tion of sodium. After the blue color disappeared the N-phenyl-β-bromopropionamide (5.7 g) was added in small amounts. The mixture was then left at room temperature. When all the ammonia had evaporated the residue was extracted with benzene. The benzene extract was washed with water and dilute hydrochloric acid and dried over magnesium sulfate. Evaporation of the solvent afforded 2.6 g (68%) of the product which was crystallized from ethanol–water mixture, mp 77–78° (lit.[17] mp 78–79°), λ_{max}^{Nujol} 5.72 μ. The proton nmr spectrum showed multiplet at τ 2.79 (5 H, aromatic), triplet centered at 6.49 (CH_2N), and another triplet at 7.03 (CH_2CO).

B. Using the Sodium Hydride–DMSO Method.—In a flame-dried, two-necked flask, fitted with a nitrogen inlet and a dropping funnel, were placed DMSO (about 10 ml) and sodium hydride (0.6 g). The flask was warmed in the oil bath carefully below 75° under vigorous stirring until the evolution of hydrogen ceased. The color of the solution in the flask turned light brown. This solution was cooled to room temperature, and a methylene chloride solution (20 ml) of N-phenyl-β-bromopropionamide (4.6 g) was added dropwise. The reaction mixture was allowed to stand for 8 hr. Water was then added to the reaction mixture and extracted with benzene. The benzene extract was treated as usual to get the β-lactams (2.86 g, 95.6%).

C. Using the Potassium *t*-Butoxide–DMSO Method.—The procedure was essentially the same as in method B excepting that potassium *t*-butoxide was substituted for sodium hydride.

Registry No.—N-*p*-Bromophenyl-2,2-dimethyl-3-chloropropionamide, 7661-06-5; in Table I—**1**, 7661-07-6; **2**, 7661-08-7; **3**, 7661-09-8; **4**, 7661-10-1; **5**, 7661-06-5; **6**, 7661-12-3; **7**, 7661-13-4; **8**, 7661-14-5; **9**, 7661-15-6; **10**, 7661-16-7; **11**, 7661-17-8; **12**, 7634-72-2; **13**, 7661-18-9; **14**, 7661-19-0; **15**, 7661-20-3; **16**, 7661-21-4; **17**, 7661-22-5; in Table II—**1**, 4458-63-3; **2**, 7661-23-6; **3**, 7661-24-7; **4**, 7661-25-8; **5**, 7661-26-9; **6**, 7661-27-0; **7**, 7661-28-1; **8**, 7661-29-2; **9**, 4641-57-0; **10**, 7661-30-5; **11**, 7661-31-6; **12**, 7661-32-7; **13**, 7661-33-8; **14**, 7661-34-9; **15**, 4789-09-7; **16**, 7661-36-1.

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Aza Steroids. VII. 18-Nor-D-Homo-8-Aza Steroids

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In a continuing study[2] on the total synthesis of aza steroids, we have prepared, *via* a novel route, the 18-nor-D-homo-8-azaestrone derivative, I, previously described by Nelson,[3] *via* II. Our approach to I began with the tetrahydroisoquinoline, III, which condensed smoothly with 1,3-cyclohexanedione to give the enamino ketone alcohol IV, in good yield.[2] However, when the latter was treated with phosphorus tribromide, an oily bromide, V, was obtained which slowly crystallized, on standing, to a salt containing ionic bromine. The ultraviolet spectrum of salt possessed a maximum at 318 mμ (ε 33,400) and infrared bands typical of the conjugated iminium linkage. As previously reported,[2] the bromide V, when treated immediately after preparation with silver perchlorate in acetonitrile, gave an unstable iminium salt (VI, X = ClO_4), which was quickly neutralized with dilute base to give VII in high yield. The structure of the salt obtained by spontaneous cyclization of V was still uncertain, but further insight into its nature was obtained when this salt produced VII when cautiously neutralized with dilute base. Alternatively, VII, upon treatment with hydrogen bromide, gave VIII (see Scheme I). On the basis of this behavior the salt was assigned the structure, VIII, which is the O-protonated form of the enamino ketone VII.

When VIII and VI each were hydrogenated in the presence of platinum oxide, the amino alcohol IX, was obtained as the sole product in both cases. The stereochemistry of IX was assigned by both chemical and spectroscopic techniques. Considering the BC-ring junction initially, IX was completely devoid of Bohlmann bands[4] in the infrared; yet the nmr spectrum exhibited the C-9 proton (steroid numbering) at τ 6.4. The data obtained from these techniques proved to be contradictory since *trans*-quinolizidines have usually been found to possess Bohlmann bands and exhibit the C-9 proton above τ 6.2.[5] In order to clarify the discrepancy of the BC fusion, the alcohol IX was oxidized to the ketone I using the Jones method.[6] Examination of I clearly showed the Bohlmann absorption of the *trans*-quinolizidine (BC rings) and the C-9 proton at 6.3–6.4 (partially masked under the *methoxyl* singlet). A search of the literature provided other examples where Bohlmann bands appeared *not* to have been observed in systems known to possess the *trans*-quinolizidine moiety.[7] The possibility still remained, however, that the Jones oxidation proceeded with epimerization at C-9, resulting in the *trans*-BC junction. This possibility was discarded when the ketone I was reduced stereospecifically back to the starting alcohol IX, and the Bohlmann bands were once again absent. With the BC-ring stereochemistry firmly established, the stereochemistry at C-13, -14, and -17a was next investigated. The CD junction can be considered to be *trans* since no epimerization occurred when the ketone I was equilibrated with base. Nelson[3] has also assigned the *trans*-CD junction to ketone I, obtained by lithium aluminum hydride reduction of VII, as well as the *trans*-BC junction. The configuration of the 17a-hydroxyl group in IX was assigned an *axial* position based upon nmr chemical shifts of axial and equatorial cyclohexanols. Eliel has shown[8] that the carbinol proton in axial alcohols appear at 210–250 cps and at 180–190 cps for equatorial alcohols. The carbinol proton in IX appeared at 240–250 cps (τ 5.8–6.0).

(1) This study was supported by funds granted by the National Institutes of Health (NIGMS-06248-06).

(2) For the previous paper in this series, *cf.* A. I. Meyers and J. C. Sircar, *Tetrahedron*, **23**, 785 (1967).

(3) N. A. Nelson and Y. Tamura, *Can. J. Chem.*, **43**, 1323 (1965).

(4) F. Bohlmann, *Ber.*, **91**, 2157 (1958); R. E. Brown, D. M. Lustgarten, R. J. Stanaback, and R. I. Meltzer, *J. Org. Chem.*, **31**, 1489 (1966).

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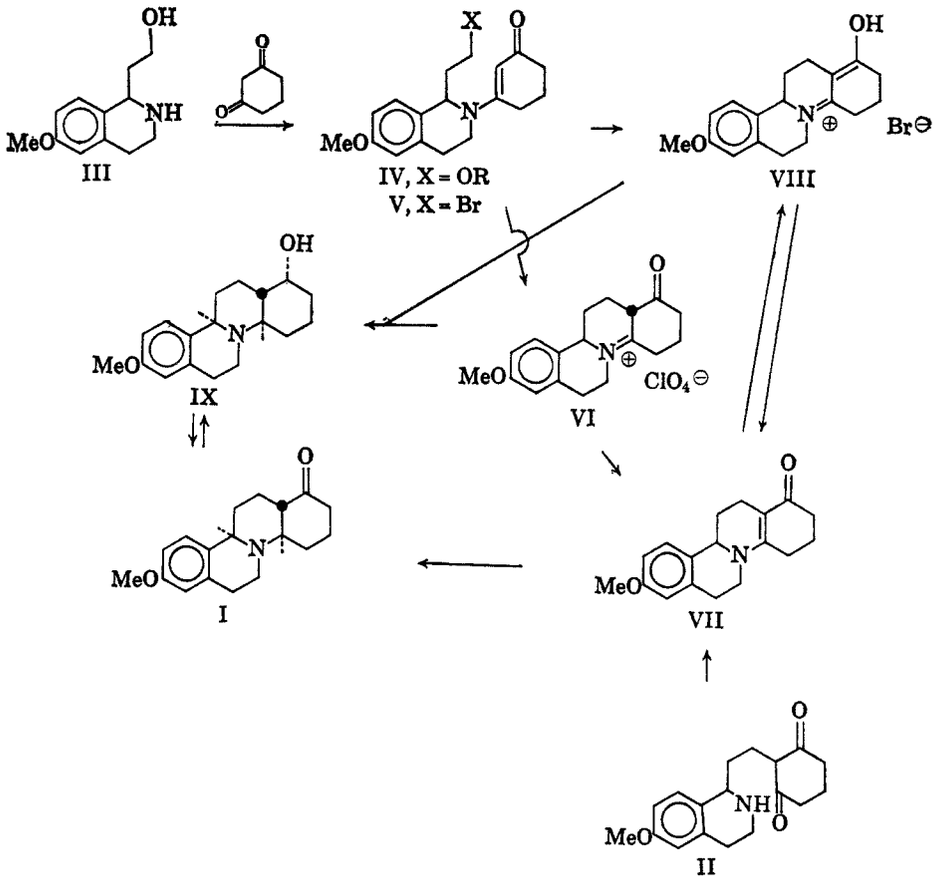
(8) E. I. Eliel, M. H. Gianni, T. H. Williams, and J. B. Stothers, *Tetrahedron Letters*, No. 17, 741 (1962).

SCHEME I



Additional support for the axial hydroxyl group stems from the observation that catalytic hydrogenation of I in acidic medium gave IX, a procedure well known to give the axially oriented alcohol.[9]

The synthetic utility of this process, leading to I is borne out by the fact that the over-all yield is 18% in five steps (III → IV → V → VI → IX → I).

Experimental Section[10,11]

Spontaneous Cyclization of Bromide V to VIII.—A solution of 1.60 g of the enamino ketone IV in 30 ml of chloroform was cooled in an ice bath and treated with 12 g of phorphorus tribromide in 40 ml of chloroform. The reaction mixture was stirred at 0° for 20 hr and heated at 55–60° for 1 hr, and then decomposed in ice. After neutralization with potassium carbonate, the product was extracted with chloroform and dried over sodium sulfate. The solvent was removed at room temperature *in vacuo* to give 1.70 g of V as an oil: λ_{max}^{EtOH} 305 mμ; λ^{CHCl_3} 6.18, 6.50 μ; nmr (τ, $CDCl_3$), 2.78–3.29, three protons (multiplet, aromatic), 4.52, one proton (singlet, vinyl), 4.81–5.07, one proton (triplet, C-9), 6.22 (singlet, methoxyl), 6.25–6.48 (triplet, CH_2Br). Upon standing at room temperature the oil began crystallizing and became completely solid after 72 hr. The latter was recrystallized from absolute ethanol (100 ml) and 1.32 g (68%) of VIII was obtained: mp 240–244° dec (admixture with the hydrobromide salt VIII, prepared by treating an ethereal solution of VII with hydrogen bromide, gave no depression in melting point); λ_{max}^{EtOH} 318 mμ (ε 33,410); λ^{Nujol} 6.18, 6.25, 6.42, 6.60 μ.

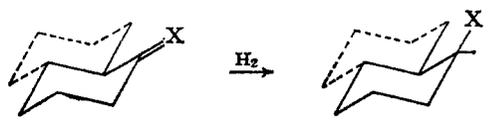
Anal. Calcd for $C_{18}H_{22}O_2NBr$: C, 59.34; H, 6.04; N, 3.85; Br, 21.98. Found: C, 59.55; H, 6.07; N, 3.90; Br, 22.01.

Conversion of Bromide V into IX *via* VI.—A mixture of 390 mg of V in 45 ml of anhydrous acetonitrile was heated with 455 mg of anhydrous silver perchlorate in a nitrogen atmosphere for 20 hr. The decrease in the absorption of V (305 mμ) was monitored periodically until no significant absorption remained. The solvent was evaporated and crude VI (X = ClO_4) immediatedly dissolved in 100 ml of absolute ethanol, treated with 150 mg of platinum oxide, and subjected to 55-psi hydrogen pressure. The hydrogenation was discontinued after 8 hr and the catalyst and solvent were removed by filtration and evaporation, respectively. The residual oil was taken up in a 1:1 mixture of ether–sodium hydroxide (20%) and the ether layer separated. The ethereal extracts were dried (sodium sulfate) and concentrated to yield a brown solid. An ethereal solution, containing 10–15% chloroform, of the crude product was passed through 1.5 g of alumina to produce a colorless solid (215 mg, 89%). Recrystallization from benzene gave the analytical sample: mp 177°; λ^{CHCl_3} 2.73, 6.18, 6.64, 6,80 μ; nmr (τ, $CDCl_3$), 2.85–3.40, three protons (multiplet, aromatic), 6.25, three protons (singlet, metoxyl), 6.05–6.45, two protons (multiplet, 17a and C-9), 7.78, one proton (singlet, OH exchanges with D_2O).

Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.70; H, 8.79; N, 4.80.

Conversion of VIII into IX.—A suspension of 287.8 mg of VIII in 50 ml of 95% ethanol was hydrogenated in the presence of 108 mg of platinum oxide for 5 hr and worked up as described above to obtain 228 mg of IX as a colorless solid, mp 174–177°.

(9) "Conformation Theory," M. Hanack, Academic Press Inc., New York, N. Y., 1965, p 269. A recent report [S. Siegal, M. Dunkel, G. V. Smith, W. Halpern, and J. Cozort, *J. Org. Chem.*, **31**, 2802 (1966)] on detailed studies of methylene cyclohexanes indicates that 2-methylmethylenecyclohexane (X = CH_2) gives predominantly the *cis* isomer (X = CH_2). If we may assume that the 17a ketone is analogous (X = O), then this data is in accord with our findings of predominantly axial alcohol (X = OH) resulting from catalytic reduction.



(10) All melting points are corrected and were determined on a Fisher-John apparatus. Nmr spectra were taken on a Varian A-60 instrument and infrared spectra and ultraviolet data were obtained using Beckman IR-5A and DB instruments, respectively. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

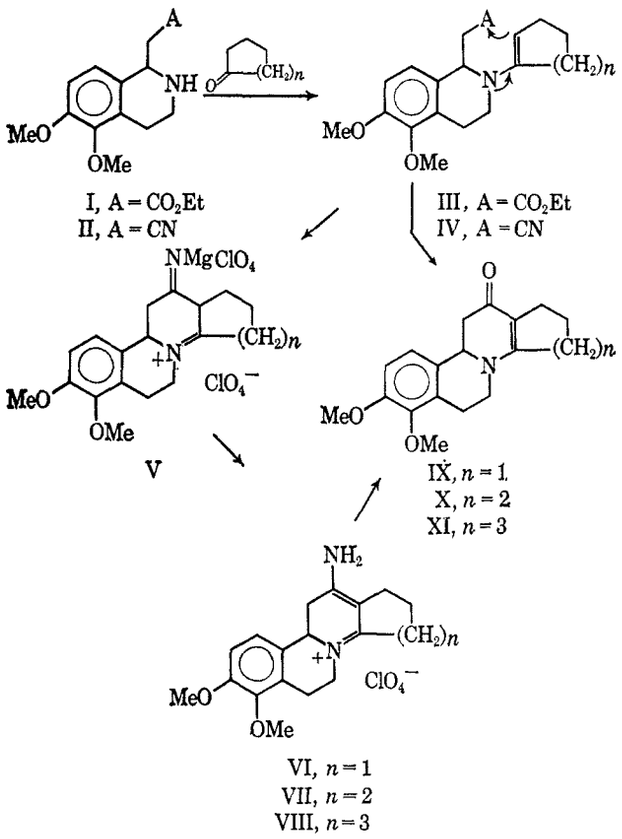
(11) We wish to acknowledge a grant for the National Science Foundation which allowed the purchase of the Varian A-60 instrument (NSF-GP-3674).

The melting point, on admixture with IX obtained from the above method, was 175–177°.

8-Aza-D-homo-18-norestrone Methyl Ether (I).—A solution of 803 mg of IX (crude material from 1.03 g of VIII) in 40 ml of acetone, cooled to 0°, was treated with 2 ml of Jones reagent over a 10-min period. The mixture was stirred for 15 min and the excess of oxidizing agent was decomposed with sulfur dioxide. The acetone was removed under reduced pressure and the aqueous solution was extracted with chloroform. The extracts were washed with water and dried (sodium sulfate). The residual oil, upon solvent removal, was dissolved in a minimum amount of benzene and passed through 5 g of alumina. Evaporation of the eluent afforded a colorless solid, which upon recrystallization from *n*-hexane gave crystalline product I (343 mg, 44% over-all yield from both steps): mp 143–144° (lit.[3] 143.5–144.0°); λ^{CHCl_3} 3.58, 3.65 (Bohlmann bands[4]), 5.81, 6.17, 6.63 μ; nmr (τ, $CDCl_3$), 2.75–3.35 three protons (aromatic, multiplet), 6.24, three protons (methoxyl, singlet), 6.28–6.40, one proton (multiplet, C-9).

Catalytic Reduction of I to IX.—A solution of 62 mg of I in 5 ml of ethanol containing 20 mg of platinum oxide and 0.05 ml of 70% perchloric acid was hydrogenated for 15 min after which the theoretical quantity of hydrogen was taken up. The solution was shaken with solid potassium carbonate for 30 min and then filtered to obtain a clear ethanolic solution, which was evaporated *in vacuo*. The residual solid was recrystallized from ether–benzene to give 51 mg (82%) of IX, mp 174–176°. The mixture melting point showed no depression. The infrared and nmr spectra were identical with those of IX prepared by reduction of VI or VIII.

Registry No.—V, 7688-14-4; VIII, 7641-74-9; IX, 7641-75-0; I, 7641-76-1.



The Synthesis of 7-Aminobenzo[*a*]cycloalkano[*f*]-quinolizinium Perchlorates. An Example of the Addition of Enamines to the Nitrile Function[1]

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The addition of enamines to electrophilic olefins,[2] acid chlorides,[2] isocyanates,[3] isothiocyanates,[3] and esters[4] is now well known. Only a few reports,[5] however, have been made concerning the direct addition of enamines to the nitrile group. We now wish to describe a facile addition of enamines to the triple bond of a nitrile function utilizing the complexing ability of the magnesium ion. In previous studies[4] from this laboratory, it was shown that the attempted enamine formation using the isoquinoline ester (I) and cyclic ketones (n = 1, 2, and 3) resulted not in the simple enamines (III), but in the tetracyclic enamino ketones (IX–XI). This intramolecular cyclization led to further studies involving enamine additions to other π-electron-containing functional groups. When the isoquinolinenitrile (II), prepared from the corresponding phenylethylamine and ethyl cyanoacetate, was treated with cyclohexanone in refluxing toluene containing a trace of acid, only a small quantity of the enamine (IV) and a 70% recovery of the isoquinoline nitrile were obtained. It, therefore, appeared that the nitrile group is not sufficiently electrophilic to allow cyclization to occur. The fact that magnesium ion forms an effective complex with the imino group (*i.e.*, Grignard reactions involving nitriles) and perchlorate salts of amines are usually quite stable, magnesium perchlorate was considered as a suitable reagent for this cyclization process.[6] When 1 equiv of anhydrous magnesium perchlorate was added to the reaction mixture, there was obtained, after 40 hr of reflux, an amorphous solid (presumably V). Upon removal of the latter from the toluene solution and treatment with aqueous alkali, a 95% yield of the aminoquinolizinium salt (VII) was obtained (Table I). The reaction was repeated, in the same manner, using cyclopentanone and cycloheptanone resulting in somewhat lower yields of the aminoquinolizinium salts. The stability of VI, VII, and VIII to aqueous alkali is surprising; however, iminium salts containing analogous structural features[7] have also been shown to be stable to aqueous alkali. Structural support for the quinolizinium salts was

(1) This study is supported by funds granted from the National Institutes of Health (RG-NIGMS-06248-07).

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(4) W. Sobtka, W. N. Beverung, G. G. Munoz, J. C. Sircar, and A. I. Meyers, *J. Org. Chem.*, **30**, 3667 (1965); N. D. Heindel, T. A. Brodof, and J. E. Kogelshatz, *J. Heterocyclic Chem.*, **3**, 222 (1966).

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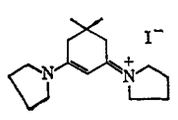
(6) Experiments designed to determine the utility of other metal ions for this reaction were performed. The results, using either silver perchlorate or cupric bromide gave tarry, polymeric, unidentifiable products along with starting materials.

(7) N. J. Leonard and J. A. Adamcik, *J. Am. Chem. Soc.*, **81**, 595 (1959). The authors described the isolation of A, which is analogous to compounds VI–VIII, from aqueous base by extraction with chloroform.



A