 and 143 (7-H atoms), 276 (3α-H), 288 and 291 (2 sets of doublets, J = 1 c.p.s., for the two protons of the methylene group at 17a), and 324 (6-H and 17-H) c.p.s. The infrared spectrum showed absorption at 3120, 1743, 1731, 1651, 1418, and 885 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.69; H, 8.96.

3β-Hydroxy-17α-methyl-D-homoandrost-5-en-17a-one (19c).—A solution of 577 mg. of 3β,17a-dihydroxy-17α-methylamino-17β-methyl-D-homoandrost-5-ene (**16**) in 80 ml. of dry acetonitrile was treated with 12 ml. of methyl iodide and 600 mg. of potassium carbonate. The solution was stirred and refluxed for 24 hr., then cooled and concentrated to dryness under reduced pressure. The residue was slurried with hot water and filtered. The precipitate was dried under reduced pressure to give 442 mg. (84%) of 3β-hydroxy-17α-methyl-D-homoandrost-5-en-17a-one (**19c**), m.p. 178–180°. An analytical sample was prepared by recrystallization from *n*-heptane, m.p. 180–182°, $[\alpha]^{25}D$ −139° (*c* 1.0, $CHCl_3$). The n.m.r. spectrum exhibited resonances at 59 (17-Me; doublet, J = 6 c.p.s.), 60 (19-Me), and 67 (18-Me) c.p.s.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.63; H, 10.26.

3β-Hydroxy-17α-methyl-D-homoandrostan-17a-one (19a).—A solution of 252 mg. of **19c** in 40 ml. of 95% ethanol was treated with 200 mg. of 20% palladium on carbon and hydrogenated at room temperature and pressure. Hydrogen uptake ceased after 1.05 equiv. had been absorbed, and the solution was filtered and concentrated to dryness under reduced pressure. The residue was recrystallized from methanol to give 135 mg. (54%) of 3β-hydroxy-17α-methyl-D-homoandrostan-17a-one, m.p. 208–210°, lit. m.p. 207–209°[23a] and 210°.[23b]

A solution of 85 mg. of **19a** in 5 ml. of acetic anhydride was refluxed 1 hr., cooled, and treated with 5 ml. of methanol. After 3 hr. at room temperature, the solution was concentrated to dryness under reduced pressure. The residue was recrystallized from methanol to yield 59 mg. (56%) of 3β-acetoxy-17α-methyl-D-homoandrostan-17a-one: m.p. 174–174.5°, $[\alpha]^{25}D$ −31° (*c* 1.0, acetone); lit. m.p. 170–171°, $[\alpha]^{26}D$ −30° (acetone)[22f]; m.p. 171°, $[\alpha]^{14}D$ −32° (*c* 0.8, acetone).[23b]

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