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Reaction of Some Steroidal Amides and Unsaturated Lactams with Nitrous Acid

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The reaction of nitrous acid with steroidal amides (I, VII, IX and X), α,β-unsaturated ε-lactams (XIX and XXI), and enamine-type lactams (XXIV, XXVIII, XXX and XXXI) was studied. The amides mainly gave esters in low or modest yield with retention of the configuration. The α,β-unsaturated lactams gave N-nitroso-lactams quantitatively. The enamine-type δ-lactams gave oximino-δ-lactams in a high yield.

Deamination of the N-nitroso derivative of amides and saturated lactams gives the corresponding esters and olefins from amides,[2] and lactones and unsaturated *seco*-acids from the lactams (Chart 1).[3] In the steroid field, examples of the application of this deamination reaction is limited. While the decomposition of the nitrosoamides of 3α- and 3β-cholestanylamines leads to the formation of olefins and esters with retention and inversion of configuration in various ratio,[4] that of 17β-aminoandrost-4-en-3-one was reported to give only the inverted product in a low yield.[5] The present paper shows the result of the reaction of sodium nitrite, in acetic anhydride-acetic acid mixture with acetamide of 17β-aminoandrostanes, readily obtained by the Beckmann rearrangement of 20-ketopregnane oximes, as well as with some steroidal α,β-unsaturated lactams and enamine-type lactams whose reactivity toward the nitrosating reagent is of some interest.

17β-Aminoandrost-5-en-3β-ol diacetate (I) was treated with excess sodium nitrite at $-5°$ for 24 hours and gave a trace of the deamination product (II). It was identified with androst-5-ene-3β,17β-diol diacetate (II) by mixed mp and from spectral data. Stable N-nitroso derivatives were not detected by thin-layer chromatography (TLC) and II was the sole deamination product. Although this condition was unsatisfactory for the deamination of I, it was found to have some synthetic utility when applied to 16α-substituted androstanes. Δ^{16}-20-Ketopregnanes undergo 1,4-addition by a variety of nucleophiles and give 16α-substituted 20-keto-pregnanes.[6,7] The Beckmann rearrangement of 16α-methoxypregn-5-en-3β-ol-20-one acetate oxime (III) by *p*-toluensulfonyl chloride in pyridine did not proceed smoothly compared with that of 16-unsabstituted analog. The 17β-acetamide (VII) was obtained in 90% yield from the oxime (III) by its conversion to the tosylate (IV), followed by heating in pyridine. Treatment of VII with sodium nitrite in a mixture of acetic anhydride and acetic acid at $-5°$ for 18 hours gave, along with the starting material, 36% of the diacetate (XI) and a trace of a by-product for which the nitrimine structure (XII) was assigned. Hydrolysis of XI gave the diol (XIII), identical with that obtained from the free amine (VIII) with sodium nitrite in aqueous acetic acid and, since hydrogenation of XIII with Adam's catalyst in acetic acid gave the known 16α-methoxy-5α-androstane-3β,17β-diol (XIV), configuration of the C-17 acetoxyl group of XI was assigned as β. The structure of nitrimine (XII) was

1) Location: *Kita-12-jo, Nishi-5-chome, Kita-ku, Sapporo, 060, Japan.*
2) E.H. White, *J. Am. Chem. Soc.*, 77, 6008 (1955).
3) G. Nischk and E. Müller, *Ann.*, **576**, 232 (1952); R. Huisgen and J. Reimertshofer, *ibid.*, **575**, 174 (1952); *idem*, *ibid.*, **575**, 197 (1952); P. Bladon and W. McMeekin, *Chem. Ind.* (London), **1960**, 1307.
4) F.W. Bachelor and E.H. White, *Can. J. Chem.*, **50**, 364 (1972); F.W. Bachelor and E.H White, *Tetrahedron Letters*, **1965**, 77.
5) F. Alvarez, *Steroids*, **2**, 393 (1963).
6) D.K. Fukushima and T.F. Gallagher, *J. Am. Chem. Soc.*, **73**, 196 (1951).
7) G.S. Abernethy, Jr. and M.E. Wall, *J. Org. Chem.*, **34**, 1607 (1969) and references cited therein.

same condition, gave 7.6% of 17-benzoate (XVI) and 38.8% of 17-acetate (XV). The configuration at C-17 in XV and XVI was also found to be β from the conversion of XV into XIII and XIII into XVI.

supported by elemental anlysis and spectral data as follows. The nuclear magnetic resonance (NMR) spectrum of XII showed a composite signal of 19-methyl and deshielded 18-methyl singlets at δ 1.03, methoxyl singlet at 3.27, and 3α- and 16β- proton signals at 4.3 to 4.9 as an ill-defined multiplet. Its infrared (IR) spectrum showed absorptions at 1655, 1580, and 1315 cm^{-1} (Nujol), characteristic of a nitrimine group.[8] In the ultraviolet (UV) spectrum, a weak absorption was present at 276 nm (ε 660).[8] The formation of XII is anomalous. At or near room temperature, free radicals are not generated in the nitrosoamide decomposition of aliphatic amines,[9] so that the formation of XII through the 17-oximino intermediate from the free radical and nitric oxide is not likely. It is suggested that XII may have been formed from the diazonium ion and two molecules of nitric oxide through the iminoxy radical, as in the case of the formation of nitrimine from diphenyl diazomethane and nitric oxide.[10] However, in the case of 3-aminocholestanes, the nitrosoamide deamination was reported to proceed without the formation of a diazonium intermediate.[4] The displaced acetyl group does not stem entirely from that of acetamide. The benzamide (IX), obtained from the tostlate (IV) by heating in ethylenediamine followed by benzoylation, when treated under the

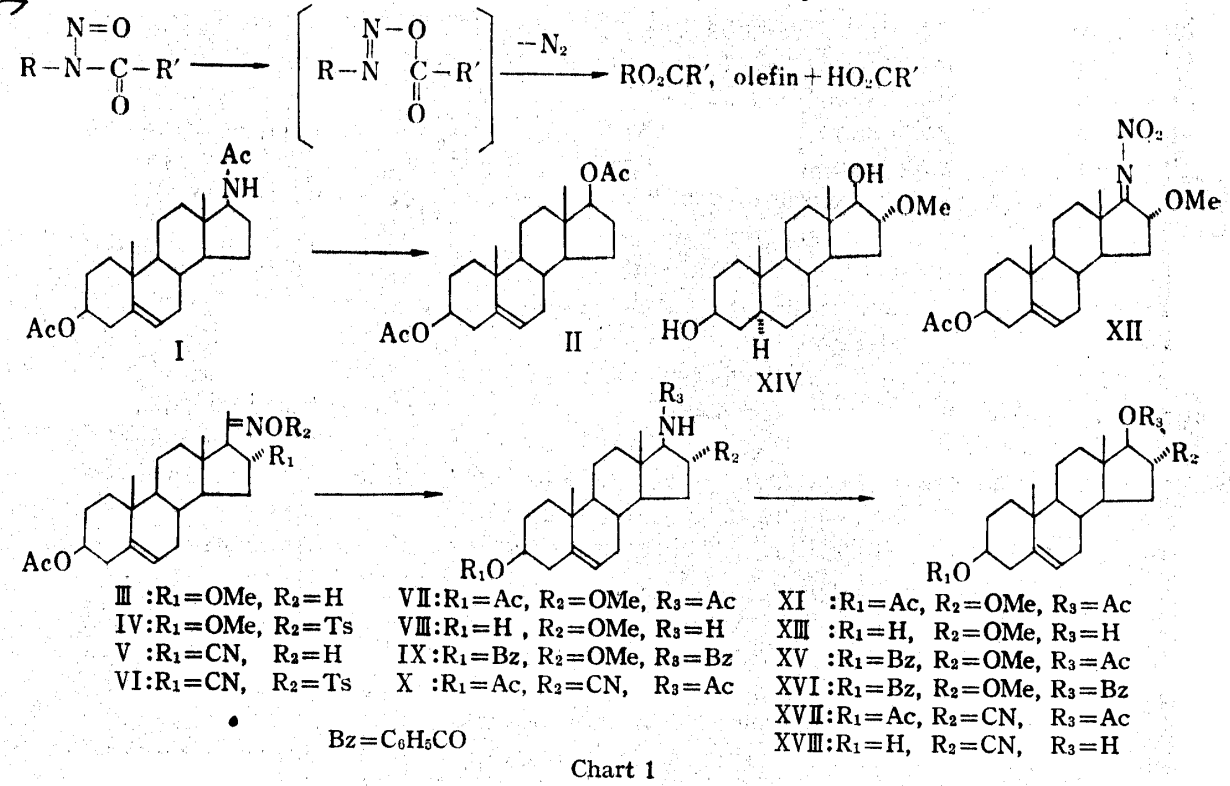

Chart 1

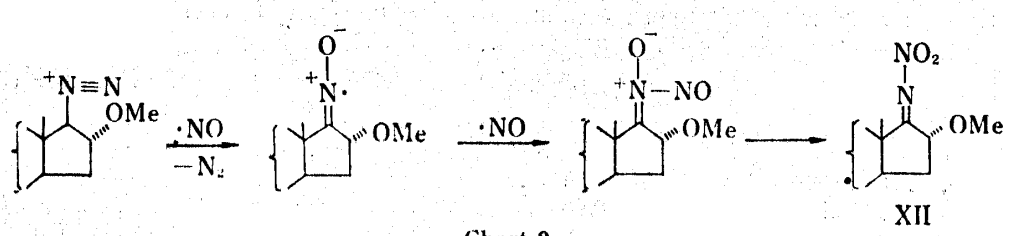

Chart 2

8) C. Shiue, K.P. Park, and L.B. Clapp, *J. Org. Chem.*, 35, 2063 (1970).
9) E.H. White and D.J. Woodcock, "The Chemistry of the Amino Group," ed. by S. Patai, John Wiley and Sons. Inc., London, New York, Sydney, 1968, p. 443.
10) O.L. Chapman and D.C. Heckert, *Chem. Commun.*, **1966**, 242.

The reaction of nitrous acid with 16α-cyano-17β-aminoandrost-5-en-3β-ol diacetate (X) also gave an appreciable amount of the deamination product under the same condition The amide (X) was prepared from the oxime[11] (V) through the tosylate (VI) in 65% yield. The NMR spectrum of X after treatment with D_2O showed 17α-proton doublet at δ 4.22 with the coupling constant of 8.5 Hz. Since the similar doublet in VII appeared at δ 3.92 with the coupling constant of 5.5 Hz, considereable conformational defference seems to have occurred between 16α-methoxy- and 16α-cyanoandrostanes. The amide (X), when treated in the same manner as above, afforded the diacetate (XVII) in 40.6% yield. The coupling constant of acetoxy-methine doublet at δ 4.93 is *ca.* 8.5 Hz, indicating that the configuration at C-17 is retained. TLC of the crude reaction mixture showed at least ten by-products though in a trace amount. When the reaction was continued until dissappearance of the starting material, the product becomes an intractable complex mixture. In this condition, addition of dinitrogen trioxide[12] to the double bond would not occur but TLC revealed the presence of an allylic oxidation product by its characteristic blue color when sprayed with antimony trichloride. This result indicates that the reaction of nitrous acid with 17β-acetaminoandrostanes proceeds by facile decomposition of the corresponding nitrosoamide to give 17-acetoxy-androstanes mainyl with retention of the configuration and, although the overall yield is small, it seems to have some synthetic utility for the preparation of 16α-substituted androstane analogs without resorting to drastic oxidative conditions which often need the protection of fragile groups such as an isolated double bond.[13]

The α,β-unsaturated lactams (XIX[14] and XXI[15]) readily reacted with nitrous acid and afforded yellow N-nitroso-lactams quantitatively. It is interesting to note that 12a-aza-C-homospirost-9(11)-en-3β-ol-12-one acetate (XXIII), the same type of lactam, was reported

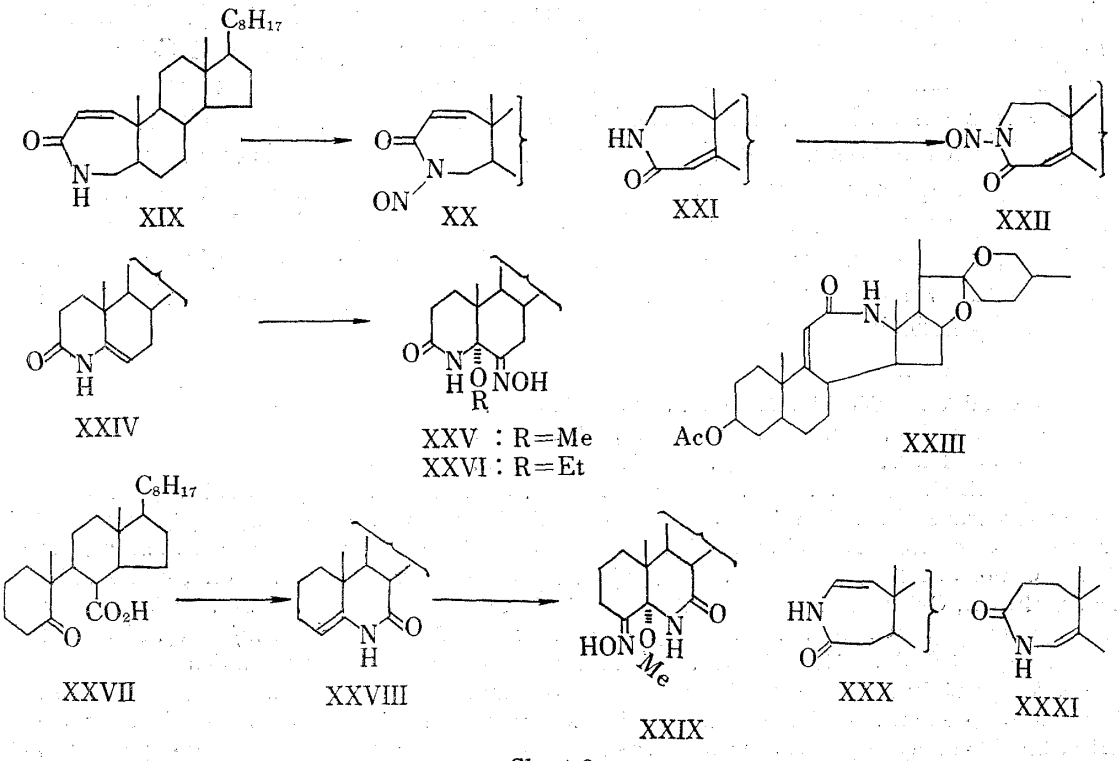

Chart 3

11) J. Romo, *Tetrahedron*, **3**, 37 (1955).
12) C.R. Narayanan, M.S. Parker, and M.S. Wadia, *Tetrahedron Letters*, **1970**, 4703; M. Onda and A. Azuma, *Chem. Pharm. Bull.* (Tokyo), **20**, 1467 (1972).
13) C. Djerassi, "Steroid Reactions," Holden-Day Inc., San Francisco, p. 403, (1963).
14) M. Kobayashi, Y. Shimizu, and H. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **17**, 1255 (1969).
15) C.W. Shopee, G. Kruger, and R.N. Mirringhton, *J. Chem. Soc.*, **1962**, 1050.

to be inert under this condition.[16] The nitroso lactams (XX and XXII) were found to be rather stable compared with saturated analogs when refluxed in cyclohexane for several hours. The nitrosation was found to occur exclusively at the vinylic position in the six-membered enamine-type lactams (XXIV[17] and XXVIII[18]). The lactam (XXIV) was obtained by merely heating 3,5-*seco*-4-norcholestan-5-on-3-oic acid in formamide[19] but the reaction was not successful for the preparation of 6-azacholest-4-en-7-one (XXVIII) because of the low solubility of the *seco*-acid (XXVII) in formamide. XXVIII was obtained in 84% yield by refluxing XXVII with ammonium acetate in acetic acid for 24 hr. The preceding paper[19] showed that the reaction of XXIV with excess sodium nitrite in a mixture of acetic acid and acetic anhydride at O to $-5°$ resulted in the formation of an oxime followed by concurrent fragmentation or hydrolysis. This time, XXIV in chloroform was treated with two molar equivalents of sodium nitrite in conc. hydrochloric acid by stirring for 5—10 min. TLC of the reaction mixture showed a complex chromatogram possibly due to manifold substitution at C-5 but when the mixture was refluxed in methanol briefly, it changed into a sole product, 5α-methoxy-6-oximinocholestan-3-one (XXV) (84% yield), one of the product from XXIV with the reaction of nitrous acid generated in acetic acid and acetic anhydride mixture followed by treatment with methanol.[19] When the mixture was treated with ethanol, 5α-ethoxy-oxime (XXVI) was obtained in 88% yield. Simillarly, the methoxy oxime (XXIX) was obtained in 84% yield by treating the lactam (XXVIII) in chloroform with two molar equivalents of sodium nitrite in conc. hydrochloric acid followed by refluxing in methanol. The structure was supported by IR absorptions of lactam grouping at 3190, 3100, 1665, and 1650 cm^{-1} and a hydroxyl at 3330 cm^{-1}, and by NMR signals of shielded methoxyl group at δ 2.91 and deshielded 3β-equatorial proton *syn* to the hydroxyl group at δ 3.30 (1H, multiplet, W_H= 14 Hz). Similar signals of XXV were at δ 2.94 for methoxy and 3.35 (doublet, J=12 Hz) for 7β-equatorial proton.[19] The configuration of the methoxyl group at C-5 was assumed to be α from the chemical shift of 19-methyl signal at δ 0.89, the same as that of XXV. The reactions was clean and no trace of N-nitroso derivatives or deaza products was detected on TLC. This result was almost the same when other mineral acids such as conc. sulfuric, nitric, or polyphosphoric acid were used in place of hydrochloric acid but conc. hydrochloric acid is the reagent of choice. The reaction is applicable only to the lactams stable toward acids. Thus, the A-homo-enamine lactams[14] (XXX and XXXI) furnished an extremely complex mixture when treated with sodium nitrite either in hydrochloric acid or acetic acid and acetic anhydride.[20]

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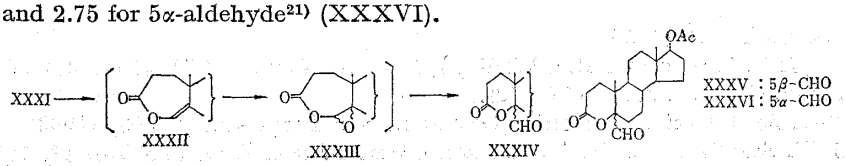
17) M. Uskokovic and M. Gut, *Helv. Chim. Acta*, **42**, 2258 (1959).
18) T.L. Jacobs and R.B. Brownfield, *J. Am. Chem. Soc.*, **82**, 4033 (1960).
19) M. Kobayashi, H. Furuse, and H. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 789 (1972).
20) However, a trace of the deamination product (XXXIV), mp 153.5—154°, $C_{27}H_{44}O_3$, was isolated from the tar obtained from XXXI and sodium nitrite in acetic acid-acetic anhydride mixture. It showed IR absorptions at 1750 and 1725 cm^{-1} (Nujol), and NMR signals at δ 1.13 (3H, singlet, 19-Me), 2.50 (2H, multiplet, C-2 methylene), and 9.70 (1H, singlet, CHO). Presence of an angular aldehyde group was supported by its mass spectrum which showed the molecular ion (M, *m/e* 416), M-CHO (*m/e* 387, base peak), and M-CHO-Me (*m/e* 372). These data are compatible with the aldehyde lactone structure (XXXIV), possibly derived by oxidation and recombination of the enol lactone (XXXII), the normal deamination product from XXXI, though the oxidation mechanism remains unsettled. In androstane series, the 5β-aldehyde (XXXV) was reported to have IR absorption of lactone grouping at 1745 cm^{-1} and NMR signals of aldehyde proton at δ 9.67 and C-2 methylene at 2.55, compared with 1732 cm^{-1} and δ 10.10 and 2.75 for 5α-aldehyde[21] (XXXVI).



21) M. Gorodetsky, N. Danieli, and Y. Mazur, *J. Org. Chem.*, **32**, 760, (1967).

Experimental[22]

Reaction of 17β-Acetylaminoandrost-5-en-3β-ol Acetate (I) with Nitrous Acid——A mixture of 3 g of I and 70 ml of Ac_2O–AcOH (5: 1) was mixed with 12 g of $NaNO_2$ during 3 hr while stirring at 0 to −5°. After stirring for another 18 hr, the mixture was poured into ice–water and left standing overnight. The brown precipitate was collected by suction, washed with water, and dried. It was dissolved in $CHCl_3$ and passed through 30 g of silica gel column to remove polar starting material. The non-polar fraction was purified by preparative TLC and recrystallized from MeOH to II as colorless plates (30 mg), mp 159—160°, mixed mp 158.5—160°, $[\alpha]_D$ −65.8° (c=1.47, $CHCl_3$).

Beckmann Rearrangement of 16α-Methoxypregn-5-en-3β-ol-20-one Oxime (III)——A solution of 1 g of the oxime (III) in 5 ml of pyridine was treated with 1.25 g of *p*-toluenesulfonyl chloride at −5° for 10 min and at room temperature for 1.5 hr. MeOH (20 ml) was added to the mixture and the precipitate was collected by suction, washed with H_2O until free from pyridine and then with a small amount of MeOH to remove moisture, and dried to afford 1.32 g (95%) of the tosylate (IV), mp 158—164°, $[\alpha]_D$ −35.0° (c= 0.34, $CHCl_3$). *Anal.* Calcd. for $C_{31}H_{43}O_6NS$: C, 66.76; H, 7.77; N, 2.51. Found: C, 66.84; H, 7.81; N, 2.91.

The tosylate (1.3 g) was dissolved in 10 ml of pyridine and warmed in a water-bath (90°) till the disappearance of the starting material (2 hr) and poured into water. The precipitate was collected, washed with water, and recrystallized from MeOH to 0.9 g of VII (90%), mp 190—192°, $[\alpha]_D$ −103.1° (c=0.55, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3290, 3210, 3090, 1740, 1660, 1560. NMR δ: 0.72 (18-Me), 1.01 (19-Me), 2.00 (6H, s, OAc and NAc), 3.26 (3H, s, OMe), 3.6 (1H, m, 16β-H), 3.92 (1H, q, $J_{16,17}$=5.5 Hz, $J_{17,NH}$=9 Hz, 17α-H), 5.8—6.2 (1H, m, NH). *Anal.* Calcd. for $C_{24}H_{37}O_4N$: C, 71.43; H, 9.24; N, 3.47. Found: C, 71.45; H, 9.49; N, 3.41.

17β-Amino-16α-methoxyandrost-5-en-3β-ol Dibenzoate (IX)——A mixture of 2 g of the oxime (III) and 2 g of *p*-toluenesulfonyl chloride in 10 ml of pyridine was left at room temperature for 2 hr then most of solvent was removed *in vacuo*. The residue was dissolved in 10 ml of ethylenediamine and warmed in a water-bath (95°) for 2 hr. Most of the solvent was evaporated, the residue was refluxed in 20 ml of 5% KOH–MeOH for 1 hr, and concentrated to a small volume. The mixture was poured into water (30 ml), extracted with $CHCl_3$, and the extract was washed with H_2O. The evaporation residue was dissolved in 10 ml of pyridine and treated with 2.8 g of BzCl at room temperature for 1 hr. The mixture was treated by stirring with 15 ml of MeOH and 5 ml of H_2O, and the precipitate was collected and recrystallized from $CHCl_3$–MeOH to 1.8 g (65%) of IX, mp 286—290°, $[\alpha]_D$ −47.8° (c=1.15, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3400, 1710, 1648, 1510. *Anal.* Calcd. for $C_{34}H_{41}O_4N$: C, 77.38; H, 7.83; N, 2.65. Found: C, 77.39; H, 7.69; N, 2.65.

17β-Amino-16α-cyanoandrost-5-en-3β-ol Diacetate (X)——The oxime (V) was treated in the same way as above for III to give VI in 95% yield, mp 185—187°. *Anal.* Calcd. for $C_{31}H_{40}O_5N_2S$: C, 67.37; H, 7.30. Found: C, 67.32; H, 7.22.

A solution of 3.45 g of VI in 40 ml of pyridine was refluxed for 10 hr and most of the solvent was evaporated. The residue was taken up in $CHCl_3$, worked up as usual, and chromatographed over 60 g of silica gel. Elution with 20—50% ether in $CHCl_3$ and recrystallization from $CHCl_3$–MeOH gave 1.6 g (66%) of X, mp 313—317°, $[\alpha]_D$ −90.0° (c=1.6, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3395, 2225, 1730, 1682, 1670, 1528. NMR δ: 0.72 (18-Me), 1.02 (19-Me), 2.01 (6H, s, OAc and NAc), 4.22 (1H t, J=8.5 Hz, 17α-H), 6.49 (1H, d, J=8.5 Hz, NH). *Anal.* Calcd. for $C_{24}H_{34}O_3N_2$: C, 72.33; H, 8.60; N, 7.02. Found: C, 72.28; H, 8.63; N, 7.29.

Reaction of VII with HNO_2——A mixture of VII (1.14 g) in 25 ml of Ac_2O–AcOH (5: 1) was treated with 4 g of $NaNO_2$ during 6 hr and stirred for 18 hr. The mixture was poured into water and trace of pyridine, and extracted with $CHCl_3$. After working up as usual, the evaporation residue was submitted to chromatography over 10 g of silica gel. Elution with benzene gave 18 mg of XII, mp 178—179° from MeOH. IR ν_{max}^{Nujol} cm^{-1}: 1735, 1655, 1580, 1315, 1255. UV λ_{max}^{EtOH} nm (log ε): 276 (2.82). NMR δ: 1.03 (6H, s, 18, 19-Me), 3.27 (OMe), 4.3—4.9 (2H, m, 3α, 16β-H), 5.35 (1H, m, 6-H). *Anal.* Calcd. for $C_{22}H_{32}O_5N_2$: C, 65.32; H, 7.77; N, 6.93. Found: C, 65.88; H, 8.06; N, 6.87. Elution with 3% ether–benzene gave 410 mg of the diacetate (XI), mp 168—170°, $[\alpha]_D$ −125.0° (c=0.6, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 1740, 1732, 1630. NMR δ: 0.76 (18-Me), 1.00 (19-Me), 3.26 (OMe), 3.85 (1H, m, 16β-H), 4.82 (1H, d, J=5.5 Hz, 17α-H). *Anal.* Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.30; H, 9.01.

Hydrolysis of the diacetate (XI) by refluxing in 3% KOH–MeOH for 20 min followed by usual work up gave 334 mg (36% overall) of XIII, mp 217—219° (from benzene), $[\alpha]_D$ −117.5° (c=0.57, $CHCl_3$). *Anal.* Calcd. for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 75.00; H, 9.95. IR ν_{max}^{Nujol} cm^{-1}: 3450, 3370, 1084, 1063, 1040.

22) Melting points were determined on a Kofler hot stage and are uncorrected. NMR spectra were measured in $CDCl_3$ solution with TMS as internal standard.

16α-Methoxyandrostane-3β,17β-diol (XIV)——A solution of 100 mg of XIII in 4 ml of AcOH was shaken with 10 mg of PtO_2 in an atomospheric pressure of H_2 and the catalyst was filtered off. The solvent was evaporated and the residue was recrystallized from benzene to 90 mg of prisms, mp 199.5—200.5°, $[\alpha]_D$ −21.4° (c=0.7, 95% EtOH) (reported,[6] mp 198.5—199.5°, $[\alpha]_D$ −16.8). *Anal.* Calcd. for $C_{20}H_{34}O_3$: C, 74.49; H, 10.63. Found: C, 74.34; H, 10.67.

Reaction of IX with HNO_2——A solution of 480 mg of IX in 40 ml of AcOH–Ac_2O (1: 5) was treated with $NaNO_2$ by the same procedure as VII. After working up, reaction mixture was submitted to preparative TLC using $CHCl_3$ as a solvent and developing twice. Three bands were detected by spraying H_2O and extracted with AcOEt after drying. (a) Upper band (35 mg, 7.6%): 16α-Methoxyandrost-5-ene-3β,17β-diol dibenzoate (XVI), mp 237—238°, $[\alpha]_D$ −46.9° (c=1.3, $CHCl_3$). *Anal.* Calcd. for $C_{32}H_{40}O_5$: C, 76.16; H, 7.99. Found: C, 76.45; H 7.44. (b) Middle band (167 mg, 38.8%): 16α-Methoxyandrost-5-ene-3β, 17β-diol 3-benzoate 17-acetate (XV), mp 220—221°, $[\alpha]_D$ −85.1° (c=2.5, $CHCl_3$). *Anal.* Calcd. for $C_{29}H_{38}O_5$; C, 74.65; H 8.21. Found: C, 74.32; H, 8.11. (c) Lower band (137 mg) was found to be IX from mp and IR spectra. Hydrolysis of XV gave the diol (XIII), mp 216—217.5°, and treatment of XIII in pyridine with BzCl gave the dibenzoate (XVI), mp 237—238.5°.

Reaction of X with Nitrous Acid——A suspension of 1.3 g of X in 80 ml of AcOH–Ac_2O (1: 5) was treated with 6.5 g of $NaNO_2$ by the same procedure as above. The $CHCl_3$ extract was passed through 10 g of silica gel to remove the starting material. Recrystallization of the eluent from $CHCl_3$–MeOH gave 0.53 g (40.6%) of the diacetate (XVII), mp 226—230°, $[\alpha]_D$ −104.5° (c=1.12, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 2240, 1745, 1733. NMR δ: 0.76 (18-Me), 1.01 (19-Me), 4.94 (1H, d, J=8.5 Hz, 17α-H), 2.00 and 2.08 (OAc). *Anal.* Calcd. for $C_{24}H_{33}O_4N$: C, 72.15; H, 8.33; N, 3.51. Found: C, 72.33; H 8.37; N, 3.27.

Hydrolysis of XVII with 3% KOH–MeOH gave the diol (XVIII), mp 268—270° from MeOH, $[\alpha]_D$ −41.0° (c=0.84, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3440, 3325, 2240, 1052.

Nitrosation of 4-Aza-A-homocholest-1-en-3-one (XIX)——A mixture of 300 mg of XIX and 12 ml of AcOH–Ac_2O (1: 5) was treated by stirring at −5° with 1 g of $NaNO_2$ during 2 hr then poured into water and trace of pyridine. The mixture was stirred for a while then the yellow precipitate was collected, washed with water, and dried to give 313 mg of N-nitroso-4-aza-A-homocholest-1-en-3-one (XX), mp 105—108°, $[\alpha]_D$ +164.7° (c=0.6, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 1690, 1615, 1528. *Anal.* Calcd. for $C_{27}H_{44}O_2N_2$: C, 75.65; H, 10.35; N, 6.54. Found: C, 75.94; H, 10.70; N, 6.39.

Nitrosation of 3-Aza-A-homocholest-4a-en-4-one (XXI)——Nitrosation was carried out by the same procedure as above and gave pure N-nitroso-3-aza-A-homocholest-4a-en-4-one (XXII) in 98% yield, mp 153—154.5°, $[\alpha]_D$ −75.0° (c=0.76, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 1681, 1615, 1528. *Anal.* Calcd. for $C_{27}H_{44}O_2N_2$: C, 75.65; H, 10.35; N, 6.54. Found: C, 75.94; H, 10.27; N, 6.88.

Nitrosation of 4-Aza-A-homocholest-4a-en-3-one (XXXI)——A mixture of 300 mg of XXXI in 12 ml of AcOH–Ac_2O (1: 5) was treated by stirring at 0 to −5° with 1 g of $NaNO_2$ during 3 hr. The mixture was stirred further for 3 hr, poured into water and, extracted with ether. The yellow extract changed colorless solution on standing. After washing with 5% $NaHCO_3$, water, and saturated NaCl solution, the evaporation residue was submitted to preparative TLC. The most nonpolar fraction (45 mg) was recrystallized from MeOH to give 20 mg of XXXIV, mp 153.5—154°. IR ν_{max}^{Nujol} cm^{-1}: 1750, 1725. NMR δ: 0.69 (18-Me), 1.13 (19-Me), 2.50 (2H, m, C-2 methylene), 9.70 (1H, s, CHO). *Anal.* Calcd. for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65. Found: C, 77.07; H, 10.37. Mass Spectrum m/e: 416 (M), 387 (M-CHO), 372 (M-CHO-Me), 303 (M-side chain), 261 (M-42-side chain).

5α-Methoxy-6-hydroximino-4-azacholestan-3-one (XXV)——A solution of 1.4 g of XXIV in 70 ml of $CHCl_3$ was stirred with 500 mg of $NaNO_2$ in 50 ml of conc. HCl at room temperature for 10 min, then the organic layer was separated, and evaporated at 20° *in vacuo*. The oily residue was taken up in 30 ml of MeOH, refluxed for 30 min, and left to crystallize. After several hours, the crystal were collected by suction and dried to give 1.35 g (84%) of XXV, mp 172—173°, which showed the same spectral data as reported previously.[19]

5α-Ethoxy-6-hydroximino-4-azacholestan-3-one (XXVI)——A solution of 463 mg of XXIV in 15 ml of $CHCl_3$ was treated with 165 mg of $NaNO_2$ in 5 ml of conc. HCl. The evaporation residue was refluxed in 15 ml of EtOH for 30 min and concentrated to 5 ml. After several hours, the crystals were collected and recrystallized from $CHCl_3$–MeOH to 490 mg (88%) of XXVI, mp 199—200°, $[\alpha]_D$ +33.9° (c=1.27, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3310, 3180, 3070, 1650. NMR δ: 1.08 (t, enveloped by another signals, J=7 Hz, primary Me), 2.8—3.45 (3H, m, OCH_2- and 7β-equatorial proton), 7.85 (1H, s, NH), 11.8 (1H, broad, hydroximino proton). *Anal.* Calcd. for $C_{28}H_{48}O_3N_2$: C, 73.00; H, 10.50; N, 6.08. Found: C, 72.70; H, 10.32; N, 5.94.

6-Azacholest-4-en-7-one (XXVIII)——A solution of 200 mg of the *seco*-acid (XXVII) and 500 mg of NH_4OAc in 10 ml of AcOH was refluxed for 24 hr. The mixture was poured into water, the precipitate was collected by suction, and recrystallized from MeOH to 150 mg of XXVIII, mp 166—170°, $[\alpha]_D$ +63.6° (c=1.0, $CHCl_3$). UV λ_{max}^{EtOH} nm (log ε): 235 (4.15).

5α-Methoxy-4-hydroximino-6-azacholestan-7-one (XXIX)——A solution of 2.0 g of XXVIII in 100 ml of $CHCl_3$ was treated with 700 mg of $NaNO_2$ in 70 ml of conc. HCl as above. The organic layer was evapo-

rated at 20° *in vacuo*, and the residue was refluxed in 100 ml of MeOH for 20 min, and concentrated to 30 ml. After several hours, the crystals were collected. mp 190—191°, $[\alpha]_D$ +15.8° (c=1.27, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3330, 3190, 3100, 1665 (shoulder), 1650. NMR δ: 2.91 (3H, s, OMe), 3.30 (1H, m, W_H=14 Hz, 3β-H), 7.72 (1H, NH), 12.0 (OH). *Anal.* Calcd. for $C_{27}H_{46}O_3N_2$: C, 72.60; H, 10.38; N, 6.27. Found: C, 72.85; H, 10.10; N, 6.57.