TABLE I

EXPERIMENTAL DATA FOR MOLECULAR WEIGHT MEASUREMENTS

Compd.	Concentration G./l.	Concentration M (solute particles) $\times 10^2$	ΔR
$C_8H_{20}I_2N_2$[a]	2.04	1.54	3.50
	4.48	3.38	6.71
$C_7H_{16}IN$[b]	4.68	3.88	7.52
	8.24	6.83	11.90
	12.19	10.11	16.10
$C_6H_{14}IN$[c]	3.53	3.11	6.09
	6.87	6.05	10.56
	10.38	9.14	14.71
	11.22	9.88	15.36
3	5.32	4.30[d]	8.18
	7.90	6.32[d]	10.90
	10.16	8.04[d]	13.30
4	6.09	4.93[d]	9.10
	10.37	8.08[d]	13.35
	11.28	9.10[d]	14.60

[a] N,N,N',N'-Tetramethylpiperazinium diiodide. [b] N,N-Dimethylpiperidinium iodide. [c] N,N-Dimethylpyrrolidinium iodide. [d] Read from plot of ΔR *vs.* M solute particle for standard compounds.

iodide, and N,N-dimethylpyrrolidinium iodide, were prepared using the same stock ethanol that was used as the instrument solvent reference. For each solution, ΔR, a measure of the temperature change caused by solvent condensation in the solutions, was obtained, and these data are included in Table I. A plot of ΔR *vs.* M solute particles gave a smooth curve with steadily decreasing slope. Using this curve, the molar concentration of solute particles for each solution of **3** and **4** was determined corresponding to the observed ΔR. These latter data, which are also included in Table I, were used to calculate the number average molecular weight (NAMW) of **3** and **4**, which were both 125. The theoretical NAMW of **3** and **4** is 127.6; for a piperazine methiodide corresponding to a dimeric product, *i.e.*, **5**, the theoretical NAMW is 170.1.

Reactions of 3 and 4 with Thiosulfate.—The method is patterned after that described in ref. 5a for the assay of aziridines.

A solution was made up to be 0.8 M acetic acid, 0.4 M sodium acetate, 0.250 M sodium thiosulfate, and 0.152 M **3**. The solution was allowed to stand at 20–25° for 12 hr., and the unchanged thiosulfate was titrated with standardized iodine–potassium iodide solution. The thiosulfate concentration was found to be 0.181 M, which indicated that 45% of the aziridinium compound had reacted with thiosulfate. Another solution, made up to be 0.8 M acetic acid, 0.4 M sodium acetate, 0.250 M sodium thiosulfate, and 0.24 M **4**, was allowed to stand for 96 hr. at 20–30°. Titration with standardized iodine–potassium iodide solution indicated that 68% of **4** had reacted with thiosulfate. The concentration of thiosulfate was not affected when similar solutions were prepared in which N,N,N',N'-tetramethylpiperazinium iodide was substituted for the aziridinium compound or in which a quaternary ammonium compound was omitted.

Acknowledgment.—We are most grateful to Mr. E. Pier of Varian Associates for the n.m.r. spectra shown in Figure 1.

The Synthesis of 17β-Amino-17-isoprogesterone

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The Neber rearrangement of 2-(3β-hydroxypregn-5-en-20-ylidine)-1,1,1-trimethylhydrazonium iodide (**2**) proceeded stereospecifically to give 3'-methylspiro-[17(1')β-androst-5-en-17,2'(2'H)-azirin]-3β-ol (**4**). Acid hydrolysis of the azirine afforded 17β-amino-3β-hydroxy-17α-pregn-5-en-20-one (**3a**). When heated, the amino ketone rearranged to 17α-amino-17β-methyl-3β-hydroxy-D-homoandrost-5-en-17a-one (**16a**) *via* the intermediate 17-imino-17aα-methyl-D-homoandrost-5-ene-3β,17aβ-diol (**11a**). The treatment of 17β-dimethylamino-3β-hydroxy-17α-pregn-5-en-20-one (**3c**) with base afforded a mixture of 3β,17aβ-dihydroxy-17aα-methyl- and 3β,17aα-dihydroxy-17aβ-methyl-D-homoandrost-5-en-17-ones (**11b** and **17**).

Substituents in the 17α-position of steroid hormones markedly affect the anabolic, progestational, glucocorticoid, and electrolyte-regulating activities of these compounds.[1] The pharmacological properties of progesterone, in particular, have been enhanced by the introduction of 17α-acyloxy,[2] 17α-alkoxy,[3] 17α-halo,[4] and 17α-alkyl[5] groups. The effect of introducing an amino or acetamino substituent into the 17α-position of progesterone, however, has not yet been investigated, although a synthesis of 17α-amino-11,20-diketopregnanes has been recently described by Winternitz and Engel.[6] In order to ascertain if such substitution would produce a beneficial change in activity, the synthesis of 17-aminoprogesterone and of some of its analogs was undertaken.

One feasible synthetic route to this type of compound was the Neber rearrangement[7] of a derivative of a 20-keto steroid. This reaction, the treatment of a nitrogenous derivative of a ketone (usually an oxime tosylate) with base, has been shown to introduce an amino group on one of the two carbon atoms adjacent to the ketone. Although it has been previously postulated that only α-methyl and α-methylene groups could participate in this rearrangement,[8] recent investigators have shown that an α-methinyl ketone system could also be converted into an α-amino ketone in this manner.[9]

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

(2) K. Junkmann, *Arch. exp. Pathol. Pharmakol.*, **223**, 244 (1954).

(3) J. Fried, E. F. Sabo, P. Grabowich, L. J. Lerner, W. B. Kessler, D. M. Brennan, and A. Borman, *Chem. Ind.* (London), 465 (1961).

(4) C. R. Engel and H. Jahnke, *Can. J. Biochem. Physiol.*, **35**, 1047 (1957); D. J. Marshall and R. Gaudry, *Can. J. Chem.*, **38**, 1495 (1960); R. Deghenghi and R. Gaudry, *ibid.*, **39**, 1553 (1961).

(5) R. Deghenghi, Y. Lefebvre, P. Mitchell, P. F. Morand, and R. Gaudry, *Tetrahedron*, **19**, 289 (1963); R. Deghenghi, C. Revesz, and R. Gaudry, *J. Med. Chem.*, **6**, 301 (1963); M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, **20**, 357 (1964).

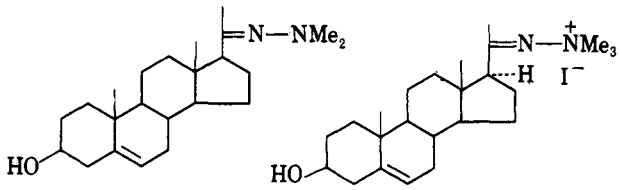
(6) F. Winternitz and C. R. Engel, Abstracts of papers presented at the Second International Symposium on the Chemistry of Natural Products, Prague, Czechoslovakia, Aug.–Sept. 1962, p. 130.

(7) This reaction has been recently reviewed: C. O'Brien, *Chem. Rev.*, **64**, 81 (1964).

(8) M. J. Hatch and D. J. Cram, *J. Am. Chem. Soc.*, **75**, 38 (1953).

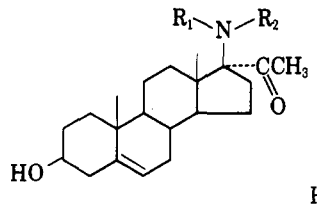
(9) (a) H. E. Baumgarten, J. M. Petersen, and D. C. Wolf, *J. Org. Chem.* **28**, 2369 (1963); (b) R. F. Parcell, *Chem. Ind.* (London), 1396 (1963).

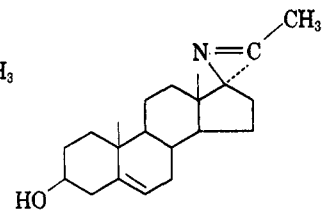
In the present work, a modification of this rearrangement reaction was used, in which the methiodide salt of the dimethylhydrazone of the ketone was used rather than the oxime tosylate.[10] With this highly activated leaving group the Neber rearrangement can be run under conditions sufficiently mild to enable the isolation of the intermediate azirine.[9b] Treatment of the dimethylhydrazone of pregnenolone (**1**)[11] with methyl iodide afforded the quaternary hydrazonium salt **2** which was heated with sodium ethoxide in ethanol and then subjected to acid hydrolysis. The product was separated into a neutral fraction, which was mainly pregnenolone, and a basic fraction, which was later shown to be 17β-amino-17α-pregn-5-en-3β-ol-20-one (**3a**). The yields of these two products were not appreciably altered by extending the time of the reaction from 2 to 24 hr. The origin of the pregnenolone is not clear, for again there was little variation in the yields of these two products whether commercial isopropyl alcohol, commercial absolute ethanol, or carefully dried ethanol was used as a solvent. The need for a very strong base in this reaction was demonstrated by the recovery of starting material in high yield from the treatment of **2** with the sodium salt of 2,2,2-trifluoroethanol in refluxing trifluoroethanol.



1

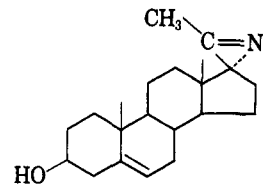
2



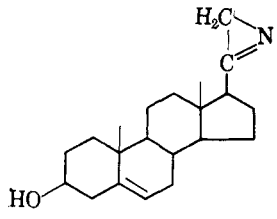


4

3a, $R_1=R_2=H$
b, $R_1=H$; $R_2=Ac$
c, $R_1=R_2=Me$
d, $R_1+R_2=CHPh$
e, $R_1=H$; $R_2=Me$
f, 3-acetate of **b**



5



6

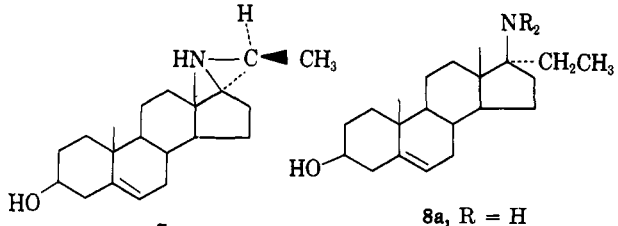
When the quaternary salt **2** was treated with sodium isopropoxide in isopropyl alcohol at room temperature, a mixture of pregnenolone and 3′-methylspiro[17(1′)β-androst-5-en-17,2′(2′H)-azirin]-3β-ol (**4**) was obtained, from which the pure azirine was isolated in low yield by repeated fractional crystallization from ether. This azirine was obtained in much higher yield (67%) with little or no accompanying pregnenolone when a nonhydroxylic solvent such as dimethyl sulfoxide was used.[12] The only by-product isolated from the latter reaction was a small amount of the dimethylhydrazone of pregnenolone (**1**); there was no evidence of the formation of any appreciable amounts of any isomeric azirines (**5** or **6**).

To our knowledge, **4** is the first example of an azirine having purely aliphatic substituents to be isolated from a Neber rearrangement. However, Smolinsky has reported the isolation of *n*-butylazirine from the pyrolysis of 2-azido-1-hexene.[13] The high-melting steroidal azirine **4** was stable at room temperature and was recovered unchanged after 2 weeks from a methanol solution. The infrared spectrum of **4** exhibited a sharp absorption peak of medium intensity at 1754 cm.$^{-1}$, which could be attributed to the highly strained carbon–nitrogen double bond. The n.m.r. spectrum of **4** showed a three-proton singlet at 2.38 p.p.m., demonstrating that the C-21 methyl group was still intact and that ring closure had involved C-17 rather than C-21, thus eliminating **6** as a possible structure. Only 1 equiv. of hydrogen was absorbed when **4** was subjected to catalytic hydrogenation with platinum in ethanol, affording 3′(*S*)-3′-methylspiro[17(1′)-β-androst-5-en-17,2′-aziridin]-3β-ol (**7**). The aziridine ring of **7** was readily opened by treatment with sodium hydrosulfide to the 17-amino-20-thiol, which was not isolated but was reduced with Raney nickel to the 17α-ethyl-17β-aminoandrostene **8a**. The latter compound was treated with methyl iodide and potassium carbonate in refluxing acetonitrile, affording the dimethylamino derivative **8b**. This was identical to an authentic sample of 17β-dimethylamino-17α-ethylandrost-5-en-3β-ol prepared from the known 17β-dimethylamino-17α-ethinylandrost-5-en-3β-ol (**9**)[14] by catalytic reduction with platinum in ethanol and acetic acid. Since the two-carbon side chain of the starting quaternary salt **2** was shown to have retained the 17β-conformation by hydrolysis under neutral conditions to pregnenolone, it was evident that inversion had occurred at C-17 during the Neber rearrangement to form the azirine **4**, and that the amino ketone **3a** was probably a 17β-amino-17α-pregn-5-en-20-one rather than the desired 17α-amino epimer. This was verified by the acid-catalyzed hydrolysis of the azirine **4** to give the same amino ketone **3a**. It is interesting to note that, when **9** was reduced instead with palladium on carbon in ethanol–acetic acid, hydrogenolysis of the dimethylamino group occurred and the crude product isolated after the absorption of 2 equiv. of hydrogen possessed no basic amine group.[15]

The stereochemical configuration produced at C-3′ (or C-20) in the formation of the aziridine **7** was shown to be 3′(*S*). The N-nitroso derivative of **7**, formed at −80° by treatment with 1 equiv. each of nitrosyl chloride and triethylamine, decomposed spontaneously

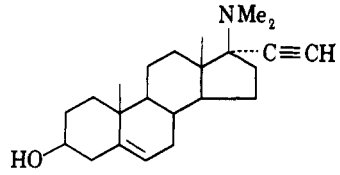
(10) P. A. S. Smith and E. E. Most, *J. Org. Chem.*, **22**, 358 (1957).
(11) R. H. Wiley and S. H. Chang, *J. Med. Chem.*, **6**, 610 (1963).
(12) A preliminary account of this work has been reported: D. F. Morrow and M. E. Butler, *J. Heterocyclic Chem.*, **1**, 53 (1964).
(13) G. Smolinsky, *J. Org. Chem.*, **27**, 3557 (1962).
(14) D. Lednicer and J. C. Babcock, *ibid.*, **27**, 2541 (1962).
(15) A similar hydrogenolysis of a tertiary 17β-alcohol under these conditions was observed by Mr. W. M. Pearlman of our high pressure laboratory.

between −20 and −17° as the temperature of the solution was slowly raised to room temperature to give "*trans*"-pregna-5,17(20)-dien-3β-ol (**10**).[16] The decomposition of N-nitrosoaziridines has been recently shown to proceed stereospecifically to give that olefin which corresponds geometrically with the starting aziridine.[17] Thus the "*trans*"-pregnadiene **10** must have originated from a 3′(*S*)-configuration of **7**, for the 3′(*R*)-epimer would have given "*cis*"-pregna-5,17(20)-dien-3β-ol. The configuration of **7** was previously postulated as 3′(*R*) on the assumption that the determining factor in its formation was steric control of the hydrogenation of the azirine **4**.[12] However, this assumption was contradicted by the results of the nitrosyl chloride degradation of **7**. If, however, the reduction proceeded *via* a two-stage ionic mechanism similar to that advanced by Brewster to explain the catalytic reduction of carbon–oxygen double bonds in neutral solution,[18] the protonation of the transient carbanion formed at C-3′ by a solvent molecule would lead to the thermodynamically more stable 3′(*S*)-aziridine **7**.[19] An attempt to synthetize **7** independently by the addition of iodine isocyanate to the 17(20)-double bond of **10** and subsequent hydrolysis and ring closure[20] was unsuccessful.

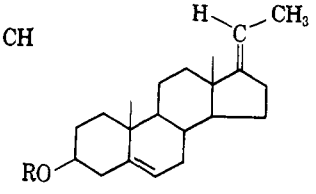


7

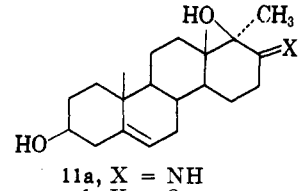
8a, R = H
b, R = Me



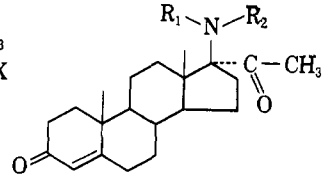
9



10a, R = H
b, R = Ac



11a, X = NH
b, X = O
c, X = <NH2 H
d, X = NOH
e, X = <NH2 H,5α-dihydro



12a, $R_1 = R_2 = H$
b, $R_1 = H$; R_2 = Ac
c, $R_1 = R_2$ = Me
d, $R_1 + R_2$ = CHPh
e, $R_1 = H$; R_2 = Me

The amino ketone **3a** was isolated and characterized as the hydrochloride salt, for the free base was unstable above room temperature. Recrystallization of the crude free base from methanol caused a marked change in the infrared spectrum of this compound. The carbonyl peak at 1699 cm.$^{-1}$ greatly diminished in intensity with the concurrent appearance of a new peak at 1655 cm.$^{-1}$, apparently due to the formation of a carbon–nitrogen double bond. The process was accelerated at higher temperatures, and at 200° the amino ketone **3a** was completely rearranged in 5 min. The product, 17-imino-17aα-methyl-D-homoandrost-5-ene-3β,17aβ-diol (**11a**), was identified by n.m.r. and infrared spectra, and by catalytic reduction with platinum in acetic acid to 17-amino-17aα-methyl-D-homoandrostane-3β,17aβ-diol (**11e**)[21]; this aminodiol was identical with an authentic sample prepared by reduction of the oxime of 3β,-17aβ-dihydroxy-17aα-methyl-D-homoandrost-5-en-17-one (**11d**).[21] It is interesting to note that, when the solvent for the reduction of the hydroxyimine **11a** was changed instead to a 1:1 mixture of ethanol and acetic acid, only 1 equiv. of hydrogen could be introduced and the product was 17-amino-17aα-methyl-D-homoandrost-5-ene-3β,17aβ-diol (**11c**).

The rearrangement of **3a** to form **11a** is analogous to the thermal rearrangement of 3β,17β-dihydroxy-17α-pregn-5-en-20-one to the corresponding D-homo ketone, 3β,17aβ-dihydroxy-17aα-methyl-D-homoandrost-5-en-17-one (**11b**).[22] The common driving force for these rearrangements is undoubtedly the greater stability achieved in forming the C–D *trans*-decalin system from the strained *trans*-hydrindane system. The greater ease with which the amino ketone rearranged in comparison with the hydroxy ketone parallels similar reactions in simpler systems in which α-amino ketones are rearranged under conditions to which the corresponding α-hydroxy ketones are stable.[23]

Treatment of the crude amino ketone **3a** with acetic anhydride in methanol produced the amide **3b**, which was shown to be homogeneous by both vapor phase and thin layer chromatography. On this basis the free amino ketone **3a** formed in the Neber rearrangement of **2** was shown to be essentially one isomer. The amide, unlike the free amine **3a**, was stable to heat and was recovered unchanged after 11 hr. at 230°. Methylation of the primary amine **3a** with methyl iodide and potassium carbonate in acetonitrile afforded the dimethylamino derivative **3c**. A large degree of steric hindrance about the nitrogen atom was indicated by the isolation of **3c** rather than a quaternary salt under these conditions. Condensation of **3a** with benzaldehyde produced the anil **3d**. The anil was treated with methyl iodide in acetonitrile to form the methiodide salt, which hydrolyzed when heated in water to give 17β-methylamino-17α-pregn-5-en-3β-ol-20-one (**3e**). The anil was also oxidized under Oppenauer conditions to the corresponding Δ^4-3-ketone **12d**, which was hydrolyzed with dilute acid to produce 17β-amino-17α-pregn-4-ene-3,20-dione (**12a**). The oxidized anil **12d** was also converted to its methiodide salt and hydrolyzed to the monomethylamino derivative **12e**. Methylation of **12a** with

(16) (a) L. Ruzicka, M. W. Goldberg, and E. Hardegger, *Helv. Chim. Acta*, **22**, 1294 (1939); (b) A. Butenandt, J. Schmidt-Thomé, and H. Paul, *Ber.*, **72**, 1112 (1939); (c) L. F. Fieser and M. Fieser, *Experientia*, **4**, 285 (1948).

(17) E. Bertele, H. Boos, J. D. Dunitz, F. Elsinger, A. Eschenmoser, I. Felner, H. P. Gribi, H. Gschwend, E. F. Meyer, M. Pesaro, and R. Scheffold, *Angew. Chem.*, **76**, 393 (1964), footnote 12; R. D. Clark and G. K. Helmkamp, *J. Org. Chem.*, **29**, 1316 (1964).

(18) J. H. Brewster, *J. Am. Chem. Soc.*, **76**, 6361 (1954).

(19) Other examples of similar two-stage hydrogenations have been reported. See R. L. Burwell, Jr., *Chem. Rev.*, **57**, 895 (1957), and references therein.

(20) A. Hassner and C. Heathcock, *Tetrahedron Letters*, 393 (1963).

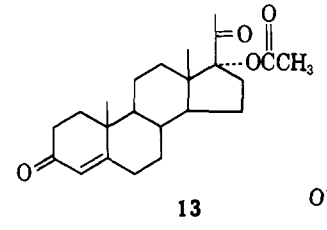
(21) D. A. Prins and C. W. Shoppee, *J. Chem. Soc.*, 494 (1946).

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

(23) C. L. Stevens, R. D. Elliott, and B. L. Winch, *J. Am. Chem. Soc.*, **85**, 1464 (1963).

methyl iodide and potassium carbonate afforded 17β-dimethylamino-17α-pregn-4-ene-3,20-dione (**12c**). This compound was also prepared by an Oppenauer oxidation of the Δ⁵-3β-hydroxydimethylamino derivative **3c**. However, a large portion of the starting material remained unoxidized, because it formed a sparingly soluble complex with the aluminum isopropoxide. The oxidized product was separated from the starting material by formation of the 3-(N-pyrrolidyl)enamine of **12c**, which precipitated from a methanol solution of the mixture, and subsequent hydrolysis back to the Δ⁴-3-ketone. The amide **12b** was prepared by a Jones oxidation[24] of the Δ⁵-3β-hydroxyamide **3b**. The structures of all of these compounds were verified by their infrared and n.m.r. spectra (with the exception of **3b**, which was too insoluble in deuteriochloroform for the latter to be obtained). The presence of the 17α-acetyl group was shown by a strong carbonyl band in the infrared spectra at 1702 to 1691 cm.$^{-1}$ and by a three-proton singlet at 2.10 to 2.21 p.p.m. in the n.m.r. spectra, which indicated that rearrangement to the isomeric D-homo compounds (*e.g.*, **3a** → **11a**) had not occurred during the preparation of these derivatives. The monomethylamino derivative **3e**, like the primary amine, was unstable to heat and began to rearrange when heated in chloroform. However, the dimethylamino derivative **3c** was more stable and was recovered essentially unchanged when heated for 6 hr. at 100° either neat or in toluene solution. This parallels the earlier findings of Stevens, who showed that tertiary α-amino ketones do not rearrange with the same facility as the corresponding primary and secondary α-amino ketones.[23]

Further confirmation that inversion had occurred at C-17 during the Neber rearrangement of **2** was afforded by the n.m.r. spectrum of 17β-acetamino-17α-pregn-4-ene-3,20-dione (**12b**). A 17α-acetyl group has been shown to cause a marked downfield shift of the 18-methyl resonance.[25] For example, the 18-methyl group of 17α-acetoxyprogesterone (**13**)[26] produced a peak at 0.69 p.p.m., whereas that of 17β-acetoxy-17-isoprogesterone (**14**)[27] exhibited a resonance at 1.04 p.p.m. The spectrum of **12b** exhibited a peak at 1.05 p.p.m. due to the 18-methyl group, indicating a β-acetamino and α-acetyl configuration at C-17.



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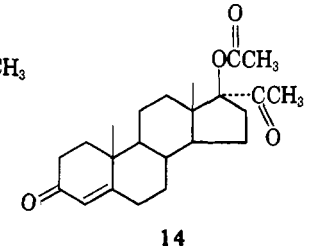

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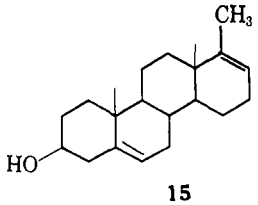

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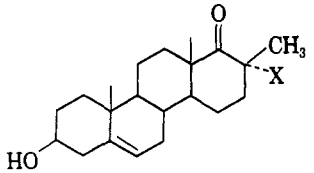
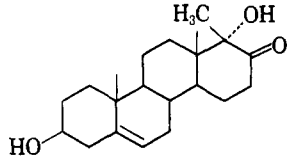


16a, X = NH₂
b, X = NHMe
c, X = $\overset{+}{N}$HMe₃I⁻
d, X = NHAc

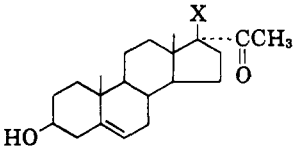


17

The optical rotatory dispersion (O.R.D.) curves of this series of amino steroids are tabulated in Table I. Although the O.R.D. curves of 17α-pregnane-3α-ol-20-one acetate[28] and 5α,17α-pregnane-3β,17β-diol-20-one diacetate[29] possessed negative Cotton effects, the curves of the 17β-amino steroids showed positive Cotton effects. The amplitude of the curves increased as the steric bulk of the 17β-substituent increased. Presumably the introduction of a bulky substituent at the 17β-position causes the 17α-acetyl group to assume a different spatial orientation in relation to the remainder of the steroid molecule than it does when the 17β-substituent is small, thus producing an inversion of the sign of the Cotton effect. A similar effect has been noted with the introduction of bulky groups into the 17α-position of 17β-acetyl steroids.[30]

TABLE I

OPTICAL ROTATORY DISPERSION CURVES OF 17β-AMINO-17α-PREGN-5-EN-20-ONES[a]



X	Compd.	λ_1[b]	$[\alpha_1]$[b]	λ_2[c]	$[\alpha_2]$[c]
H[d] (5β-3-OAc)		310	−1280	267	+1680
OAc[e] (5α-3-OAc)		307.5	−377	262.5	+584
NH_2	**3a**	331	−90 (max)	297	−841
NH_3^+	**3a**	311	+235	...	...
NHMe	**3e**	336	+375	294	−1385
NH_2Me^+	**3e**	319	+454	...	...
NMe_2	**3c**	342	+2125	286	−3340
$NHMe_2^+$	**3c**	331	+906	274	−1533
NHAc	**3b**	318	+165	...	...

[a] The use of a Rudolph automatic recording spectropolarimeter was made available to us through the courtesy of Professor M. L. Wolfrom of Ohio State University. The curves were obtained from a 0.2% solution in methanol in a 1.0-cm. tube at 28°. [b] Wave length (in mμ) and amplitude (in degrees) of first extremum. [c] Wave length (in mμ) and amplitude (in degrees) of second extremum, if above 260 mμ. [d] See ref. 28. [e] See ref. 29.

A Wolffe–Kishner reduction of 17β-dimethylamino-3β-hydroxy-17α-pregn-5-en-20-one (**3c**) afforded 17a-methyl-D-homoandrosta-5,17-dien-3β-ol (**15**).[31] The formation of this product was very unexpected, since a normal Kishner elimination[32] should lead to pregna-5,17(20)-dien-3β-ol (**10a**). The formation of the D-homo steroid structure from **3c** was shown to involve a rearrangement which also occurred in the absence of hydrazine. Heating a solution of **3c** in diethylene

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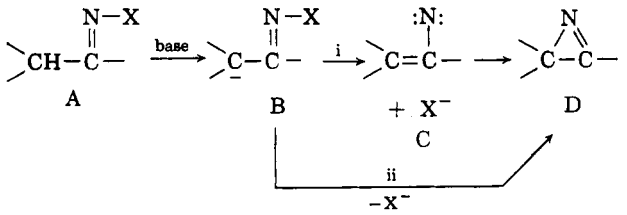
glycol with potassium hydroxide on a steam bath converted a portion of the amino steroid into a mixture of 3β,17aα-dihydroxy-17aβ-methyl-D-homoandrost-5-en-17-one (**17**)[33] and 3β,17aβ-d hydroxy-17aα-methyl-D-homoandrost-5-en-17-one (**11b**),[33] both of which are known to yield 17a-methyl-D-homoandrosta-5,17-dien-3β-ol (**15**) upon Wolffe–Kishner reduction.[31,34] A more detailed study of this rearrangement is currently in progress.

When either the amino ketone **3a**, the hydroxyimine **11a**, or the methylamino ketone **3e** was heated at 200° for a prolonged period of time (6–10 hr.), further rearrangement occurred to give 17α-amino- (or methylamino-) 17β-methyl-3β-hydroxy-D-homoandrost-5-en-17a-one (**16a,b**). Other examples of this type of thermal rearrangement of an amino ketone to yield another amino ketone are known,[23] and the conversion of steroidal α-hydroxyimines to rearranged α-amino ketones was recently reported.[35] The methylamino compound **16b** was identical to a sample prepared previously by heating either 3β,17aβ-dihydroxy-17aα-methyl-D-homoandrost-5-en-17-one (**11b**) or 3β,17aα-dihydroxy-17aβ-methyl-D-homoandrost-5-en-17-one (**17**) with methylamine at 200°.[35] The intermediates in these reactions are presumably the corresponding N-methylimines (**11**, X = NCH_3 or its 17a-epimer). The structure of the primary amine **16a** was related to that of the secondary amine by the conversion of both compounds to the same quaternary iodide **16c**.[35]

Although the exact mechanism of the Neber rearrangement is still uncertain, it has been postulated that the initial abstraction of an α-proton by base to give the carbanion B is followed by loss of the leaving group X (tosylate or, in this case, trimethylamine) affording an α,β-unsaturated nitrene C, which then attacks the double bond to give an azirine D (path i).[36] Alternatively, the carbanion B may undergo a direct 1,3-displacement of X at the doubly bonded nitrogen atom to



give an azirine directly (path ii).[36] It has been shown that the configuration of the ketone derivative (*syn* or *anti*) has little, if any, influence upon the direction of the reaction.[8,36] In the case of unsymmetrical ketones bearing active hydrogens on both α-carbon atoms, in which there was a considerable difference between the acidities of these α-protons, the Neber rearrangement inserted the amine group exclusively upon that carbon atom bearing the more acidic hydrogen atom (*i.e.*, on that carbon which formed the more stable enolate carbanion) irrespective of the configuration of the ketone derivative.[36] House and Kramar have shown that for unsymmetrical ketones having only alkyl substituents on the α-carbons, the less substituted enolate anion is more stable than the more highly substituted one in dimethoxyethane solvent.[37] Although the proportion of the more highly substituted enolate anion is increased somewhat in more polar solvents, such as dimethyl sulfoxide, the data of House and Kramer indicate that treatment of a 20-keto steroid with base affords an approximately 4:1 ratio of the $\Delta^{20,21}$- and $\Delta^{17(20)}$-enolate anions. Thus, if the relative acidities of the α-protons were the only factor determining the direction of this reaction, the major product from the present reaction should have been the isomeric azirine **6**, which, upon hydrolysis, would have afforded 21-aminopregnenolone. Since this azirine was formed only in very low yield, if at all, some additional factors must be considered in explaining the formation of **4** as the major product. Perhaps, in a case such as this where there is a relatively large concentration of the minor enolate anion in the reaction mixture (*ca.* 20%), the configuration of the ketone derivative does have a directing influence upon the reaction. In either path i or ii, a more favorable backside attack of the C-17 enolate anion to dispel the trimethylamine molecule, which lies away from the C-17 side of the ketone, would be preferred to the frontside attack of the C-21 anion. Alternatively, if the nitrene (path i) is a discrete intermediate in this reaction, the relative stabilities of the two possible isomeric nitrenes might influence the course of the rearrangement. The small, uncharged, and unsolvated nitrenes would be far more comparable to the corresponding enol acetates than to the large, charged, and solvated enolate anions, and on this basis one might expect the $\Delta^{17(20)}$-nitrene to be more stable than the Δ^{20}-isomer.[38]

Little is known about the stereochemical configurations of amino groups introduced *via* a Neber rearrangement. It has been shown that the Neber rearrangement of cyclohexanone oxime tosylates leads to equatorial 2-aminocyclohexanones,[7,39] but it is not clear if this orientation could have resulted simply from base-catalyzed equilibration of the initial product to the more stable epimer. Although in the present case epimerization at C-17 should occur rapidly once the carbanion B is formed,[40] epimerization of the product **4** is not possible once the pseudo-equatorial C-17β–N bond is formed.

The formation of the C-17β–N bond (**4**) rather than the epimeric C-17α–N bond (**5**) can be explained by an examination of the transition states leading to these two epimeric azirines. In either of the two postulated mechanisms (paths i and ii), the transition states leading to the azirines should greatly resemble these intermediates, and on this basis, the configuration at C-17 should correspond to that of the more stable azirine. Inspection of models of the two epimeric azirines **4** and **5** indicates that there should be little difference in the stabilities of these two compounds. However, the two alternate transition states (in i or ii) leading to the C-17α–N azirine **5** involve a fairly close proximity of the C-18 and C-21 methyl groups. The steric repul-

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(40) The same carbanion and thus the same azirine **4** would be the expected product formed from the epimeric 17α-pregnan-20-one derivative.

sion of these two groups must cause the reaction to proceed stereoselectively to the epimeric azirine **4** through the lower energy C-17β–N transition state, in which no such interaction occurs.

Experimental[41]

2-(3β-Hydroxypregn-5-en-20-ylidine)-1,1,1-trimethylhydrazonium Iodide (2).—A suspension of 74.2 g. of the dimethylhydrazone of pregnenolone[11] in 400 ml. of benzene and 2000 ml. of acetonitrile was treated with 250 ml. of methyl iodide and stirred at room temperature for 24 hr. During this time the hydrazone slowly dissolved and the quaternary salt began to precipitate. At the end of the 24-hr. period, 2000 ml. of ether was added; the product was separated by filtration, washed well with ether, and dried. The crude salt, 84.7 g. (82%), was sufficiently pure to be used directly in the next step. A sample was recrystallized from acetonitrile for analysis, m.p. 214–215°.

Anal. Calcd. for $C_{24}H_{41}IN_2O$: C, 57.59; H, 8.26; I, 25.36; N, 5.60. Found: C, 57.48; H, 8.36; I, 25.13; N, 5.66.

3′-Methylspiro[17(1′)β-androst-5-en-17,2′(2′H)-azirin]-3β-ol (4).—A solution of 10.00 g. of 2-(3β-hydroxypregn-5-en-20-ylidine)-1,1,1-trimethylhydrazonium iodide (**2**) in 125 ml. of dimethylsulfoxide was treated with 1.10 g. of a 51% suspension of sodium hydride in mineral oil and stirred at room temperature for 3 hr. The solution then was poured into 600 ml. of water and extracted with 1200 ml. of a 1:1 benzene–ether mixture. The organic layer was washed well with water, dried over magnesium sulfate, and concentrated to dryness on a steam bath. The residue was recrystallized from ether, affording 4.45 g. of crude product, m.p. 215–220°, which was sublimed at 170° (0.1 mm.) to give 4.21 g. (67%) of 3′-methylspiro[17(1′)β-androst-5-en-17,2′(2′H)-azirin]-3β-ol, m.p. 229–231°. A sample was recrystallized from acetonitrile for analysis, m.p. 234–236°, $[\alpha]^{24}D$ −93°, ν_{max} 1754 cm.$^{-1}$ (KBr) and 1751 cm.$^{-1}$ ($CHCl_3$). The n.m.r. spectrum exhibited three sharp peaks, each of which integrated for three protons, at 0.85 (18-Me), 1.01 (19-Me), and 2.38 (3′-Me) p.p.m.

Anal. Calcd. for $C_{21}H_{31}NO$: C, 80.46; H, 9.97; N, 4.47. Found: C, 80.35; H, 9.95; N, 4.61.

The residue from the sublimation was shown to be mainly the dimethylhydrazone of pregnenolone by thin layer chromatography and by comparison of infrared spectra. The mother liquor from the recrystallization was concentrated to an oil which, after extraction with a small amount of petroleum ether to remove the mineral oil, weighed 0.83 g. The infrared spectrum of the oil exhibited only very weak absorption in the 1750-cm.$^{-1}$ region. Attempts to isolate crystalline material from this fraction were unsuccessful, and sublimation (170°, 0.1 mm.) afforded only a very small amount of material with a weak absorption bond at 1710 cm.$^{-1}$ in the infrared spectrum.

7β-Amino-3β-hydroxy-17α-pregn-5-en-20-one (3a). A. From 21-(3β-Hydroxypregn-5-en-20-ylidine)-1,1,1-trimethylhydrazonium Iodide.—A solution of 15.00 g. of **2** in 100 ml. of dimethyl sulfoxide was diluted with 1000 ml. of absolute ethanol, treated with 7.50 g. of a 51% dispersion of sodium hydride in mineral oil, and refluxed for 2 hr. The solution then was cooled to room temperature, concentrated under reduced pressure to about 150 ml., and poured into 1000 ml. of water. The suspension was extracted with a 1:1 mixture of benzene and ether, and the organic layer was washed well with water, dried over magnesium sulfate, and concentrated to an oil on a steam bath. The oil was dissolved in 250 ml. of ethanol, treated with 100 ml. of 6 *N* hydrochloric acid, and warmed on a steam bath for 30 min. The solution then was poured into 3 l. of water and filtered to give 5.4 g. of crude pregnenolone, identified by its infrared spectrum. The filtrate was washed once with ether, cooled in ice, and neutralized with a cold concentrated solution of sodium hydroxide. The product was separated by filtration, washed well with water, and dried in air, affording 4.03 g. (40%) of crude 17β-amino-3β-hydroxy-17α-pregn-5-en-20-one. The crude material melted at 210°, resolidified, and remelted at 251–254°. The n.m.r. spectrum of the crude base exhibited three sharp peaks, each of which integrated for three protons, at 0.90 (18-Me), 1.02 (19-Me), and 2.20 (21-Me) p.p.m.

The **hydrochloride salt** was prepared by the addition of anhydrous hydrogen chloride to an ether solution of the free base. The salt was recrystallized from methanol–ethyl acetate, m.p. 256–258°, $[\alpha]^{26}D$ −7°.

Anal. Calcd. for $C_{21}H_{34}ClNO_2$: C, 68.68; H, 9.32; Cl, 9.64; N, 3.81. Found: C, 68.54; H, 9.49; Cl, 9.35; N, 3.71.

B. From 3′-Methylspiro[17(1′)β-androst-5-en-17,2′(2′H)-azirin]-3β-ol.—A solution of 200 mg. of **4** in 20 ml. of ethanol was treated with 2 ml. of 6 *N* hydrochloric acid, warmed on a steam bath for 1 hr., and poured into water. The solution was washed with ether, cooled, and neutralized with cold concentrated sodium hydroxide solution. The precipitate was filtered, washed well with water, and dried under reduced pressure to give 129 mg. (61%) of crude 17β-amino-3β-hydroxy-17α-pregn-5-en-20-one (**3a**). The infrared spectrum of the product was identical with one of the free base prepared directly from **2**.

17β-Acetamino-3β-hydroxy-17α-pregn-5-en-20-one (3b).—A solution of 2.61 g. of crude 17β-amino-3β-hydroxy-17α-pregn-5-en-20-one (**3a**) in 250 ml. of methanol was treated with 20 ml. of acetic anhydride and left overnight at room temperature. The solution was concentrated to dryness under reduced pressure, and the residue was recrystallized from methanol to give 2.18 g. (74%) of 17β-acetamino-3β-hydroxy-17α-pregn-5-en-20-one, which did not melt below 310°, $[\alpha]^{24}D$ −31°.

Anal. Calcd. for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.45; N, 3.75. Found: C, 73.75; H, 9.40; N, 3.77.

17β-Acetamino-3β-acetoxy-17α-pregn-5-en-20-one (3f).—A suspension of 850 mg. of 17β-acetamino-3β-hydroxy-17α-pregn-5-en-20-one (**3b**) in 40 ml. of acetic anhydride was refluxed for 1 hr., cooled, and treated cautiously with 50 ml. of methanol. The solution then was refluxed an additional 15 min., cooled to room temperature, and concentrated to dryness under reduced pressure. The residue was recrystallized from methanol, affording 700 mg. (74%) of 17β-acetamino-3β-acetoxy-17α-pregn-5-en-20-one, m.p. 284–285°, $[\alpha]^{24}D$ −39°.

Anal. Calcd. for $C_{25}H_{37}NO_4$: C, 72.25; H, 8.98; N, 3.37. Found: C, 72.42; H, 9.05; N, 3.58.

17β-Dimethylamino-3β-hydroxy-17α-pregn-5-en-20-one (3c).—A solution of 3.42 g. of crude 17β-amino-3β-hydroxy-17α-pregn-5-en-20-one (**3a**) in 60 ml. of methanol and 340 ml. of acetonitrile was treated with 3.8 g. of potassium carbonate and 49 ml. of methyl iodide, and the mixture was stirred at room temperature overnight. In the morning the mixture was refluxed for 3 hr., cooled to room temperature, and concentrated to dryness under reduced pressure. The residue was dissolved in ether and water, and the organic layer was washed with water, dried over magnesium sulfate, and treated with anhydrous hydrogen chloride. The precipitate was separated by filtration, affording 2.91 g. of crude product. The salt was recrystallized from isopropyl alcohol to give 1.87 g. (46%) of the **hydrochloride salt** of 17β-dimethylamino-3β-hydroxy-17α-pregn-5-en-20-one, m.p. 243–245° (on at 235°), $[\alpha]^{26}D$ +4° (*c* 1.0, $CHCl_3$).

Anal. Calcd. for $C_{23}H_{38}ClNO_2$: C, 69.75; H, 9.67; Cl, 8.95; N, 3.54. Found: C, 69.60; H, 9.76; Cl, 9.03; N, 3.56.

The free base was prepared by neutralizing a water solution of the hydrochloride salt with potassium carbonate, filtering the resulting precipitate, and recrystallizing it from ether–petroleum ether, m.p. 76–78° and 143–145°, $[\alpha]^{26}D$ +36°.

Anal. Calcd. for $C_{23}H_{37}NO_2$: C, 76.83; H, 10.37; N, 3.90. Found: C, 76.68; H, 10.42; N, 3.91.

17β-Benzylideneamino-3β-hydroxy-17α-pregn-5-en-20-one (3d).—A solution of 5.90 g. of crude 17β-amino-3β-hydroxy-17α-pregn-5-en-20-one (**3a**) in 750 ml. of benzene was treated with 12 ml. of benzaldehyde and refluxed 1.5 hr., separating water as it formed. The solution then was cooled and concentrated to dryness under reduced pressure. The residue was recrystallized from acetonitrile, affording 5.06 g. (68%) of 17β-benzylideneamino-3β-hydroxy-17α-pregn-5-en-20-one, m.p. 221–223°, $[\alpha]^{24}D$ +142° (*c* 1.0, $CHCl_3$), λ_{max} 281 mμ (ϵ 2050) and 249 mμ (ϵ 20,400).

Anal. Calcd. for $C_{28}H_{37}NO_2$: C, 80.15; H, 8.89; N, 3.34. Found: C, 80.26; H, 8.81; N, 3.38.

17β-Methylamino-3β-hydroxy-17α-pregn-5-en-20-one (3e).—A suspension of 720 mg. of 17β-benzylideneamino-3β-hydroxy-17α-

(41) Melting points were determined on a Fisher-Johns block and are corrected. The ultraviolet spectra were run in methanol. Optical rotations were determined on a 1% solution in methanol unless otherwise noted. The n.m.r. spectra were obtained on a Varian A-60 instrument; the spectra were determined in deuteriochloroform solution, and the shifts are expressed as parts per million downfield from tetramethylsilane, used as an internal standard. All compounds had infrared spectra which agreed with the assigned structures.

pregn-5-en-20-one (**3d**) in 250 ml. of acetonitrile was treated with 12 ml. of methyl iodide and stirred and refluxed for 3 days. The solution then was cooled to room temperature, concentrated under reduced pressure to about 20 ml., and diluted with 500 ml. of ether. The precipitate was filtered, washed well with ether, and dried in air, affording 918 mg. of crude methiodide salt. The salt was dissolved in 500 ml. of water and 5 ml. of 12 *N* hydrochloric acid and stirred for 0.5 hr. at room temperature. The solution was washed with ether, neutralized with potassium carbonate, and filtered. The precipitate was washed well with water and dried in air, affording 578 mg. (97%) of crude 17β-methylamino-3β-hydroxy-17α-pregn-5-en-20-one, $[\alpha]^{24}D$ −49° (*c* 1.0, $CHCl_3$). The compound rearranged when heated.

The **hydrochloride salt** was prepared in the usual manner and crystallized from isopropyl alcohol only after a few drops of water was added. The salt was obtained as a monohydrate, m.p. 216–217° dec. (on at 205°), $[\alpha]^{24}D$ +5°.

Anal. Calcd. for $C_{22}H_{36}ClNO_2 \cdot H_2O$: C, 66.05; H, 9.57; Cl, 8.86; N, 3.50. Found: C, 66.27; H, 9.69; Cl, 8.92; N, 3.48.

3′(*S*)-3′-Methylspiro[17(1′)β-androst-5-en-17,2′-aziridin]-3β-ol (7).—A solution of 8.95 g. of 3′-methylspiro[17(1′)β-androst-5-en-17,2′(2′H)-azirin]-3β-ol (**4**) in 250 ml. of absolute ethanol was treated with 1.5 g. of platinum oxide and hydrogenated at 50 p.s.i. and room temperature until hydrogen uptake ceased. One equivalent of hydrogen was absorbed. The catalyst was removed by filtration and the solution was concentrated to dryness under reduced pressure. The residue was recrystallized from ether, affording 7.16 g. (80%) of 3′(*S*)-3′-methylspiro[17-(1′)β-androst-5-en-17,2′-aziridin]-3β-ol, m.p. 199–203°. A sample was recrystallized from ether for analysis, m.p. 200–202°, $[\alpha]^{24}D$ −61°. The n.m.r. spectrum exhibited resonances at 0.94 (18-Me), 1.02 (19-Me), and a doublet (J = 5 c.p.s.) which integrated for three protons centered at 1.33 (3′-Me) p.p.m.

Anal. Calcd. for $C_{21}H_{33}NO$: C, 79.94; H, 10.54; N, 4.44. Found: C, 79.73; H, 10.29; N, 4.42.

17β-Dimethylamino-3β-hydroxy-17α-pregn-5-ene (8b). A. From 3′(*S*)-3′-Methylspiro[17(1′)β-androst-5-en-17,2′-aziridin]-3β-ol (7).—A solution of 4.06 g. of **7** in 500 ml. of absolute ethanol was treated with 4.0 g. of sodium hydrosulfide and stirred and refluxed overnight. The solution was cooled and concentrated to dryness under reduced pressure. The residue was dissolved in ether and dilute ammonium chloride solution, and the organic layer was washed well with water, dried over magnesium sulfate, and concentrated on a steam bath. The oily residue was dissolved in 600 ml. of methanol, treated with 40 g. of Raney nickel, and stirred and refluxed for 4 hr. The solution was cooled, filtered, and concentrated to dryness under reduced pressure. The residue was extracted with anhydrous ether, and hydrogen chloride was added to the ether solution. The precipitate was separated by filtration, washed with ether, and dried, affording 2.69 g. (59%) of the crude hydrochloride salt of 17β-amino-3β-hydroxy-17α-pregn-5-ene (**8a**).

A solution of 170 mg. of this salt in 10 ml. of absolute ethanol and 40 ml. of acetonitrile was treated with 400 mg. of potassium carbonate and 7 ml. of methyl iodide and stirred at room temperature for 4 hr. The mixture was concentrated to dryness under reduced pressure and the residue was extracted with boiling ether. The ether solution was filtered and concentrated to dryness on a steam bath. The residue was recrystallized from methanol, affording 76 mg. (46%, 27% over-all from **7**) of 17β-dimethylamino-3β-hydroxy-17α-pregn-5-ene, m.p. 156–157°, $[\alpha]^{24}D$ −62°.

Anal. Calcd. for $C_{23}H_{39}NO$: C, 79.94; H, 11.38; N, 4.05. Found: C, 79.88; H, 11.53; N, 4.06.

B. From 17β-Dimethylamino-3β-hydroxy-17α-pregn-5-en-20-yne (9).—A solution of 1.11 g. of **9**[14] in 150 ml. of methanol and 5 ml. of acetic acid was treated with 400 mg. of platinum oxide and hydrogenated at room temperature and atmospheric pressure until 2 equiv. of hydrogen had been absorbed (*ca.* 1 hr.). The catalyst was removed by filtration and the solution was concentrated to dryness under reduced pressure. The residue was dissolved in ether and treated with anhydrous hydrogen chloride. The precipitate was filtered and recrystallized from isopropyl alcohol, affording 0.65 g. (52%) of the **hydrochloride salt** of 17β-dimethylamino-3β-hydroxy-17α-pregn-5-ene, m.p. 281–283°, $[\alpha]^{24}D$ −70°.

Anal. Calcd. for $C_{23}H_{40}ClNO$: C, 72.31; H, 10.55; Cl, 9.28; N, 3.67. Found: C, 72.21; H, 10.50; Cl, 9.18; N, 3.70.

The free base was prepared in the usual manner and was recrystallized from methanol, m.p. 157–158°. The melting point of a mixture of the compounds prepared from the two different starting materials **7** and **9** was 156–157°.

***trans*-Pregna-5,17(20)-dien-3β-ol (10a).**—A stirred solution of 2.00 g. of 3′(*S*)-3′-methylspiro[17(1′)β-androst-5-en-17,2′-aziridin]-3β-ol (**7**) in 200 ml. of 1,2-dimethoxyethane was cooled to −80° and treated with 2 ml. of triethylamine and 400 mg. of nitrosyl chloride. The mixture was allowed to warm gradually to room temperature over a 1-hr. period. The yellow color which appeared upon the addition of the nitrosyl chloride remained unchanged until the temperature reached −20° but then faded rapidly, and, when the temperature had reached −17°, the mixture was completely white. The mixture was poured into dilute potassium carbonate solution and filtered. The precipitate was dissolved in ether and washed rapidly with ice-cold 5% hydrochloric acid and with water. The solution was dried over magnesium sulfate and concentrated to dryness on a steam bath. The residue was recrystallized from methanol, affording 0.74 g. (37%) of *trans*-pregna-5,17(20)-dien-3β-ol, m.p. 132–133°, $[\alpha]^{24}D$ −67° (*c* 1.0, $CHCl_3$), identified by comparison with an authentic sample.[16b]

17-Imino-17aα-methyl-D-homoandrost-5-ene-3β,17aβ-diol (11a).—A Pyrex test tube was charged with 2.2 g. of crude 17β-amino-3β-hydroxy-17α-pregn-5-en-20-one (**3a**) and inserted in a Woods metal bath heated at 210°. An atmosphere of nitrogen was maintained over the steroid. After 10 min., the sample was cooled and recrystallized from ethanol–acetonitrile, affording 1.32 g. (66%) of 17-imino-17aα-methyl-D-homoandrost-5-ene-3β,17aβ-diol, m.p. 263–264°. The n.m.r. spectrum, run as a saturated solution in deuteriochloroform, exhibited resonances at 0.77 (18-Me), 0.98 (19-Me), and 1.34 (17-Me) p.p.m. These resonances correlate well with those from the corresponding ketone **11b** (0.72, 0.98, and 1.34 p.p.m.).[35]

Anal. Calcd. for $C_{21}H_{33}NO_2$: C, 76.09; H, 10.03; N, 4.23. Found: C, 76.05; H, 9.98; N, 4.24.

17ξ-Amino-17aα-methyl-D-homoandrost-5-ene-3β,17aβ-diol (11c).—A solution of 300 mg. of 17-imino-17aα-methyl-D-homoandrost-5-ene-3β,17aβ-diol (**11a**) in 8 ml. of absolute ethanol and 7 ml. of acetic acid was added to a prereduced suspension of 150 mg. of platinum oxide in 10 ml. of acetic acid and 5 ml. of ethanol and hydrogenated at room temperature and atmospheric pressure until hydrogen uptake ceased (*ca.* 1 hr.). Only 1 equiv. of hydrogen was absorbed. The catalyst was removed by filtration, and the solution was concentrated to a small volume under reduced pressure and poured into dilute potassium carbonate solution. The product was collected by filtration and recrystallized from methanol–water, affording 195 mg. (65%) of the hemihydrate of 17ξ-amino-17aα-methyl-D-homoandrost-5-ene-3β,17aβ-diol, m.p. 237–238°.

Anal. Calcd. for $C_{21}H_{35}NO_2 \cdot 0.5H_2O$: C, 73.64; H, 10.59; N, 4.09; H_2O, 2.63. Found: C, 73.32; H, 10.63; N, 4.06; H_2O, 2.85.

17ξ-Amino-17aα-methyl-D-homoandrostane-3β,17aβ-diol (11e).—A solution of 305 mg. of **11a** in 10 ml. of acetic acid was added to a prereduced suspension of 150 mg. of platinum oxide in 10 ml. of acetic acid and hydrogenated at room temperature and atmospheric pressure until hydrogen uptake ceased (*ca.* 1.5 hr.). Two equivalents of hydrogen were absorbed. The catalyst was separated by filtration, and the filtrate was concentrated to a small volume under reduced pressure and poured into potassium carbonate solution. The product was collected by filtration and recrystallized from aqueous methanol, affording 230 mg. (75%) 17ξ-amino-17aα-methyl-D-homoandrostane-3β,17aβ-diol, m.p. 240–241°, $[\alpha]^{24}D$ +12°. The reported melting point for this compound is 240–244°,[21] and the melting point of a mixture of this compound and an authentic sample (m.p. 236–238°) prepared by catalytic reduction of the oxime of 17aα-methyl-D-homoandrost-5-ene-3β,17aβ-diol-17-one[21] was 237–239°.

Anal. Calcd. for $C_{21}H_{37}NO_2$: C, 75.17; H, 11.12. Found: C, 75.16; H, 11.14.

17β-Amino-17α-pregn-4-ene-3,20-dione (12a).—A solution of 2.40 g. of 17β-benzylideneamino-3β-hydroxy-17α-pregn-5-en-20-one (**3d**) in 140 ml. of toluene was treated with 29 ml. of cyclohexanone and 3.6 g. of aluminum isopropoxide and refluxed for 1.25 hr. The mixture then was cooled, diluted with 500 ml. of ether, and washed with sodium potassium tartrate solution and with water. The organic layer was dried over magnesium sulfate and concentrated to a yellow oil under reduced pressure. The

oil was dissolved in 500 ml. of ether and treated with anhydrous hydrogen chloride. The precipitate was collected by filtration, dissolved in 350 ml. of 2% hydrochloric acid, and warmed on a steam bath for 15 min. The solution was cooled to room temperature, washed well with ether, and neutralized with cold sodium hydroxide solution. The product was separated by filtration and dried under reduced pressure, affording 1.49 g. (62%) of crude 17β-amino-17α-pregn-4-ene-3,20-dione, λ_{max} 240 mμ (ε 15,700), $[\alpha]^{25}D$ +83°. The n.m.r. spectrum exhibited three sharp resonances, each of which integrated for three protons, at 0.92 (18-Me), 1.17 (19-Me) and 2.21 (21-Me) p.p.m.

The **hydrochloride salt** was prepared in the usual manner and was recrystallized from isopropyl alcohol–ethyl acetate, λ_{max} 239 mμ (ε 16,800), $[\alpha]^{24}D$ +117°. It did not melt below 305°.

Anal. Calcd. for $C_{21}H_{32}ClNO_2$: C, 68.92; H, 8.81; Cl, 9.69; N, 3.83. Found: C, 68.83; H, 8.76; Cl, 9.57; N, 3.75.

17β-Acetamino-17α-pregn-4-ene-3,20-dione (12b).—A solution of 1.78 g. of 17β-acetamino-3β-hydroxy-17α-pregn-5-en-20-one (**3b**) in 750 ml. of purified acetone was cooled to 5°, covered with an atmosphere of nitrogen, treated with 1.38 ml. of Jones reagent,[24] and stirred at 5° for 10 min. The excess chromium trioxide was decomposed by the addition of 10 ml. of methanol, and the solution was concentrated to a small volume under reduced pressure and poured into a concentrated solution of sodium chloride. The precipitate was collected by filtration, washed with water, and dried under reduced pressure, yielding 1.00 g. (56%) of 17β-acetamino-17α-pregn-5-ene-3,20-dione, λ_{max} 238 mμ (ε 2120), λ_{max}^{KOH} 240 mμ (ε 14,100).

This crude compound was dissolved in 30 ml. of 95% ethanol, treated with 0.10 g. of oxalic acid, and refluxed for 30 min. The solution was poured into dilute potassium carbonate solution and filtered. The precipitate was washed well with water and recrystallized from methanol, affording 0.57 g. (32%) of 17β-acetamino-17α-pregn-4-ene-3,20-dione with one molecule of methanol of crystallization, m.p. 238–240°, $[\alpha]^{23}D$ +64°, λ_{max} 240 mμ (ε 14,300). The n.m.r. spectrum exhibited five sharp peaks, each of which integrated for three protons, at 1.05 (18-Me), 1.20 (19-Me), 2.04 (amide Me), 2.13 (21-Me), and 3.48 (MeOH) p.p.m. The amide N–H appeared as a singlet at 6.56 p.p.m.

Anal. Calcd. for $C_{23}H_{33}NO_3 \cdot CH_3OH$: C, 71.43; H, 9.24; N, 3.47. Found: C, 71.38; H, 9.32; N, 3.47.

17β-Dimethylamino-17α-pregn-4-ene-3,20-dione (12c). A. From 17β-Amino-17α-pregn-4-ene-3,20-dione.—A solution of 1.50 g. of **12a** in 30 ml. of methanol and 150 ml. of acetonitrile was treated with 1.50 g. of potassium carbonate and 22 ml. of methyl iodide and stirred at room temperature overnight. The mixture then was concentrated to dryness under reduced pressure, and the residue was extracted with boiling ether. The ether solution was treated with anhydrous hydrogen chloride. The precipitate was collected by filtration, washed with ether, and dried under reduced pressure, affording 1.49 g. (82%) of the crude **hydrochloride salt** of 17β-dimethylamino-17α-pregn-4-ene-3,20-dione. The salt was recrystallized from aqueous acetone to give 0.84 g. (47%) of the monohydrate, m.p. 207–209°, $[\alpha]^{24}D$ +129°, λ_{max} 239 mμ (ε 15,000). The infrared spectrum run as a Fluorolube mull exhibited strong sharp absorption peaks at 3610, 3455, and 1613 cm.$^{-1}$ produced by the water of crystallization.

Anal. Calcd. for $C_{23}H_{36}ClNO_2 \cdot H_2O$: C, 67.05; H, 9.30; Cl, 8.61; N, 3.40. Found: C, 67.01; H, 9.22; Cl, 8.71; N, 3.54.

The free base was prepared in the usual manner and was recrystallized from aqueous methanol, m.p. 145–146°, $[\alpha]^{24}D$ +174°, (*c* 0.5, $CHCl_3$), λ_{max} 240 mμ (ε 16,600).

Anal. Calcd. for $C_{23}H_{35}NO_2$: C, 77.26; H, 9.87; N, 3.92. Found: C, 77.08; H, 9.83; N, 4.03.

B. From 17β-Dimethylamino-3β-hydroxy-17α-pregn-5-en-20-one.—A solution of **3c** (1.14 g.) in toluene (125 ml.) was treated with 2.0 g. of aluminum isopropoxide and 13 ml. of cyclohexanone and stirred and refluxed for 6 hr. The mixture was cooled, diluted with 500 ml. of ether, and washed with aqueous sodium potassium tartrate solution and with water. The organic layer was dried over magnesium sulfate and treated with anhydrous hydrogen chloride. The precipitate was collected by filtration, washed well with ether, and dried under reduced pressure to give 0.97 g. of very crude product, λ_{max} 239 mμ (ε 8300). The salt was converted to the free base in the usual manner. The crude base was dissolved in 3 ml. of methanol, treated with 0.30 ml. of pyrrolidine, and warmed on a steam bath for 5 min. The solution then was cooled to 0° and filtered. The precipitate was washed well with cold methanol and dried under reduced pressure, affording 0.34 g. of the crude 3-(N-pyrrolidyl)enamine of the product, λ_{max} 276 mμ (ε 20,500). The enamine was dissolved in 10 ml. of methanol, 1.0 ml. of water, and 1.5 ml. of acetic acid and treated with 1.5 g. of sodium acetate. The solution was refluxed for 3.5 hr., cooled, and poured into water. The precipitate was collected by filtration, washed with water, dissolved in ether, dried over magnesium sulfate, and treated with anhydrous hydrogen chloride. The salt was filtered and dried under reduced pressure, affording 0.17 g. (9%) of the hydrochloride salt of 17β-dimethylamino-17α-pregn-4-ene-3,20-dione, λ_{max} 239 mμ (ε 14,800). The infrared spectrum of this sample was identical with that of the sample prepared from **12a**.

17β-Benzylideneamino-17α-pregn-4-ene-3,20-dione (12d).—A solution of 2.0 g. of 17β-benzylideneamino-3β-hydroxy-17α-pregn-5-en-20-one (**3d**) in 120 ml. of toluene was treated with 3.0 g. of aluminum isopropoxide and 24 ml. of cyclohexanone and refluxed for 1 hr. The cooled mixture was diluted with 500 ml. of ether, washed well with sodium potassium tartrate solution and with water, and dried over magnesium sulfate. The volatile solvents were removed on a steam bath and the residual oil was steam distilled to remove the cyclohexanone. The precipitate was collected by filtration and recrystallized from acetonitrile to give 1.08 g. (54%) of 17β-benzylideneamino-17α-pregn-4-ene-3,20-dione, m.p. 233–235°, $[\alpha]^{24}D$ +292° (*c* 1.2, $CHCl_3$), λ_{max} 288 mμ (ε 2180) and 248 mμ (ε 35,000).

Anal. Calcd. for $C_{28}H_{35}NO_2$: C, 80.53; H, 8.46; N, 3.35. Found: C, 80.41; H, 8.26; N, 3.49.

17β-Methylamino-17α-pregn-4-ene-3,20-dione (12e).—A suspension of 1.73 g. of 17β-benzylideneamino-17α-pregn-4-ene-3,20-dione (**12d**) in 375 ml. of acetonitrile was treated with 25 ml. of methyl iodide and refluxed for 3 days. The solution then was cooled to room temperature, concentrated to about 25 ml. under reduced pressure, and diluted with a large volume of ether. The precipitate was collected, washed with ether, and dried under reduced pressure, affording 1.45 g. of the crude methiodide salt. The salt was dissolved in 1.5 l. of 1% hydrochloric acid, and the solution was washed well with ether and neutralized with cold sodium hydroxide solution. Solid potassium carbonate was added, and the precipitate was collected by filtration, washed well with water, and dried in air, affording 0.76 g. (53%) of crude 17β-methylamino-17α-pregn-4-ene-3,20-dione. The free base was dissolved in ether and treated with anhydrous hydrogen chloride. The precipitate was collected and recrystallized from methanol–acetonitrile, affording 0.31 g. (19%) of the **hydrochloride salt** with 0.5 mole of methanol of crystallization, λ_{max} 240 mμ (ε 16,500).

Anal. Calcd. for $C_{22}H_{34}ClNO_2 \cdot 0.5CH_3OH$: C, 68.25; H, 9.16. Found: C, 68.51; H, 9.08.

Wolffe–Kishner Reduction of 17β-Dimethylamino-3β-hydroxy-17α-pregn-5-en-20-one.—A solution of 500 mg. of **3c** in 25 ml. of diethylene glycol and 3 ml. of 95% hydrazine was treated with 2.5 g. of potassium hydroxide and refluxed for 1.75 hr. At the end of this time, the condenser was removed and the solution was distilled until the temperature of the solution reached 210°. The condenser was replaced and the solution was refluxed for an additional 1.5 hr. The solution then was cooled and poured into water. The precipitate was extracted with ether, and the ether solution was washed with water. Extraction of the ether solution with dilute hydrochloric acid and subsequent neutralization of the aqueous extract with sodium hydroxide afforded no water-insoluble material. The ether solution was washed again with water, dried over magnesium sulfate, and concentrated to dryness on a steam bath. The residue was crystallized from methanol, affording 155 mg. (36%) of 17a-methyl-D-homoandrosta-5,17-dien-3β-ol (**15**), m.p. 156–160°. A small sample which was recrystallized from methanol melted at 161–163° (lit.[31] m.p. 161–162°) and was identical with an authentic sample of this compound prepared previously by a Wolffe–Kishner reduction of 3β,17aα-dihydroxy-17aβ-methyl-D-homoandrost-5-en-17-one.[31,34]

Basic Degradation of 17β-Dimethylamino-3β-hydroxy-17α-pregn-5-en-20-one.—A solution of 1.59 g. of **3c** in 80 ml. of diethylene glycol was treated with a solution of 8.0 g. of potassium hydroxide in 10 ml. of water and heated under an atmosphere of nitrogen on a steam bath for 6 hr. The solution was poured into water and the precipitate was extracted with ether. The ether solution was washed with water, dried over magnesium sulfate, and treated with anhydrous hydrogen chloride. The precipitate was collected by filtration, washed with ether, and

dried, affording 0.97 g. (57%) of the hydrochloride salt of the starting material. The filtrate was washed with water until neutral, dried over magnesium sulfate, and concentrated on a steam bath. The residue, which weighed 0.40 g. (27%), was dissolved in 8 ml. of pyridine, treated with 12 ml. of acetic anhydride, and left overnight at room temperature. The solution was poured into dilute hydrochloric acid, and the precipitate was collected by filtration, dried in air, and chromatographed on Florisil. Elution with 5% ether in benzene afforded 0.23 g. of a mixture of the 3-acetates of 3β,17aα-dihydroxy-17aβ-methyl-D-homoandrost-5-en-17-one and 3β,17aβ-dihydroxy-17aα-methyl-D-homoandrost-5-en-17-one. The compounds were identified by thin layer chromatography. Repeated fractional crystallization of the mixture from ether afforded 52 mg. of the 3-acetate of **17**, m.p. 269–271° (lit.[33] m.p. 277–279°), and 75 mg. of the 3-acetate of **11b**, m.p. 179–180° (lit.[33] m.p. 176–178°). Saponification of each acetate with sodium hydroxide in methanol at room temperature for 1 hr. afforded the corresponding 3-alcohols, m.p. 298–300° (**17**) and 182–184° (**11b**), respectively, which were identical with authentic samples of these two compounds.

17α-Amino-17β-methyl-3β-hydroxy-D-homoandrost-5-en-17a-one (16a).—A suspension of 2.8 g. of 17β-amino-3β-hydroxy-17α-pregn-5-en-20-one (**3a**) in 40 ml. of Dowtherm A was covered with an atmosphere of nitrogen and heated at 200° for 10 hr. The solution then was cooled to room temperature, diluted with 1 l. of cold ether, and filtered, affording 0.95 g. (34%) of 17α-amino-17β-methyl-3β-hydroxy-D-homoandrost-5-en-17a-one. A sample was recrystallized from methanol for analysis, m.p. 227–229°, $[\alpha]^{24}D$ −47°.

Anal. Calcd. for $C_{21}H_{33}NO_2$: C, 76.20; H, 9.97; N, 4.24. Found: C, 76.30; H, 10.12; N, 4.28.

The ether filtrate was treated with anhydrous hydrogen chloride. The precipitate was collected and recrystallized from methanol to give 0.34 g. (11%) of the **hydrochloride salt** of **16a** with 0.5 mole of methanol of crystallization, m.p. 272–282° dec.

Anal. Calcd. for $C_{21}H_{34}ClNO_2 \cdot 0.5CH_3OH$: C, 67.34; H, 9.45; Cl, 9.24; N, 3.65. Found: C, 67.48; H, 9.48; Cl, 9.27; N, 3.83.

17α-Methylamino-17β-methyl-3β-hydroxy-D-homoandrost-5-en-17a-one (16b).—A suspension of 708 mg. of 17β-methylamino-3β-hydroxy-17α-pregn-5-en-20-one (**3e**) in 10 ml. of Dowtherm A was covered with an atmosphere of nitrogen and heated at 200° for 10 hr. The cooled solution was diluted with ether and treated with anhydrous hydrogen chloride. The brown gum which deposited was crystallized from methanol–ethyl acetate, affording 217 mg. (28%) of the hydrochloride salt of 17α-methylamino-17β-methyl-3β-hydroxy-D-homoandrost-5-en-17a-one. The infrared spectrum of the salt was identical with that of an authentic sample prepared earlier.[35] The salt was converted in the usual manner to the free base, m.p. 205–207°, which exhibited no depression in melting point when mixed with an authentic sample prepared earlier.[35]

17α-Acetamino-17β-methyl-3β-hydroxy-D-homoandrost-5-en-17a-one (16d).—A solution of 288 mg. of 17α-amino-17β-methyl-3β-hydroxy-D-homoandrost-5-en-17a-one (**16a**) in 35 ml. of methanol was treated with 4 ml. of acetic anhydride and left overnight at room temperature. The solution was concentrated to dryness under reduced pressure, and the residue was recrystallized from methanol, affording 137 mg. (42%) of 17α-acetamino-17β-methyl-3β-hydroxy-D-homoandrost-5-en-17a-one (**16d**), m.p. 305–307°, $[\alpha]^{24}D$ −55°.

Anal. Calcd. for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.45; N, 3.75. Found: C, 74.00; H, 9.50; N, 3.74.

(3β-Hydroxy-17β-methyl-D-homoandrost-5-en-17a-on-17α-yl)-trimethylammonium Iodide (16c).—A solution of 133 mg. of the hydrochloride salt of 17α-amino-17β-methyl-3β-hydroxy-D-homoandrost-5-en-17a-one (**16a**) in 12 ml. of acetonitrile was treated with 200 mg. of potassium carbonate and 2.5 ml. of methyl iodide and stirred and refluxed overnight. The mixture was concentrated under reduced pressure to a small volume, diluted with water, and filtered. The precipitate was air dried, affording 147 mg. (80%) of (3β-hydroxy-17β-methyl-D-homoandrost-5-en-17a-on-17α-yl)trimethylammonium iodide (**16c**), m.p. 235–237°. The infrared spectrum of the salt was identical with the spectrum of the salt (m.p. 240–242°) prepared previously from **16b** in similar manner.[35]

Hydrolysis of 2-(3β-Hydroxypregn-5-en-20-ylidine)-1,1,1-trimethylhydrazonium Iodide.—A suspension of 500 mg. of **2** in 50 ml. of water was refluxed for 24 hr., cooled, and extracted with ether. The ether solution was dried over magnesium sulfate and concentrated to dryness, affording 125 mg. (40%) of pregnenolone, m.p. 190–191°, $[\alpha]^{24}D$ +25° (*c* 1.0, EtOH). The reported rotation in ethanol of pregnenolone is +28°,[42] whereas that of 17-isopregnenolone is −140°.[42] When the reaction was repeated with the addition of 200 mg. of sodium bicarbonate, 255 mg. (81%) of pregnenolone, $[\alpha]^{24}D$ +24° (*c* 1.0, EtOH), was isolated.

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Cupric Halide Halogenations

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Cupric bromide and cupric chloride in refluxing methanol and higher alcohols effect the following transformations: β-alkoxylation α-halogenation of carbonyl-conjugated vinyl groups, halogenation of isolated double bonds, *trans* halogenation of internal acetylenes, and trihalogenation of terminal acetylenes. In a reaction of undefined scope, ethanol is oxidatively halogenated with cupric bromide to dibromoacetaldehydediethyl acetal. Kinetics of some representative transformations have been examined. Cupric bromide but not cupric chloride functions as a source of low concentrations of halogen. Mechanisms for some of the conversions are suggested.

The high-temperature gas phase halogenation of aromatic,[1a] unsaturated aliphatic,[1b] and alicyclic compounds[1c] with solid cupric halides has been industrially employed. Recently, the gas phase chlorination of olefins with cupric chloride supported on pumice has been described[2] to proceed with *trans* addition of halogen.

The relatively low temperature liquid phase reduction of copper salts by organic molecules has not received early attention. Thus, although the reduction of cupric chloride by acetone in aqueous media was noted[3] at the turn of the century, the synthetic and

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