Aza Steroids. IX. Synthesis and Stereochemistry of 12-Keto-17-deoxo-8-azaestrone Methyl Ether[1,2]

A. H. REINE AND A. I. MEYERS

Department of Chemistry, Louisiana State University in New Orleans, Lakefront, New Orleans, Louisiana 70122

Received July 24, 1969

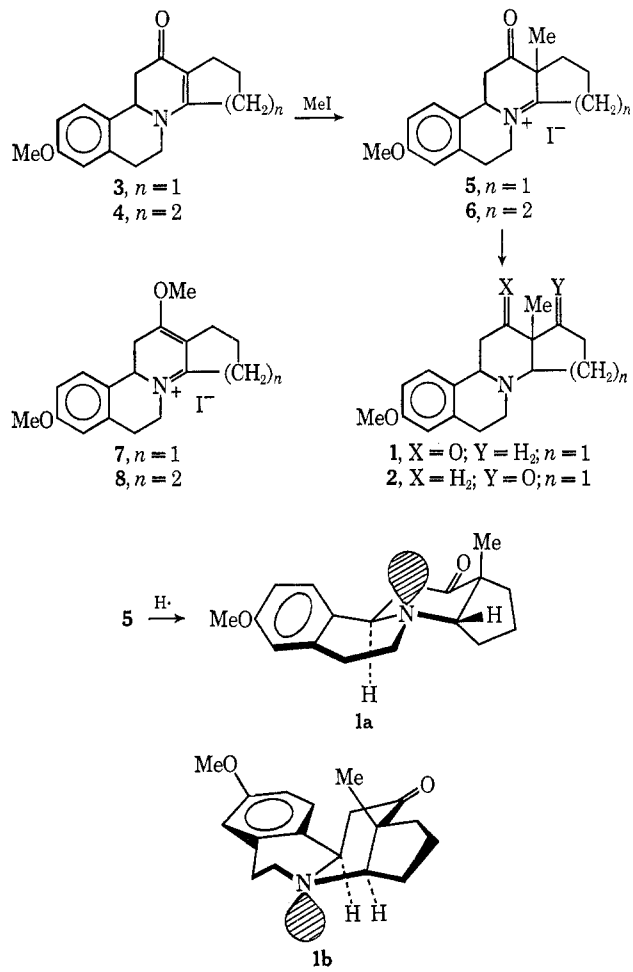
The synthesis of the title compounds was effected in a simple two-step sequence (**3** → **5** → **1**). Reduction of the iminium salt **5** produced, *via* catalytic or metal hydride means, varying mixtures of only two isomers, **1a** and **1b**. The complete stereochemical assignments for these isomers have been accomplished.

In a preliminary communication[3] we reported the synthesis of model systems related to 8-aza steroids. To further explore the utility of this approach, we focused our attention on the synthesis of 12-keto-17-deoxo-8-azaestrone methyl ether (**1**), an isomer of the recently syntheszied[4] 8-azaestrone (**2**). The key intermediates were the readily accessible[5-7] tetracyclic β-amino-α,β-unsaturated ketones (enamino ketones), **3** and **4**, which contain the requisite steroidal skeleton as well as the oxygen function at C-12.

Treatment of **3** with neat methyl iodide produced a mixture of two products which, based upon spectral evidence (Experimental Section), were shown to be the C-methyl salt, **5** (90%), and the O-methyl salt, **7** (10%). The latter could be formed as the sole product when **3** was treated with methyl iodide in methanol. This effect of solvent upon the site of alkylation of the tetracyclic enamino ketone (**3**) has recently been the subject of a study in simple related systems.[8]

The facile introduction of an angular methyl substituent at C-13 in **3** prompted the extension of this same reaction to **4** in an effort to obtain the D-homo-iminium salt, **6**. The results of this experiment indicated that O methylation (**8**) was overwhelmingly favored under all conditions (solvents, temperature, and time).[8]

With the ready accessibility of the aza steroid system (**5**) as a vantage point, the introduction of hydrogen at C-14 became our next task.[9] Reduction of **5** with Adams catalyst in aqueous acid resulted only in reduction of the $\Delta^{8,14}$ iminium bond, yielding two crystalline isomers (**1a**, **1b**) of 12-keto-17-deoxo-8-azaestrone methyl ether (**1**). Separation was effected by the combined methods of fractional crystallization and



preparative layer chromatography. The two isomers obtained (**1a**, mp 90°, and **1b**, mp 139°) were present in highly disproportionate amounts: **1a**, 95%, and **1b**, 5%. This result is somewhat surprising in view of the low order of stereoselectivity observed in the catalytic reduction of the $\Delta^{8,14}$ iminium bond in the 17-keto-8-aza steroid.[4c] This difference in behavior is rationalized on the basis of a "conformational transmission effect" which may be operating in the C-12 keto derivative *vs.* the C-17 isomer.[10] Reduction of **5** with lithium aluminum hydride afforded a mixture of four components (tlc) which were all isomeric 12-hydroxy derivatives (**9**) as shown by the absence of the carbonyl band and the presence of the hydroxyl

(1) This study was supported by the National Institutes of Health (Grant NIGMS-06248) and the Eli Lilly Co., Indianapolis, Ind.

(2) Taken from the Ph.D. Dissertation of A. H. Reine, June 1968.

(3) A. I. Meyers, G. G. Munoz, W. Sobotka, and K. Baburao, *Tetrahedron Lett.*, No. 4, 255 (1965).

(4) (a) R. E. Brown, D. M. Lustgarten, R. J. Stanaback, and R. I. Meltzer, *J. Org. Chem.*, **31**, 1489 (1966); (b) R. Clarkson, *J. Chem. Soc.*, 4900 (1965); (c) A. I. Meyers and J. C. Sircar, *Tetrahedron*, **23**, 785 (1967).

(5) W. Sobotka, W. N. Beverung, G. G. Munoz, J. C. Sircar, and A. I. Meyers, *J. Org. Chem.*, **30**, 3367 (1965).

(6) A. I. Meyers, A. H. Reine, J. C. Sircar, K. B. Rao, S. Singh, H. Weidmann, and J. M. Fitzpatrick, *J. Heterocycl. Chem.*, **5**, 151 (1968).

(7) Systems of the type **2** and **3** have also been reported by an interesting and facile ring closure involving dihydro isoquinolines and 1,3 diketones: M. VonStrandtmann, M. P. Cohen, and J. Shavel, *J. Org. Chem.*, **31**, 797 (1966).

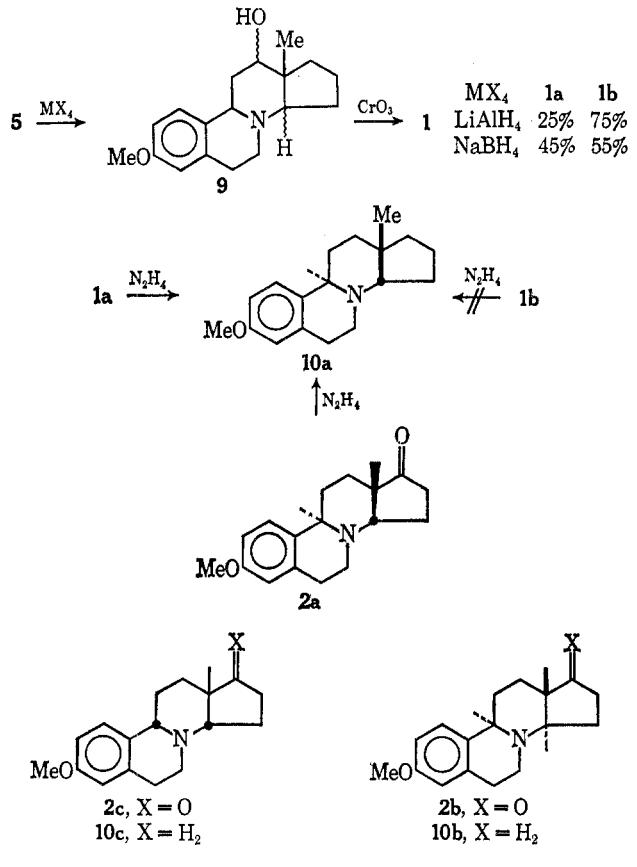
(8) A. I. Meyers, A. H. Reine, and R. Gault, *ibid.*, **34**, 698 (1969).

(9) Since **5** possesses two asymmetric centers (C-8 and C-13), it should have been obtained as a mixture of diastereoisomers. However, extensive attempts to detect any inhomogeneity in **5** were without success. It is difficult to envision, using models, why the methyl iodide should enter the enamino ketone **2** from a single pathway; yet the total C-methyl salt formed gave after recrystallization 90% recovery of pure material. Thus if the other diasteriomer was present it could not have exceeded 10% of the 3-methyl salt obtained during the alkylation. The use of nmr also failed to detect any presence of mixed methyl singlets, since the signal observed was indeed very sharp (half band width < 1 cps).

(10) D. H. R. Barton, *J. Chem. Soc.*, 955 (1957).

absorption in the infrared. The mixture was subjected to Jones oxidation[11] and **1b** and **1a** in a 3:1 mixture were the only products isolated. The reduction was also performed on **5** with sodium borohydride in aqueous ethanol, producing a four-component mixture of 12-hydroxy derivatives (**9**) which were subsequently oxidized by the Jones method to a 55:45 mixture of **1a** and **1b**, respectively.

In order to establish the configuration of the isomers of **1**, a direct comparison with the 17-keto aza steroids (**2**) would be possible. However, only three (**2a–2c**) of the four possible isomers have been identified.[4] Both **1a** and **1b** were reduced to their respective 12-deoxo derivatives (**10**) and comparisons were made with the 17-deoxo derivatives of **2**. It was found that **10a** was identical in every respect with the *trans,syn,cis* (9α,14β) isomer obtained by the Warner–Lambert group[12] by reduction of **2a**. The 12-deoxo derivative of **1b**, however, was not comparable with any of the other available or known systems. It was anticipated that the **1b** isomer would be stereochemically identical with **2b**, since the entry of hydride in **5** could only come

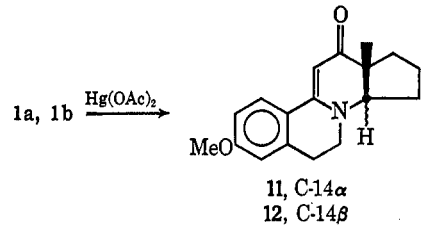


from the β side, which gave ultimately **10a** (14β H), or attack from the α side to give **10b** (14α H). It was therefore surprising to find that the reduction product of **1b** was not identical with the 17-deoxo derivative, **10b**. The new isomer then became the subject for complete spectroscopic scrutiny.

The infrared spectrum of the 12-deoxo derivative of **1b** displayed simple absorption in the CH region, indicating the absence of Bohlmann bands,[13] whereas the nmr spectrum exhibited a downfield signal for the C-9 proton at τ 5.76.[14] The infrared spectrum revealed the absence of Bohlmann bands and the C-9 proton resonance at τ 5.32. These data support the presence of a *cis*-quinolizidine (BC-*cis*) in **1b** and its 12-deoxo isomer. The C-18 protons were also found to be axially situated by virtue of an upfield shift in changing solvents from chloroform to benzene.[15]

Attempts at direct thermal isomerization of 12-deoxo **1b** to **10a–10c** by refluxing for 24 hr in toluene afforded unchanged material. *The failure of* **1b** *(or its 12-deoxo derivative) to isomerize to a trans-quinolizidine moiety indicates the high conformational stability of the cis-quinolizidine structure in this tetracyclic system.* It is generally assumed that the *trans* conformation in quinolizidines is the more stable one.[16] However, it has been shown that in certain cases of substituted quinolizidines, the *cis* conformation is preferred.[13,17] Hence, it was not surprising that the *cis*-quinolizidine moiety in **1b** should show such resistance to isomerization.

The possibility of converting isomers **1a** and **1b** into a common product without affecting the configuration at C-14 was considered. The most accessible product was thought to be the enamino ketone, 12-keto-17-deoxo-8-aza-9,11-dehydroestrone methyl ether (**11**), resulting from the mercuric acetate oxidation of isomers **1a** and **1b**. If **1a** and **1b** had the same configuration at C-13 and C-14, then mercuric acetate oxidation would lead to the same enamino ketone in both cases. However, if **1a** and **1b** were configurationally different at C-14, then mercuric acetate oxidation would produce two different enamino ketones, **11** and **12**, respectively. Mercuric



acetate oxidation of **1a** led to the phenyl-conjugated enamino ketone, **11**. The structure of this product was established on the basis of the infrared spectrum, which exhibited no carbonyl stretching band below 6.5 μ and showed a broad maximum at 6.45 μ previously associated with the vinylogous amide structure.[5,6,18] The ultraviolet spectrum had maxima at 424 (shoulder), 365, and 288 mμ. Conclusive evidence for the location of the double bond in **14** was provided by the nmr spectrum, which exhibited a vinyl proton singlet at τ 4.43.

The relative rates of mercuric acetate oxidation of **1a** and **1b** at room temperature were determined by measuring the increase in ultraviolet absorption at 365 mμ.

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

(12) We wish to thank Dr. R. E. Brown (Warner–Lambert) for supplying us with samples of the three characterized isomers of 17-deoxo-8-azaestrone methyl ether.

(13) F. Bohlmann, *Chem. Ber.*, **91**, 2517 (1958).

(14) M. Uskakovic, H. Bruderer, C. vonPlanta, T. Williams, and A. Brossi, *J. Amer. Chem. Soc.*, **86**, 3364 (1964).

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

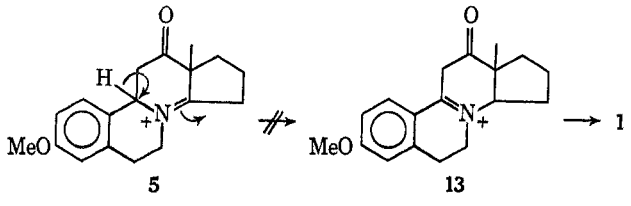
(16) F. Galinovsky and N. Nesvadba, *Montash. Chem.*, **85**, 1300 (1954); N. J. Leonard and W. K. Musker, *J. Amer. Chem. Soc.*, **82**, 5148 (1960).

(17) K. Schofield and R. J. Wells, *Chem. Ind.* (London), 572 (1963); S. F. Mason, K. Schofield, and R. J. Wells, *Proc. Chem. Soc.*, 337 (1963).

(18) N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Franck, and D. J. Wallace, *J. Amer. Chem. Soc.*, **71**, 3337 (1949).

Oxidation was over 90% complete for **1a** after 12 hr. On the other hand, **1b** exhibited no absorption at 365 mμ even after 48 hr. The failure of **1b** to oxidize cleanly to the desired enamino ketone (**11** or **12**), coupled with the results from the relative rate studies, provided additional evidence for the BC-*cis* ring fusion in this compound. The failure of *cis*-quinolizidine moieties to undergo mercuric acetate oxidation has been noted previously.[19,20] The electron pair on the nitrogen atom and the α tertiary hydrogen (C-9) must be *trans* diaxial to each other. This preferred stereochemistry is absent in a conformationally rigid structure with a *cis*-quinolizidine moiety such as **1b**.[21]

The possibility that isomerization of **5** to **13** had occurred *via* an ylide prior to reduction of the C=N link was eliminated when $LiAlD_4$ was employed and showed only deuterium at C-14 and the total absence of deuterium at C-9.



5 13

Experimental Section[22]

8-Methoxy-1 2,5,6,10b,11-hexahydro-3H,12H-benzo[*a*]cyclopentano[*f*]quinolizin-12-one (**3**) was prepared as previously described,[5] mp 185–187°.

9-Methoxy-1,2,3,4,6,7,11b,12-octahydro-13H-dibenzo[*a*,*f*]-quinolizin-13-one (**4**).—A mixture of 5.0 g (0.02 mol) of isoquinoline ester[5] and 30 g (0.3 mol) of cyclohexanone in 100 ml of toluene was heated with a Dean–Stark separator in an inert atmosphere of nitrogen for 4 days. Evaporation of the solvent afforded an oil, which on trituration with ether gave 4.28 g (76%) of a crystalline solid: mp 157–160°; ir (CCl_4) 6.08 (s), 6.40 (br s), and 6.95 μ; uv (EtOH) 336 mμ (ε 13,600) and 288 (2900). Recrystallization of this material from ethanol–ether gave 2.25 g of colorless crystals, mp 156.5–159°. The perchlorate salt was prepared by adding 1:1 perchloric acid–ether to an alcoholic solution of **9**. The salt was recrystallized from 1:1 acetonitrile–ether, mp 252–253°, uv (EtOH) 336 mμ (ε 14,000).

Anal. Calcd for $C_{18}H_{21}NO_2$: C, 56.33; H, 5.78; N, 3.65. Found: C, 56.12; H, 5.90; N, 3.76.

8-Methoxy-12a-methyl-1,2,5,6,10b,11-hexahydro-3H,12H-oxobenzo[*a*]cyclopentano[*f*]quinolizinium Iodide (**5**). **A. In Methyl Iodide.**—A mixture of 9.0 g (3.3 mmol) of **2** and 200 ml of methyl iodide on heating under nitrogen for 15 days deposited 11.1 g (83%) of an off-white, amorphous solid, which was washed with chloroform and air dried. The ultraviolet spectrum of this material exhibited maxima at 336 and 276 mμ and indicated that the product was a mixture of about 90% C-methylated salt **4** and 10% O-methylated salt **7**. The infrared spectrum (Nujol) had absorption bands at 5.78 (s), 5.95 (w), 6.15 (m), 6.28 (m), 6.45 (m), and 6.00 μ.

Recrystallization of this material from acetonitrile gave **5** as colorless crystals: mp 247–250°; ir (Nujol) 5.78, 5.95, 6.15, 6.30, and 6.60 μ; uv (EtOH) 276 mμ (ε 2800). The absorption in the ultraviolet region at 336 mμ, characteristic of **7**, disappeared after one recrystallization. The nmr spectrum of pure **5** in hexadeuteriodimethyl sulfoxide showed that the product was isomerically homogeneous with a single, symmetrical methyl hydrogen signal at τ 8.87.

The analytical sample was recrystallized from ethanol, mp 248–250°.

Anal. Calcd for $C_{18}H_{22}NO_2I$: C, 52.56; H, 5.29; N, 3.40. Found: C, 52.40; H, 5.52; N, 3.47.

Evaporation of the excess methyl iodide solvent gave a solid residue, mp 170–177°, whose infrared spectrum was identical with that of the starting tetracyclic enamino ketone, **3**.

8,12-Dimethoxy-1,2,5,6,10b,11-hexahydro-3H-benzo[*a*]cyclopentano[*f*]quinolizinium Iodide (**7**).—A mixture of 1.55 g (5.7 mmol) of **3** and 14.0 g (0.1 mmol) of methyl iodide in 50 ml of methanol was refluxed for 24 hr, cooled to room temperature, and reduced to smaller volume, and 50 ml of anhydrous ether was added, causing precipitation of 1.54 g (65%) of a light yellow, amorphous solid. The infrared spectrum of this material showed no carbonyl peaks but had absorption at 5.95, 6.25, 6.40, and 6.80 μ. The ultraviolet spectrum had maxima at 336 and 276 mμ.

Recrystallization from methanol yielded 1.06 of **7** as colorless crystals: mp 245–247°; ir (Nujol) 5.95, 6.25, 6.40, and 6.80 μ; uv (EtOH) 336 mμ (ε 14,600) and 276 (2800).

Anal. Calcd for $C_{18}H_{22}NO_2I$: C, 52.56; H, 5.39; N, 3.40. Found: C, 52.44; H, 5.33; N, 3.41.

9,13-Dimethoxy-1,2,3,4,5,6,11b,12-octahydrodibenzo[*a*,*f*]-quinolizinium Iodide (**8**).—A mixture of 1.0 g (3.5 mmol) of **4** and 50 ml of methyl iodide was heated at reflux for 7 days to give 0.155 g (10.5%) of an amorphous solid. The infrared spectrum (Nujol) of this material showed very minor absorption at 5.75 μ and very strong absorption at 6.09, 6.15, 6.25 (m), and 6.61 μ. The ultraviolet spectrum had maxima at 335 (ε 12,800) and 228 mμ (ε 3600).

Recrystallization of this solid, yield 0.155 g, from ethanol–ethyl acetate gave fine, white crystals, mp 275–280°. A second recrystallization from acetonitrile afforded white crystals: mp 277–280°; ir (Nujol), 6.10, 6.17, 6.27, and 6.61 μ; uv (EtOH) 335 mμ (ε 14,460) and 228 (3900).

Anal. Calcd for $C_{19}H_{24}NO_2I$: C, 53.65; H, 5.68; N, 3.29. Found: C, 53.45; H, 5.49; N, 3.30.

Evaporation of the methyl iodide solvent gave a solid residue, 0.900 g, identified as the starting tetracyclic enamino ketone **4** by melting point, mixture melting point, and infrared spectral comparison with an authentic sample.

12-Keto-17-deoxo-8-azaestrone Methyl Ether (**1a**, **1b**). **A. Catalytic Hydrogenation of Quaternary Iminium Salt** (**5**).—A suspension of 2.05 g (0.05 mol) of methiodide salt **5** in 100 ml of water was acidified with 6.0 g of concentrated hydrochloric acid and 10 ml of glacial acetic acid. After 0.3 g of Adams catalyst had been added, the mixture was hydrogenated in a Paar apparatus for 24 hr. The catalyst was removed by filtration and washed with water. Addition of sodium hydroxide rendered the aqueous solution alkaline and it was extracted with ether several times. Drying (Na_2SO_4) and evaporation left 0.824 g (66%) of crude 12-keto-17-deoxo-8-azestrone methyl ether (**1**) as a yellow oil, ir (CCl_4) 3.55, 3.60 (Bohlmann bands), 5.80, 6.19, 6.55, and 6.83 μ. Analytical tlc [silica gel G, hexane–ethyl acetate (7:3)] showed the presence of two components (iodide vapor detector), a minor component (**1b**) of R_f 0.25 and a major component (**1a**) of R_f 0.50. Crystallization of this material from hexane afforded isomer **1a** as off-white crystals: yield 0.485 g; mp 85–90°; ir (CCl_4) 3.51, 3.57 (Bohlmann bands), 5.81, 6.15, 6.63, and 6.80 μ. Analysis of this substance by tlc showed it to be homogeneous, since only a single spot was evident (R_f 0.52). The analytical sample was recrystallized from hexane, mp 90–93°.

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.60; H, 7.99; N, 5.09.

The hexane filtrate from the crystallization, on evaporation, yielded 0.300 g of an oily residue, which was shown to be a mixture of the same two components (R_f 0.50 and 0.25) by tlc. This residue was purified by preparative thin layer chromatography on neutral silica gel G. The plate (0.5 mm × 20 cm × 20 cm) was developed with ethyl acetate–hexane (3:7, v/v) to give two bands detectable by ultraviolet light. The silica gel in each band was removed from the plate and the compound was

(19) F. L. Weisborn and P. A. Diassi, *J. Amer. Chem. Soc.*, **78**, 2023 (1956).

(20) N. J. Leonard and D. F. Morrow, *ibid.*, **80**, 371 (1958).

(21) The stereochemical elucidation of configuration and conformation for **1b** was partially based on application of the nmr and infrared methods mentioned above and in addition on the use of the 220-MHz spectrum of **1b** and its corresponding C-14 deuterated analog. The details have been published earlier [N. S. Bhacca, A. I. Meyers, and A. H. Reine, *Tetrahedron Lett.*, No. 19, 2293 (1968)] and need not be reiterated here.

(22) The nmr spectra were measured with a Varian A-60 spectrometer and are reported in τ values using tetramethylsilane as an internal standard. Unless otherwise stated, all spectra were run using deuteriochloroform as solvent. Infrared spectra were determined on a Beckman IR-5 instrument. Thin layer chromatography was caried out on silica gel G (PF_{254}). All melting points were determined on a Fisher-Johns block and are corrected. Elemental analysis was done by Galbraith Laboratories, Inc., Knoxville, Tenn.

recovered by elution with chloroform. The main zone gave 136.5 mg of **1a** as an oil which solidified to a waxy solid on standing. Recrystallization from hexane gave colorless needles, mp 88–91°. The infrared spectrum in carbon tetrachloride was identical with that of isomer **1a**.

The minor zone near the origin gave 39.5 mg of an oil which solidified to a waxy solid on standing. Recrystallization from hexane gave colorless rods, mp 136–139°. The infrared spectrum exhibited no Bohlmann bands, only peaks at 5.80, 6.19, 6.65, 6.80, and 6.93 μ. Analysis of this material by tlc showed it to be isomer **1b**, the minor isomer in the original mixture of amino ketones. In the nmr spectrum, the C-9 proton signal appeared downfield as two doublets centered at τ 5.32 equal in area to one proton, the methoxyl group appeared as a three-proton singlet at τ 6.22, and the C-18 methyl protons appeared as a three-proton singlet at τ 8.77. The analytical sample was recrystallized from hexane, mp 137–139°.

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.78; H, 8.15; N, 5.04.

B. Lithium Aluminum Hydride Reduction and Oxidation of Quaternary Iminium Salt 5.—To a stirred suspension of 0.50 g (1.21 mmol) of the methiodide salt **5** in 50 ml of anhydrous ether was added 1.0 g of lithium aluminum hydride. The reaction mixture was refluxed for 24 hr and cooled in a Dry Ice–ethanol bath, and excess hydride was decomposed by successive addition of 2 ml of water, 2 ml of 15% sodium hydroxide, and 6 ml of water. After vigorous stirring for another 15 min, the mixture was filtered with suction, the granular precipitate was washed thoroughly with ether, and the combined ethereal solution was dried (K_2CO_3). Evaporation of the ether solvent gave 0.281 g (80%) of an off-white solid: mp 120–133°; ir (CCl_4) 2.73, 3.51, 3.59, 6.18, 6.65, and 6.80 μ. Analysis of this product by tlc [silica gel G, ethyl acetate–methanol (9:1), iodine vapor chamber] gave four bands (R_f 0.18, 0.33, 0.46, and 0.64) of an isomeric mixture of **9**.

A solution of 0.281 g (1.0 mmol) of the above amino alcohol mixture in 15 ml of acetone was cooled to 0° and treated with 1.5 ml of Jones reagent[11] over a period of 5 min. The reaction mixture was actively stirred for 2.5 hr and diluted with 15 ml of water, and the volatile solvents were removed under reduced pressure at room temperature. The aqueous solution was then made alkaline with powdered potassium hydroxide and extracted three times with chloroform. Evaporation of the dried chloroform extract afforded 0.121 g (43%) of yellow oil, ir (CCl_4) 3.56, 3.60, 5.80, 6.17, 6.65, 6.80, and 6.95 μ. Thin layer chromatography of this material showed a major spot for the high-melting isomer **1b** (mp 136–139°, R_f 0.23) and a weak spot for the low-melting isomer **1a** (mp 89–91°, R_f 0.51).

Crystallization of the amino ketone mixture from petroleum ether (bp 30–60°) gave 72 mg of **1b**, mp 134–136°. The mother liquor was evaporated to give 62 mg of a yellow oil which was separated into 20 mg of **1b** and 21 mg of **1a** on preparative tlc (0.5 mm × 20 cm × 20 cm plate) on elution with ethyl acetate–hexane (3:7).

The C-14 deuterated analogs of **1a** and **1b** were prepared as above by treatment of the C-methyl salt **5** with lithium aluninum deuteride.

C. Sodium Borohydride Reduction and Oxidation of Quaternary Iminium Salt 5.—A solution containing 1.0 g of sodium borohydride in 15 ml of ethanol was added at once to a stirred suspension 0.500 g of quaternary iminium salt **5** in 15 ml of water. A clear, effervescent mixture immediately resulted and was allowed to stir at room temperature for 1 hr. The excess reagent was destroyed by the addition of glacial acetic acid, and the solution was concentrated *in vacuo* to *ca.* 15 ml, made alkaline with 40% sodium hydroxide, and extracted with ether. Evaporation of the dried ether extract afforded 0.379 g of pale yellow oil, ir (CCl_4) 2.73, 2.85, 6.18, 6.68, and 6.81 μ. Analysis of this amino alcohol **9** mixture by tlc [silica gel G, ethyl acetate–methanol (9:1), iodine vapor chamber] gave three spots.

A solution of 0.379 g of the above amino alcohol mixture was treated with Jones reagent and yielded 0.200 g (53%) of a yellow oil which was shown by tlc to be a mixture of amino ketone isomers **1a** and **1b**. The product mixture was subjected to preparative thin layer chromatography as previously described to yield 81 mg of isomer **1a** and 105 mg of isomer **1b**.

17-Deoxo-8-Azaestrone Methyl Ether (10a). Wolff–Kishner Reduction of Isomer 1a.—A mixture of 200 mg of 12-keto-17-deoxo-8-azaestrone methyl ether (**1a**), 3 ml of triethylene glycol, and 1.0 ml of 85% hydrazine was heated at 130° (bath temperature) for 24 hr. After 500 mg of anhydrous potassium *t*-butoxide, had been added, the temperature was gradually raised to 215° by distilling out the low-boiling material; the mixture was heated at this temperature for 60 min and cooled; and ice–water was added. The solution was extracted three times with 20-ml portions of ether which were combined and dried (K_2CO_3). Evaporation afforded 128 mg of a yellow oil. The crude product was chromatographed (hexane) on a column containing 1.0 g of Woelm activity I alumina. The solvent was evaporated *in vacuo* to afford 97 mg of the reduced product, 17-deoxo-8-azestrone methyl ether (**10a**), as a colorless oil, ir (CCl_4) 3.55, 3.62 (Bohlmann bands), 6.18, 6.65, 6.80, and 6.95 μ. Analysis by tlc showed it to be a homogeneous product. The nmr spectrum of the reduced product, **10a**, and that derived from **2a** were superimposable and showed no signal downfield from τ 6.25 (OCH_3) except for the three aromatic proton signals at τ 2.95–3.53.

The hydrobromide was prepared by treating an ethereal solution of **10a** with dry hydrogen bromide, mp 293–295° from methanol. The melting point of the hydrobromide of **10a** on admixture with that obtained from **2a** showed no depression, mp 295–298°.

The perchlorate was prepared by treating an ethereal solution of **10a** with 70% perchloric acid and recrystallized from methanol as colorless crystals, mp 239–242°.

Anal. Calcd for $C_{18}H_{26}NO_5Cl$: C, 58.14; H, 7.05; N, 3.77. Found: C, 58.27; H, 7.13; N, 3.81.

Wolff–Kishner Reduction of Isomer 1b.—The C-12 keto group in isomer **1b** (140 mg) was reduced by the previously described procedure to afford 79 mg of the corresponding 17-deoxo derivative as a visuous oil which solidified to a waxy solid: ir (CCl_4) 6.20, 6.68, 6.85, and 6.95 μ; nmr ($CDCl_3$) τ 2.70–3.33 (m, 3 H, aromatic), 5.76 (m, 1 H, C-9), 6.24 (s, 3 H, OMe), and 9.05 (s, 3 H, C-18).

12-Keto-17-deoxo-8-aza-9,11-dehydroestrone Methyl Ether (11). Mercuric Acetate Oxidation of Isomer 1a.—The amino ketone **1a** (100 mg, 0.35 mmol) was added to a solution of 300 mg (1 mmol) of mercuric acetate in 4 ml of acetic acid and the mixture was kept at room temperature for 24 hr. A 10-μl aliquot was removed and diluted to 10 ml with distilled water. The ultraviolet spectrum exhibited maxima at 365 and 310 mμ. The precipitated mercurous acetate was removed by filtration, water was added to the filtrate, the solution was saturated with hydrogen sulfide, and the resulting black precipitate was removed by centrifugation. The resulting clear centrifugate was basified with 40% sodium hydroxide and extracted with three 19-ml portions of chloroform. Evaporation of the dried chloroform extract gave 92 mg of 12-keto-17-deoxo-8-aza-9,11-dehydroestrone methyl ether (**11**) as a yellow oil which darkened on standing: ir (CCl_4) 6.15, 6.30, 6.45, and 6.71 μ; uv (EtOH) 424 mμ (shoulder), 365 (ϵ 10,270), and 288 (10,000); nmr ($CDCl_3$) τ 4.42 (s, 1 H, C-11). The picrate was prepared with a saturated solution of picric acid in ethanol. Recrystallization from ethanol gave long, yellow needles, mp 210–214°.

Anal. Calcd for $C_{24}H_{24}N_4O_9$: C, 56.25; H, 4.72; N, 10.93. Found: C, 55.85; H, 5.09; N, 10.89.

Registry No.—**1a**, 19518-45-7; **1b**, 19518-46-8; **4**, 5206-92-8; **4** perchlorate, 22955-68-6; **5**, 22955-69-7; **7**, 22955-70-0; **8**, 22955-71-1; **10a**, 22966-36-5; **10a** perchlorate, 22966-37-6; **11**, 22966-38-7; **11** picrate, 22966-39-8.