8-Azasteroids. III.[1] 8-Azaestrogens and 8-Aza-19-norandrogens

RICHARD E. BROWN, DAVID M. LUSTGARTEN, R. JOHN STANABACK, AND ROBERT I. MELTZER

Warner-Lambert Research Institute, Morris Plains, New Jersey

Received November 22, 1965

A general route to 8-azaestrogens and 8-aza-19-norandrogens is described. Condensation of 2-methyl-2-β-carboxyethyl-cyclopentane-1,3-dione with *m*-methoxyphenethylamine gives a lactam intermediate which can be reduced and cyclized under various conditions to afford the *trans-anti-trans* skeleton of natural steroids or isomeric products. The stereochemistry of these isomeric 8-azasteroids is discussed.

In recent years, much work has been directed toward the synthesis of azasteroids.[2] In some of this work, natural steroids served as starting materials, and ring opening and subsequent closure were used for introduction of the nitrogen atom. In other approaches, total synthesis of the tetracyclic nucleus was accomplished. This report describes in detail the total synthesis of 8-azaestrone, published earlier[1] in preliminary form, and extends the method to the preparation of other 8-azaestrogens and several 8-aza-19-norandrogens.

A synthetic route to the 8-azasteroid nucleus utilizing model compounds was described in part II[3] of this series. Application of the method to the synthesis of 8-azaestrogens and 8-aza-19-norandrogens required the synthesis of 2-methyl-2-(β-carboxyethyl)cyclopentane-1,3-dione (**1c**). The known 2-methylcyclopentane-1,3-dione[4] was found to resist Michael addition to ethyl acrylate;[5] however, addition to acrylonitrile was effected in excellent yield (although only moderate conversion) by suitable modification of the procedure described by Nazarov[6] for cyanoethylation of the corresponding cyclohexanedione. The cyanoethyl adduct thus obtained, **1a**, was hydrolyzed either to the ester **1b** or to the acid **1c** *via* the imidate.

Reaction of ester **1b** with *m*-methoxyphenethylamine[3] did not lead to the expected keto lactam **2**, but instead resulted in a reverse Michael reaction from which the expelled ethyl acrylate was the only definable product. However, condensation of the amine with acid **1c** in refluxing xylene with azeotropic removal of water readily gave lactam **2** in 50% yield. Attempted cyclization of lactam **2** with phosphorus oxychloride resulted in extensive tar formation, and the only product which could be isolated (in poor yield) was the tetracyclic lactam **3**. This product was obtained in somewhat better yield by cyclization of **2** with polyphosphoric acid and is structurally analogous to the aromatic erythrinane lactams prepared by Mondon.[7]

Catalytic reduction of **2** proceeded stereospecifically to give a single keto lactam, **4**. The expected *cis* ring junction in this product was established when the amine and acid were subjected to reductive condensation (palladium on carbon in ethanol). Under these conditions, lactam **4** was obtained in 45% yield along with 15% of the crystalline amino acid, **5**. The latter product cyclized at its melting point to the crystalline *trans* keto lactam, **6**. Stereochemical assignments to the two cyclic products (**4** and **6**) were made on the basis of the widely differing ease of lactam formation, such behavior being consistent with the expected ease of ring closure (*cis* > *trans*) based on inspection of molecular models. In addition, a chemical proof of the *cis* and *trans* nature of analogously prepared less-substituted lactams was effected and described in part II.[3]

Although the reductive condensation procedure served to establish the stereochemistry of the ring fusions in lactams **4** and **6**, the method was not satisfactory for the preparation of the *trans* compound in quantity. An alternate procedure which afforded **6** in moderate yield was suggested by the observation[8] that 17β-substituted Δ^{14} steroids gave *trans*-fused products on reduction, while 17α substituents directed the reduction toward *cis* products. When lactam **2** was reduced with potassium borohydride in methanol, a single alcohol, **7**, was obtained. Reduction of **7** (10% palladium on carbon in ethanol at 50-psi hydrogen pressure) gave a mixture of epimeric hydroxy lactams **8** and **9** in which *cis* **9** predominated. However, modified reduction conditions (30% palladium on carbon in ethyl acetate at 2000-psi hydrogen pressure) resulted in reversal of the isomer ratio so that it was possible to isolate the *trans* alcohol **8** in 75% yield by direct crystallization. Subsequent oxidation of **8** and **9** by the Jones[9] procedure afforded the pure ketones **6** and **4**, respectively. Pure **6** was thus obtained in 27% overall yield through the sequence **1c** → **2** → **7** → **8** → **6**.

The configurations of the hydroxyl groups in **8** and **9** were established in the following way. Catalytic reduction of diketo acid **1c** resulted in a rapid uptake of hydrogen which stopped abruptly after absorption of 1 equiv. Work-up afforded a 75% yield of lactone **10** and a 25% yield of hydroxy acid **11**; the configurations of these two products were assigned on the basis of the expected greater ease of lactone formation from the

(1) This work was presented in part before the Division of Organic Chemistry, 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1963, Abstracts, p. 39M, and has been published in preliminary form: R. I. Meltzer, D. Lustgarten, R. J. Stanaback, and R. E. Brown, *Tetrahedron Letters*, 1581 (1963).

(2) (a) H. O. Huisman, W. N. Speckamp, H. deKoning, and U. K. Pandit, *Tetrahedron Letters*, 1275 (1964); (b) J. P. Kutney and I. J. Vlattas, *Steroids*, **4**, 595 (1964); (c) S. V. Kessar, A. L. Rampal, K. Kumar, and R. R. Jogi, *J. Ind. Chem. Soc.*, 240 (1964); (d) T. L. Jacobs and R. B. Brownfield, *J. Am. Chem. Soc.*, **82**, 4033 (1960); (e) J. H. Burckhalter and H. Watonabe, Abstracts, 142nd National Meeting of the American Chemical Society, Cincinnati, Ohio; *Biochemistry*, **23**, 14a (1963); (f) M. Gut, *Tetrahedron Letters*, 223 (1964); (g) A. I. Logothetis, *J. Org. Chem.*, **29**, 1834 (1964); (h) C. W. Shoppee and L. N. Mander, *J. Chem. Soc.*, 1971 (1965); (i) N. J. Doorenbos and M. T. Wu, *J. Hetero. Chem.*, **2**, 212 (1965); (j) A. I. Meyers, G. G. Munoz, W. Sobotka, and K. Baburao, *Tetrahedron Letters*, 255 (1965); (k) N. A. Nelson and Y. Tamura, *Can. J. Chem.*, **43**, 1323 (1965).

(3) R. E. Brown, D. M. Lustgarten, R. J. Stanaback, M. W. Osborne, and R. I. Meltzer. *J. Med. Chem.*, **7**, 232 (1964).

(4) J. J. Panouse and C. Sannie, *Bull. Soc. Chim. France*, 1036 (1955).

(5) Addition to ethyl acrylate was successfully accomplished subsequent to this phase of our work by using dimethylformamide as solvent. See ref 2c.

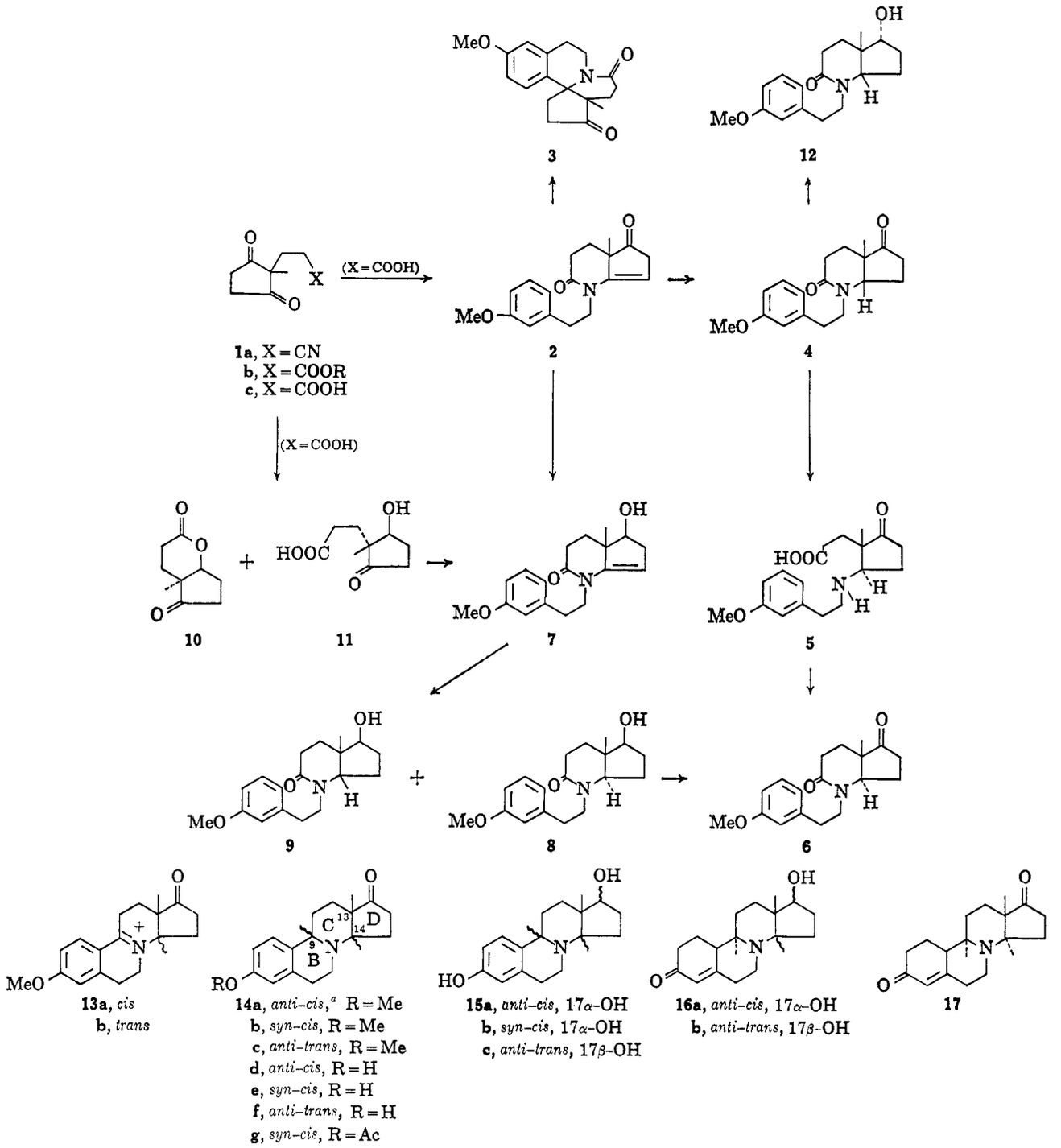
(6) I. N. Nazarov and S. I. Zavyalov, *J. Gen. Chem.* (Eng transl), 479 (1954).

(7) A. Mondon, *Ann. Chem.*, **628**, 123 (1959).

(8) L. F. Fieser and M. Fieser, "Steroids." Reinhold Publishing Corp., New York. N. Y., 1959, p. 567.

(9) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

CHART I

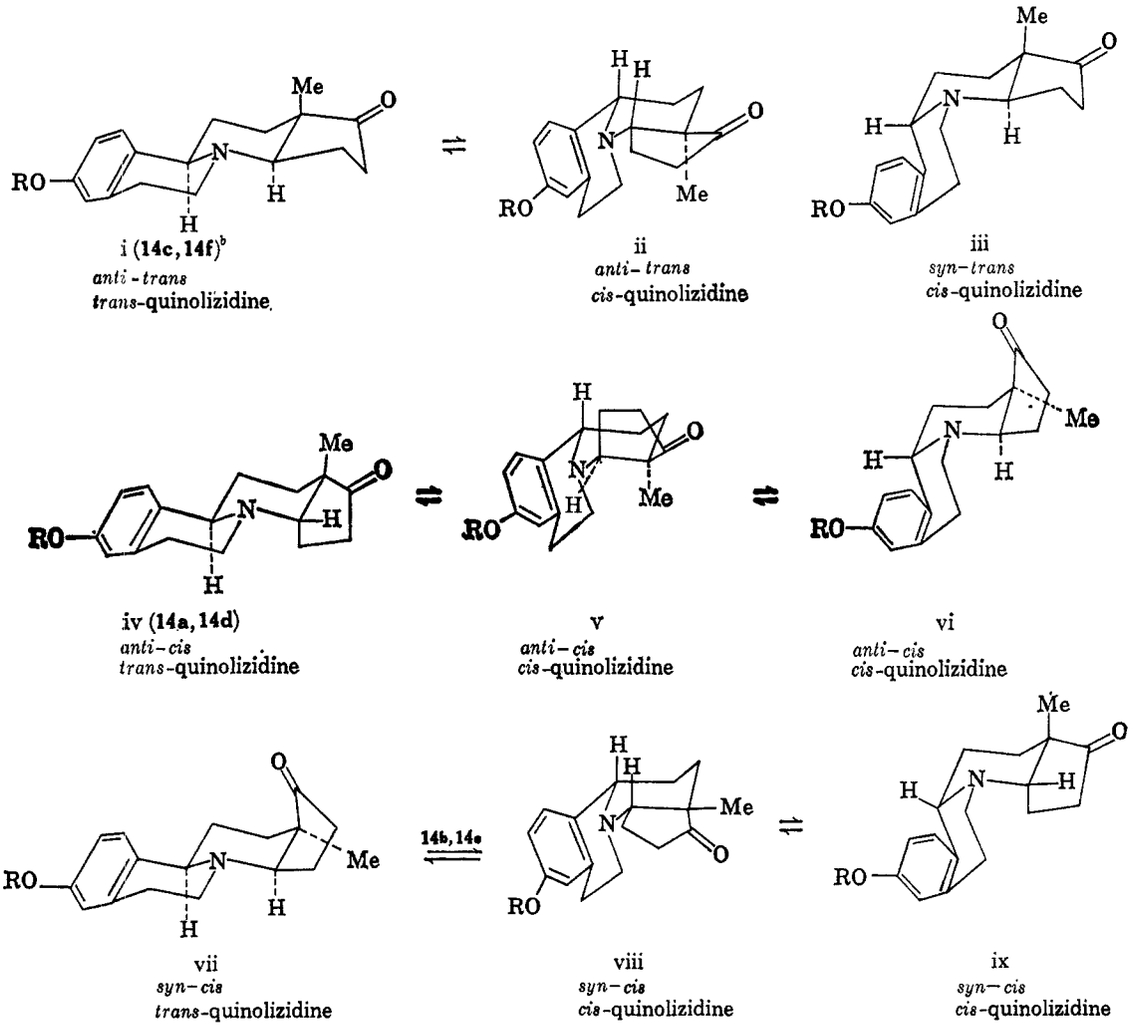


[a] See ref 15.

hydroxy acid in which the hydroxyl and carboxyl groups are *cis* to each other. Since the isolated hydroxy acid **11** reacted further with *m*-methoxyphenethylamine to give hydroxy lactam **7**, it is apparent that this product, and the saturated products prepared therefrom (**8** and **9**) all have a *cis* relationship of the hydroxyl and angular methyl groups. In this connection, it is noteworthy that alcohol **8** was the sole product of borohydride reduction of the *trans* keto lactam **6**, but similar reduction of the *cis* keto lactam **4** gave only alcohol **12**, epimeric with **9**. In this product, a *trans* relationship of the methyl and hydroxyl groups exists.

Treatment of *cis* lactam **4** and *trans* lactam **6** (or its precursor, *trans* amino acid **5**) with phosphorus oxychloride in benzene gave high yields of the quaternary salts **13a** and **13b**, respectively, conveniently isolated as the perchlorates. Catalytic reduction of the *cis* perchlorate **13a** gave a mixture of saturated bases, **14a** and **14b**, which were easily separated by fractional crystallization of the hydrobromide salts. In contrast, *trans* perchlorate **13b** gave a single saturated base **14c**, on reduction. Treatment of the three bases with 48% hydrobromic acid gave three of the four possible isomers of 8-azaestrone, **14d**, **14e**, and **14f**, respectively.

CHART II[a]



[a] For the sake of convenience in representation, some conformational isomers are here depicted in enantiomer rather than identical configurations. The actual compounds studied were all *dl* pairs. [b] See ref 15.

Assignment of configurations to these tetracyclic bases[10] requires consideration of the various possible ring conformations. Examination of molecular models reveals no reason to expect any boat forms to exist in preference to the chair forms, and consequently, further discussion will be concerned only with the all-chair conformations.

For the 8-azasteroid nucleus with C–D *trans* ring junction, three all-chair configurations or conformations must be considered. These are shown in conformational diagrams i, ii, and iii below. When the C–D ring junction is *cis*, six all-chair configurations or conformations are possible, as shown in diagrams iv–ix. Further examination reveals three forms (i, iv, vii) to possess a *trans*-quinolizidine ring junction with the angular proton axial to both rings B and C. The remaining six forms have a *cis*-quinolizidine ring junction with the angular proton equatorial to one ring and axial to the other. It is also evident that structures vi, vii, and viii have the angular methyl equatorial to ring C while the others have this group axially oriented.

Application of nmr[11,12,14] and infrared[13] methods have made it possible to distinguish between these configurations and conformations, and have allowed firm assignments to be made to bases **14a**, **14b**, and **14c**. The pertinent data are summarized in Table I.

TABLE I

	C–D ring	Mp, °C,		Bohlmann	Nmr, ppm C-9	Nmr, ppm C-13		
Base	junction	·HBr	base	bands	$CDCl_3$	$CDCl_3$	Benzene
14a	*cis*	275–278	125	+	3.2	1.0	0.76
14b	*cis*	243–244	122	−	3.8	1.17	1.21
14c	*trans*	246–248	171–172	+	3.2	1.02	0.90

The single C–D *trans* base obtained, **14c**, shows strong Bohlmann[13a] bands in the infrared and an upfield signal (above 3.2 ppm and lost under the broad methylene hump) for the angular C-9 proton. Both observations are indicative[13,14] of a *trans*-quinolizidine conformation with an axial C-9 hydrogen. Since the *trans* fusion of rings C and D requires an axial angular methyl group, the C-9 hydrogen and the C-13 methyl group must be

(10) The following assignments, based largely on nmr[11,12] and infrared[13] evidence, represent, in the case of compounds **14a**, **14b**, **14d**, and **14e**, a reversal of the configurations proposed in the preliminary communication on the basis of less extensive data. The configurations of the corresponding 18-nor compounds (compounds **8–13** in ref 3) should presumably also be reversed.

(11) N. S. Bhacca and D. H. Williams, *Tetrahedron Letters*, 3127 (1964).

(12) D. H. Williams and N. S. Bhacca, *Tetrahedron*, **21**, 2021 (1965).

(13) (a) F. Bohlmann, *Ber.*, **91**, 2157 (1958); (b) W. E. Rosen, *Tetrahedron Letters*, 481 (1961).

(14) M. Uskokovic, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, *J. Am. Chem. Soc.*, **86**, 3364 (1964).

anti[15] to each other. Thus, the configuration and conformation of this product is depicted by the conformational diagram i; the alternative *syn-trans* configuration (sole conformation iii) is excluded because it has the C-9 hydrogen equatorial.

The infrared and nmr spectra of C–D *cis* base **14a** show clear Bohlmann bands and no discernable signal for the C-9 hydrogen, respectively. This product, like *trans* **14c** has an axial C-9 hydrogen atom and *trans* quinolizidine ring fusion. However, in this case, the *cis* fusion of the C and D rings allows both possible C-9 epimers to exist with an axial C-9 hydrogen, as shown in diagrams iv and vii. These two structures have axial and equatorial angular methyl groups, respectively. A recent report[11,12] correlating changes in the chemical shift of a methyl group proximate to a carbonyl on passing from deuteriochloroform to benzene as solvent allows a distinction to be made between these two structures. Thus, for **14a**, δ_{Me} in deuteriochloroform is 1.0 ppm, whereas in benzene δ_{Me} is 0.76 ppm. This upfield shift of 0.24 ppm on changing solvent is consistent with that reported for an axial methyl group, and **14a** is therefore assigned the *anti-cis* configuration shown in iv.

The epimeric base in the C–D *cis* series, **14b**, must then have the *syn-cis* configuration. This product shows no Bohlmann bands and a downfield C-9 hydrogen signal (multiplet centered at 3.8 ppm under the methoxy signal) attributed to a *cis*-quinolizidine ring fusion. Two conformations of the *syn-cis* configuration incorporating a *cis*-quinolizidine B–C ring junction are possible. The first of these is diagrammed in viii and has an equatorial angular methyl group with the C-9 hydrogen axial to ring C and equatorial to ring B. The second conformation is diagrammed in ix, and has an axial methyl group with the C-9 hydrogen axial to ring B and equatorial to ring C. The nmr spectrum of this base shows a downfield shift of the methyl signal of 0.04 ppm on passing from deuteriochloroform to benzene; this is consistent[11,12] with an equatorial methyl group. Thus, base **14b** would appear to exist mainly in conformation viii. However, this base does undergo mercuric acetate oxidation[16] to the quaternary salt **13a**, although at a greatly reduced rate relative to the *anti-cis* isomer **14a**. Since this reaction has been correlated[16] with systems in which the angular proton is axial to both rings, the conclusion is drawn that there is a conformational equilibrium for base **14b** between vii and viii. Conformation vii must exist to a sufficient extent at 90° to provide a path for the oxidation, but not enough at room temperature to cause Bohlmann bands to appear in the infrared spectrum. Analogy in a related system for such a conformational equilibrium is to be found in the work of Shamma[17] on the epialloyohimbine alkaloids.

Also pertinent to the question of the conformation of **14b** is the nmr correlation of Uskokovic,[14] in which the two *cis*-quinolizidine conformations can be distinguished by the splitting pattern of the angular hydrogen signal. In the case of **14b**, this signal is masked by the methoxyl signal, and the nmr spectrum was obtained on the 3-acetate, **14g**. The quartet which would be expected from the *gauche* and *trans* diaxial relationship between the C-9 proton and the two C-11 protons in conformation viii was not observed. Instead, the signal for the angular proton appeared as a broad doublet centered at 3.8 ppm, which may be interpreted as further evidence for a conformational mixture.

From the products thus far described, further transformations were carried out by standard procedures to give other 8-azasteroids. Lithium aluminum hydride reductions of the three isomers of 8-azaestrone proceeded stereospecifically to give three isomers of 8-azaestradiol, **15a**, **15b**, and **15c**. The orientation of the derived 17-hydroxyl group is assigned β for the C–D *trans* base **15c** on the basis of the well-known[18] direction of hydride reductions of 17-keto steroids. Confirmation for this assignment was obtained by preparation of **15c** directly from lactam **8**, for which the configuration was established as described earlier. For the two C–D *cis* bases **15a** and **15b**, tentative assignment of the α configuration to the 17-hydroxyl group is made on the basis of the reported[18] reductions of several 17-keto C–D *cis* steroids to predominantly α alcohols.

Birch reductions of **14a** and **14c** followed by acid hydrolysis gave two isomers of 8-aza-19-nortestosterone, **16a** and **16b**, respectively. The preparation of 8-aza-19-norandrostenedione, **17**, was accomplished by preparation of the ethylene ketal of **13b**, borohydride reduction to the ketal of **14c**, followed by Birch reduction, and acid hydrolysis. Assignment of the β configuration to the hydrogen introduced at the newly formed assymetric center at C-10 in these three products is based on the well-established[19] production of the more stable (β) configuration upon acid treatment of Birch reduction products from various aromatic steroids.

trans keto lactam **6** has served as starting material for synthesis of various other 8-azasteroids, including 19-norprogesterone and cortisol derivatives. This work will be described in subsequent papers.

Experimental Section[20]

2-Methyl-2-(β-cyanoethyl)cyclopentane-1,3-dione (1a).—To a solution of 6.4 g of sodium hydroxide in 512 ml of water was added 113.6 g (1.024 moles) of 2-methyl-1,3-cyclopentanedione.[4] The mixture was heated with stirring for 10 min on the steam bath; then a solution of 256 g of freshly distilled acrylonitrile in 320 ml of dioxane was added all at once. The resulting mixture was refluxed with stirring for 25 hr, then cooled, and filtered. The filter cake of polymer was washed with water–dioxane and the combined filtrate and washings were acidified with 80 ml of 2 *N* hydrochloric acid. The solution was concentrated to an oily solid. This residue was refluxed with 300 ml of ethyl acetate, cooled, and filtered. The cake was washed with ethyl acetate and dried to give 54.3 g of unreacted dione. The combined ethyl acetate filtrate and washings were diluted with *ca.* 500 ml of chloroform, dried, and concentrated to a deep red oil. The oil was distilled to give 83.5 g (49%, for 96% based on recovered dione) of a pale yellow oil, bp 120° (0.05 mm), containing a

(15) *syn* and *anti* refer to the relative configurations of the angular hydrogen at C-9 and the angular methyl group at C-13.

(16) F. L. Weisenborn and P. A. Diassi, *J. Am. Chem. Soc.*, **78**, 2022 (1956).

(17) M. Shamma and J. M. Richey, *ibid.*, **85**, 2507 (1963).

(18) L. J. Chinn, *J. Org. Chem.*, **27**, 54 (1962).

(19) C. Djerassi, A. E. Lipmann, and J. Grossman, *J. Am. Chem. Soc.*, **78**, 2479 (1956).

(20) Melting points were taken on a Fisher-Johns block and are uncorrected. Ultraviolet, infrared, and nmr spectra were determined on Beckman DK-1, Baird Model 455, and Varian A-60 instruments, respectively. The silica gel G used for thin layer chromatography was according to Stahl, and was purchased from Brinkmann Instruments, Inc.

small amount of suspended solid which is unreacted dione: $n^{20}D$ 1.4845; ν_{max}^{film} 2300, 1760, and 1720 cm^{-1}.

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.43; H, 6.71; N, 8.48. Found: C, 65.23; H, 6.90; N, 8.29.

2-Methyl-2-(β-carbomethoxyethyl)cyclopentane-1,3-dione (1b).—A solution of 58.5 g of 2-methyl-2-(β-cyanoethyl)cyclopentane-1,3-dione in 200 ml of methanol was cooled to 0° and saturated with dry hydrogen chloride. The solution was stored overnight in the freezer and concentrated at a temperature below 30° to an amorphous solid. To this residue was added 100 ml of water. A clear solution resulted which quickly deposited an oil. The oil was extracted with ether; the ether was washed with 5% sodium bicarbonate solution and water, dried, and concentrated to a light yellow oil. This was distilled to give 61.1 g of off-white oil: bp 101–102° (0.1 mm), $n^{22}D$ 1.4719, ν_{max}^{film} 1720–1760 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.66; H, 7.35.

In the same way, use of ethanol gives the ethyl ester: bp 140–142° (4 mm), $n^{20}D$ 1.4678, ν_{max}^{film} 1720–1760 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.24; H, 7.59. Found: C, 62.20; H, 7.76.

2-Methyl-2-(β-carboxyethyl)cyclopentane-1,3-dione (1c).—A solution of 169.4 g of the cyanoethyl adduct **1a** in 1 l. of methanol was converted to the amorphous solid imidate, as described for preparation of the ester. The imidate was taken up in 1.8 l. of 1 *N* hydrochloric acid and heated for 0.5 hr on the steam bath. The solution was cooled in an ice bath and the crystals were filtered to give a first crop of 57 g, mp 119–122°. The filtrate was saturated with sodium chloride and extracted well with ethyl acetate. The combined extracts were dried and concentrated to a white solid, mp 102–114°. This second crop was recrystallized from 850 ml of benzene to give 82.5 g, mp 121–123°, total yield 139.5 g (81%). The analytical sample was prepared by recrystallization from ether: mp 126°, ν_{max}^{Nujol} 3040, 1750, 1730, and 1700 cm^{-1}.

Anal. Calcd for $C_9H_{12}O_4$: C, 58.68; H, 6.57. Found: C, 58.88; H, 6.72.

Unsaturated Lactam 2.—To a refluxing solution of 5.52 g (0.03 mole) of acid **1c** in 400 ml of xylene was added dropwise with stirring over a 1-hr period a solution of 4.53 g (0.03 mole) of *m*-methoxyphenethylamine[3] in 20 ml of xylene. Reflux was continued for an additional hour under a Dean–Stark trap, by which time 1.05 ml of water (1.08 theoretical) had been collected. The xylene was removed to a small (*ca.* 20-ml) volume, and the residue was placed on a column of 500 g of neutral alumina. The column was washed well with benzene and anhydrous ether. Elution of the column with 2 l. of 20% ethyl acetate–ether mixture gave 4.12 g (46%) of yellow oil. This material showed a single spot on tlc (silica gel G; ethyl acetate, R_f 0.8, visualized in an iodine chamber); ν_{max}^{film} 1750, 1670, and 1630 cm^{-1}.

Anal. Calcd for $C_{13}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.03; H, 7.20; N, 4.64.

Cyclization of 2 to Tetracyclic Lactam 3.—A mixture of 1.9 g of lactam **2** and 25 g of polyphosphoric acid was heated with stirring on the steam bath for 2 hr. The mixture was cooled, diluted with water, and extracted with chloroform. The chloroform layer was washed with 5% sodium bicarbonate solution and water, dried, and concentrated to a solid. This was recrystallized twice from ethyl acetate to give an analytical sample: mp 220–221°, yield 58%, ν_{max}^{Nujol} 1740 and 1630 cm^{-1}.

Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.33; H, 7.19; N, 4.54.

Reductive Condensation of Acid 1c with Amine.—A mixture of 9.2 g of acid **1c** and 7.55 g of *m*-methoxyphenethylamine (0.05 mole of each) in 250 ml of ethanol was hydrogenated overnight over 3.5 g of 10% palladium on carbon at 50 psi and 25°. Hydrogen uptake ceased after absorption of 1 equiv. The catalyst and solvent were removed. The residual off-white oil was scratched with a little ether; the slurry was cooled for 1 hr and filtered to give 2.4 g (15%) of the amino acid, **5**. The filtrate was diluted with more ether and washed in succession with 0.1 *N* hydrochloric acid, 5% sodium bicarbonate, and water. The ether solution was dried and concentrated to 6.8 g (45%) of off-white, oily *cis* lactam **4**. A sample of the lactam was distilled to give an analytical sample: bp 215° (0.18 mm), ν_{max}^{film} 1740 and 1640 cm^{-1}.

Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.15; H, 7.94; N, 4.63.

A sample of the amino acid was recrystallized from acetonitrile to give an analytical sample: mp 142–144°, ν_{max}^{Nujol} 2600, 2400, 1740, 1630, 1610, and 1560 cm^{-1}.

Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.68; H, 7.89; N, 4.39. Found: C, 67.93; H, 8.08; N, 4.62.

Thermal Cyclization of Amino Acid 5 to *trans* Lactam 6.—Thirty grams of amino acid **5** were heated under nitrogen to a bath temperature of 180° and maintained at this temperature until bubbling stopped (15 min). The melt was cooled, taken up in benzene, and washed successively with 0.1 *N* hydrochloric acid, 5% sodium bicarbonate, and water. The benzene was removed by distillation to leave an oily residue which crystallized. Recrystallization from ether afforded 20.8 g (77%) of white crystals, mp 81–83°. The analytical sample had mp 87–88°, ν_{max}^{Nujol} 1740 and 1640 cm^{-1}.

Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.65; H, 7.71; N, 4.40.

On tlc (silica gel G, 25:75% ethyl acetate–acetone, iodine chamber as visualizing agent) the *trans* lactam **6** clearly migrates faster than the *cis* lactam **4**, R_f values *ca.* 0.75 and 0.68, respectively.

Reduction of 2 to Saturated Lactam 4.—A solution of 4.6 g of **2** in 50 ml of ethanol was hydrogenated overnight at 50 psi and 25° over 1.5 g of 10% palladium on carbon catalyst. Hydrogen uptake ceased after absorption of 1 equiv. The residual off-white oil gave a single spot on tlc identical with that of the *cis* lactam **4**, obtained by the reductive condensation procedure, and an identical infrared curve.

Unsaturated Hydroxy Lactam 7.—Acid **1c** (92 g, 0.5 mole) and *m*-methoxyphenethylamine (75.5 g, 0.5 mole) were condensed in 2.5 l. of xylene as described for preparation of lactam **2**. The dark oily residue from removal of the xylene was taken up in 1.25 l. of methanol. The solution was cooled to 15°, and, with stirring, 30 g of potassium borohydride were added in portions over 0.5 hr. The mixture was stirred at room temperature overnight. The methanol was removed, and the gummy residue was partitioned with water and ether. The water layer was extracted with two portions of ethyl acetate, and the combined ether and ethyl acetate phases were dried and concentrated to 127 g of dark brown oil. This was taken up in about 100 ml of ethyl acetate and scratched to induce crystallization, and the slurry was cooled overnight in the freezer. The solid was filtered and washed with cold ethyl acetate to give 70 g of pale yellow solid, mp 98–103°. The mother liquors were concentrated to an oil, and the oil was flash distilled to give 25 g of yellow oil, bp 220–240° (0.15 mm). This distillate crystallized readily on rubbing with ethyl acetate to afford an additional 15.8 g of off-white solid, total 85.8 g (57%). The analytical sample was prepared by recrystallization from ether: mp 102–103°; ν_{max}^{Nujol} 3400, 1660, and 1630 cm^{-1}.

Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.82; H, 7.77; N, 4.57.

***trans* Hydroxy Lactam 8.**—A solution of 27.2 g of unsaturated lactam **7** in 900 ml of ethyl acetate was hydrogenated for 46 hr over 15 g of 30% palladium-on-carbon catalyst at 2000 psi and 28°. The catalyst was filtered, and the filtrate was concentrated to 300-ml volume, at which point 16.55 g of white crystals, mp 114–117°, were filtered. The filtrate was concentrated to an oily solid and the residue was slurried in a small amount of ethyl acetate and ether. This was filtered to give an additional 4.1 g of white crystals, mp 113–116°, total 20.65 g (75% yield) of material sufficiently pure for oxidation. The mother liquor from the second crop consisted of a mixture of *trans* alcohol **8** and *cis* alcohol **9**. The analytical sample was prepared by recrystallization from acetonitrile: mp 122–123°; ν_{max}^{Nujol} 3350, 1620, and 1590 cm^{-1}.

Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.31; N, 4.62. Found: C, 71.42; H, 8.31; N, 4.91.

***cis* Hydroxy Lactam 9.**—A solution of 6.4 g of unsaturated ketone **2** in 280 ml of ethanol was treated with 5 g of potassium borohydride in portions, then left overnight at room temperature. The mixture was filtered, and the filtrate was hydrogenated over 4.0 g of 10% palladium on carbon at 50 psi and room temperature. Hydrogen uptake ceased after absorption of 1 equiv in *ca.* 6 hr. The catalyst and solvent were removed, and the residue was partitioned with water and ether. The ether was dried and concentrated to an oil which crystallized. The solid was removed by trituration with ether: yield 3.4 g (53%), mp 89–92°. The analytical sample was prepared by recrystallization

from ethyl acetate: mp 95–96°; ν_{max}^{Nujol} 3450, 1620, and 1590 cm^{-1}.

Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.31; N, 4.62. Found: C, 71.36; H, 8.28; N, 4.73.

Borohydride Reduction of *trans* Keto Lactam 6.—A solution of 0.5 g of lactam **6** in 20 ml of methanol was treated with 0.5 g of potassium borohydride, and the mixture was allowed to stand overnight. The solvent was removed and the residue was partitioned with water and ether. The ether was dried and concentrated to a solid, mp 118–121°. The material after recrystallization from acetonitrile melted at 122–123° and weighed 0.4 g. It was identical in every respect with the material prepared by reduction of hydroxy lactam **7** with 30% palladium on carbon.

Borohydride Reduction of *cis* Keto Lactam 4.—In the same way as described for the *trans* compound, the *cis* keto lactam **4** was reduced with potassium borohydride in methanol to give a single crystalline alcohol, **12**. The analytical sample was prepared by recrystallization from ethyl acetate: mp 133–134°; ν_{max}^{Nujol} 3380, 1610, and 1590 cm^{-1}.

Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.31; N, 4.62. Found: C, 71.32; H, 8.26; N, 4.49.

Oxidation of *trans* Hydroxy Lactam 8 to *trans* Keto Lactam 6.—A solution of 52.5 g of lactam **8** in 2.3 l. of acetone was cooled to 0° and treated with rapid stirring with 47.7 ml of Jones reagent[9] over a period of 4 min. The green slurry was stirred for 3 min at 0°; then sulfur dioxide was passed in for 5 min to decompose excess oxidant. The acetone was removed and water was added to the residue. The precipitated oil was extracted with ether. The aqueous phase was then brought up to pH 6 by addition of 5% sodium hydroxide and the solution was extracted with four additional portions of ether. The combined ether extracts were washed with two small portions of 5% sodium hydroxide and then four times with water, dried, and concentrated to 54 g of yellow oil. This crystallized on scratching with ether. The slurry was cooled overnight to give 42.1 g of off-white solid: mp 82–84°, yield 80%. This material was identical with that prepared by thermal cyclization of amino acid **5**.

In the same way, both of the *cis* hydroxy lactams **9** and **12** were oxidized to the *cis* keto lactam **4**.

Reduction of Acid 1c.—A solution of 10 g (0.0545 mole) of acid **1c** in 275 ml of ethanol was reduced at 50 psi and room temperature over 0.6 g of platinum oxide catalyst. Hydrogen uptake stopped abruptly after absorption of 1 equiv in 1 hr. The catalyst and solvent were removed and the oily residue was taken up in 20 ml of water containing 4.6 g (0.0548 mole) of sodium bicarbonate. This solution was extracted five times with 100-ml portions of methylene chloride. The combined organic phases were dried and concentrated to 7.53 g (82%) of thin water-white oil. This lactone (**10**) was homogeneous by tlc (silica gel G, ethyl acetate, iodine chamber as visualizing agent, R_f 0.70). A sample was distilled for analysis: bp 118–119° (0.03 mm), ν_{max}^{film} 1720–1760 cm^{-1}.

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 63.87; H, 7.43.

The aqueous phase was neutralized with 50 ml of 1 *N* hydrochloric acid and concentrated to a semisolid. This was taken up in methylene chloride, dried, and concentrated to 2.0 g (20%) of a viscous pale yellow oil. This hydroxy acid, **11**, gave a single sharp spot on tlc (silica gel G, 1-butanol–acetic acid–water (5:1:1.5), iodine chamber as visualizing agent, R_f *ca.* 0.6). Its infrared curve showed broad absorption in the 3300- and 1700-cm^{-1} regions. It was used without analysis.

Condensation of Hydroxy Acid 11 with *m*-Methoxyphenethylamine.—A mixture of 1.0 g of acid **11** (5.4 mmoles) and 0.816 g (5.4 mmoles) of *m*-methoxyphenethylamine in 50 ml of xylene was refluxed for 0.5 hr, during which time 0.22 ml of water (0.20 ml theoretical) was collected in the Dean–Stark trap. The xylene was removed to leave 1.68 g of oil which crystallized. This was slurried in a little ether and filtered to give 0.6 g of off white crystals, mp 94–97°. This material was identical with lactam **7** by tlc and infrared spectrum.

Cyclization of Lactams 4 and 6 to Quaternary Salts 13a and 13b.—A solution of 19.6 g of *cis* keto lactam **4** in 600 ml of refluxing benzene was treated with 60 ml of phosphorus oxychloride all at once. The mixture was refluxed for 20 min, then concentrated under vacuum to a red oil. The oil was dissolved in 300 ml of water by warming on the steam bath for 10 min. The solution was clarified with decolorizing carbon, and the yellow filtrate was treated with 10% perchloric acid until precipitation of the oil was complete. The aqueous supernatant was decanted, and the oil was crystallized by rubbing with methanol. The solid **13a** was filtered to give 24.5 g (97%) of material of mp 153–155°. The analytical sample was prepared by recrystallization from methanol: mp 157–158°; ν_{max}^{Nujol} 1740, 1630, 1610, and 1570 cm^{-1}.

Anal. Calcd for $C_{18}H_{22}NO_6Cl$: C, 56.32; H, 5.78; Cl, 9.24. Found: C, 56.20; H, 5.82; Cl, 9.22.

In the same way, both *trans* keto lactam **6** and amino acid **5** were cyclized to the corresponding *trans* quaternary salt (**13b**) isolated as the perchlorate. The analytical sample was recrystallized from methanol: mp 216–218°; ν_{max}^{Nujol} 1745, 1610, 1600, and 1550 cm^{-1}.

Anal. Calcd for $C_{18}H_{22}NO_6Cl$: C, 56.32; H, 5.78; Cl, 9.24. Found: C, 56.08; H, 5.96; Cl, 9.47.

Catalytic Reduction of *cis* Quaternary Salt 13a.—A solution of 53.5 g of quaternary perchlorate **13a** in 3 l. of methanol was hydrogenated over 3 g of platinum oxide catalyst at room temperature and 50 psi. After shaking for 5 min, 1 equiv of hydrogen had been taken up, and absorption stopped. The catalyst was filtered and the filtrate was concentrated to *ca.* 100-ml volume. One liter of water was added followed by 1 l. of 5% sodium hydroxide. The base was extracted with three portions of methylene chloride. The combined organic phase was diluted with ether and dried, and dry hydrogen bromide was passed in. The mixture was concentrated to a white solid. This was dissolved in 3 l. of boiling methanol, and the solution was concentrated until crystallization began (*ca.* 1.8 l.). The solution was cooled and filtered to give 17.5 g of white needles, mp 278–281°, **14a** hydrobromide. The filtrate was concentrated to a semisolid, and the residue was taken up in 400 ml of boiling ethanol. A small second crop of **14a** hydrobromide was filtered from the hot ethanol solution, and the solution was then concentrated to 250 ml and cooled in the freezer. Filtration gave 23.5 g of **14b** hydrobromide as small, off-white plates, mp 232–235°. The yields of the two isomers were 34 and 40%, respectively. On tlc (silica gel G, 1-butanol–acetic acid–water (5:1:1.5), iodine chamber for visualization), **14a** and **14b** hydrobromides migrated as single spots of R_f values of *ca.* 0.35 and 0.40, respectively. The analytical sample of **14a** hydrobromide was prepared by recrystallization from methanol: mp 280–281°; ν_{max}^{Nujol} 2700, 2600, 1745, and 1620 cm^{-1}.

Anal. Calcd for $C_{18}H_{24}NO_2Br$: C, 59.02; H, 6.60; Br, 21.82. Found: C, 59.17; H, 6.72; Br, 22.02.

The free base of **14a** was recrystallized from acetone–water: mp 125–126°; $\nu_{max}^{CCl_4}$ 2790, 2740, 1740, and 1610 cm^{-1}.

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.89; H, 8.39; N, 4.99.

The analytical sample of **14b** hydrobromide was prepared by recrystallization from acetonitrile–ethyl acetate: mp 243–246°; ν_{max}^{Nujol} 2580, 1750, and 1610 cm^{-1}.

Anal. Calcd for $C_{18}H_{24}NO_2Br$: C, 59.02; H, 6.60; Br, 21.82. Found: C, 59.04; H, 6.80; Br, 22.03.

The free base of **14b** was recrystallized from acetone–water: mp 122–123° (with **14a**, mmp 95–97°), $\nu_{max}^{CCl_4}$ 1735 and 1610 cm^{-1}.

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.67; H, 8.37; N, 4.94.

On tlc (silica gel G, ethyl acetate, iodine chamber for visualization), **14a** and **14b** free bases migrated as sharp round spots of R_f values of *ca.* 0.80 and 0.70, respectively.

Catalytic Reduction of *trans* Quaternary Salt 13b.—*trans* quaternary perchlorate **13b** was reduced in the same way as described for the *cis* compound to give a single product, **14c**, in 90% yield. The hydrobromide was recrystallized from ethanol for analysis: mp 246–248°; ν_{max}^{Nujol} 2680, 2580, 1750–1760, and 1620 cm^{-1}.

Anal. Calcd for $C_{18}H_{24}NO_2Br$: C, 59.02; H, 6.60; Br, 21.82. Found: C, 58.75; H, 6.50; Br, 21.88.

The free base was recrystallized from acetone: mp 171–172°; $\nu_{max}^{CCl_4}$ 2800, 2730, 1745, and 1615 cm^{-1}.

Anal. Calcd for $C_{18}H_{23}NO_2$: N, 4.91. Found: N, 5.00.

General Procedure for Demethylation to Phenols 14d, 14e, and 14f.—A mixture of the 8-azaestrone methyl ether and *ca.* 15–20 parts of freshly distilled 48% hydrobromic acid was refluxed for 1 hr. The solution was concentrated to dryness and the semisolid residue was recrystallized. The yields were 80–90%.

14d hydrobromide was recrystallized for analysis from methanol–ether: mp 285–288°; ν_{max}^{Nujol} 3260, 2700, 2600, 1730, 1625, and 1590 cm^{-1}.

Anal. Calcd for $C_{17}H_{22}NO_2Br$: C, 57.96; H, 6.30; Br, 22.69. Found: C, 57.83; H, 6.40; Br, 22.93.

The free base was recrystallized from acetone–water for analysis: mp 226–229°; ν_{max}^{Nujol} 3250, 1710, and 1610 cm^{-1}.

Anal. Calcd for $C_{17}H_{21}NO_2$: N, 5.16. Found: N, 5.32.

14e hydrobromide was recrystallized from methanol–ether for analysis: mp 278–280°; ν_{max}^{Nujol} 3200, 2680, 1745, and 1610 cm^{-1}.

Anal. Calcd for $C_{17}H_{22}NO_2Br$: C, 57.96; H, 6.30; Br, 22.69. Found: C, 58.23; H, 6.33; Br, 22.95.

The free base was recrystallized from acetone–water for analysis: mp 191–193°; ν_{max}^{Nujol} 3400, 1715, and 1610 cm^{-1}.

Anal. Calcd for $C_{17}H_{21}NO_2$: N, 5.16. Found: N, 5.08.

14f hydrobromide was recrystallized from methanol for analysis: mp 284–287°; ν_{max}^{Nujol} 3150, 2680, 2560, 1750, 1620, and 1585 cm^{-1}.

Anal. Calcd for $C_{17}H_{22}NO_2Br$: C, 57.96; H, 6.30; Br, 22.69. Found: C, 58.13; H, 6.47; Br, 22.46.

The free base was recrystallized from acetone for analysis: mp 225–258°; ν_{max}^{Nujol} 3360, 1710, 1620, and 1585 cm^{-1}.

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.13; H, 7.85; N, 4.92.

General Procedure for Reduction of 14 to 15.—The free base of the phenol **14** (5 g) was dissolved in 500 ml of dry tetrahydrofuran and added to a suspension of 5 g of lithium aluminum hydride in 1.5 l. of dry tetrahydrofuran. The suspension was stirred and refluxed for 16 hr. The mixture was decomposed by addition of a small amount of water. The white solid was filtered and washed with tetrahydrofuran and the combined filtrate and washings were concentrated to dryness. The residual white solid was taken up in 2 *N* hydrochloric acid and made basic with dilute ammonium hydroxide, and the white solid was filtered and recrystallized: yield 75–85%.

The *anti-cis* base **15a** was recrystallized from acetone–water for analysis: mp 212–215°; ν_{max}^{Nujol} 3150 and 1610 cm^{-1}.

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.92; H, 8.60; N, 5.21.

The *syn-cis* base **15b** was recrystallized for analysis from methyl ethyl ketone: mp 183–185°; ν_{max}^{Nujol} 3300, 3200, and 1610 cm^{-1}.

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.73; H, 8.48; N, 5.21.

The *anti-trans* base **15c** was recrystallized from acetone for analysis: mp 223–225°; ν_{max}^{Nujol} 3250, 1625, and 1595 cm^{-1}.

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.63; H, 8.25; N, 4.91.

Procedure for Birch Reduction to 16a and 16b.—A solution of 7.6 g (0.024 mole) of base **14a** in 80 ml each of *t*-butyl alcohol and tetrahydrofuran was added to 200 ml of liquid ammonia. Lithium (3 g) was added in small pieces, and the mixture was refluxed with stirring for 2 hr, by which time the blue color was discharged. The ammonia was allowed to evaporate and the solvent was removed. The white solid residue was partitioned between water and ether. The ether layer was extracted with three portions each of 70 ml of 3 *N* hydrochloric acid. The combined acid extracts were diluted with 360 ml of methanol, and the mixture was refluxed for 20 min, then concentrated to dryness. The residue crystallized on rubbing with a little ethanol, and the solid was filtered. The hydrochloride of **16a** was crystallized from ethanol–ether for analysis: mp 191–193°; yield 53%; ν_{max}^{Nujol} 3350, 2680, 2600, 1670, and 1630 cm^{-1}; λ_{max}^{EtOH} 230 mμ (ε 15,400).

Anal. Calcd for $C_{17}H_{26}NO_2Cl$: C, 65.47; H, 8.40; Cl, 11.37. Found: C, 65.53; H, 8.16; Cl, 11.24.

The *trans* base **14c** was subjected to Birch reduction and acid hydrolysis in the same way to give **16b** in 69% yield. The hydrochloride of **16b** formed a partial hydrate which gave a poor analysis. The free base was recrystallized from ethyl acetate for analysis: mp 121–122°; ν_{max}^{Nujol} 3250, 1670, and 1630 cm^{-1}; λ_{max}^{EtOH} 233 mμ (ε 16,600).

Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.14; H, 9.27; N, 5.30.

8-Aza-19-norandrostenedione (17).—A mixture of 27.8 g (0.0726 mole) of the *trans* quaternary perchlorate **13b**, 200 ml of ethylene glycol, 2 l. of benzene and 2 g of *p*-toluenesulfonic acid was refluxed with stirring under a Dean–Stark trap for 16 hr. On cooling the solution, crystallization occurred. The solid was filtered to give 22.8 g (74%) of the ethylene ketal of **13b**, transparent in the carbonyl region of the infrared spectrum.

A solution of 10.2 g of the above quaternary ketal perchlorate in 500 ml of ethanol was treated with stirring with 8 g of potassium borohydride in portions over 0.5 hr. The mixture was stirred for 1 hr and filtered, and the filtrate was concentrated to dryness. The residue was partitioned with water and ether. The ether was dried and concentrated to 6.1 g (78%) of white solid. This material had no absorption in the infrared above 1620 cm^{-1}.

The above 6.1 g of base **14c** ethylene ketal was subjected to Birch reduction and acid hydrolysis as described for *cis* base **14a**. The free base of **17** was recrystallized from ethanol for analysis: mp 193–195°; ν_{max}^{Nujol} 1735, 1670, and 1630 cm^{-1}; λ_{max}^{EtOH} 232 mμ (ε 17,100).

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.44; H, 8.44; N, 5.25.

syn-cis **Acetate 14g.**—A solution of 0.9 g of the hydrobromide salt of *syn-cis* phenol **14e** in a mixture of 20 ml each of acetic acid and acetic anhydride was heated with stirring on the steam bath for 16 hr. The solution was concentrated to dryness, dissolved in water, and made basic with cold 5% sodium hydroxide. The oily base was extracted with methylene chloride; the solution was dried and concentrated to an oil. The oil crystallized readily and was recrystallized from acetone–water for analysis: mp 126–127°; ν_{max}^{Nujol} 1750, 1730, and 1610 cm^{-1}.

Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.97; H, 7.37; N, 4.45.

Acknowledgment.—We thank the Analytical and Physical Chemistry Section under the supervision of Mr. Arnold D. Lewis. In particular, we thank Mrs. Unni Zeek for microanalyses and Mr. Robert Puchalski and Mr. Robert DeSimone for the spectra.