NMR spectrometer. Spectra were recorded at four [L]/[S] values for each substrate compound, and δ_n values were obtained from the spectra. The $\Delta\delta_i/\Delta\delta_n$ obsd values were constant within the experimental accuracy of the measurements. The values for **2** and for **1α–δ**, which were used in the calculations, are given in Tables I and III, respectively.

Calculations. The coordinates for each atom in each of the substrate structures were calculated with the COORD program.[7] Two coordinate systems were calculated for each molecule. The origins for systems A and B were OA and OB, respectively. The agreement between the observed shift ratios for a given substrate were calculated with the SHIFT program.[7]

Preparation of 4,11,11-Trideuteriomultistriatin Isomers (1α–δ). A sample of multistriatin (1) was refluxed in 1 M D_3PO_4–tetrahydrofuran solution and worked up according to the previously described method.[3]

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Registry No.—1α, 54815-06-4; 1β, 54832-20-1; 1γ, 54832-21-2; 1δ, 54832-22-3; **2**, 28401-39-0.

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Synthesis of Samandarine-Type Alkaloids and Analogues[1,2]

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Facile stereoselective syntheses of samandarine and its regioisomers are described.

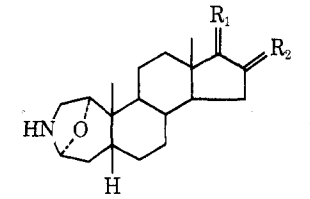
European salamanders, *Salamandra maculosa taeniata* and *S. maculosa maculosa*, are known to secrete alkaloidal venoms from the glands located on the skin, probably for defensive purposes. The chemical structures of these alkaloids had been vigorously investigated by Schöpf and Habermehl's group over a number of years, and the structure of the major alkaloid, samandarine (1), was first established by X-ray crystallography in 1961.[3]

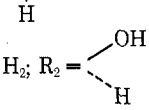
A group of alkaloids represented by samandarine are characterized by the presence of a peculiar 6-aza-8-oxabicyclo[3.2.1]octane ring system in the A ring of steroidal nuclei.

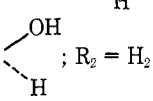
Owing to this peculiar bridged system and the reported neurotoxicity of these naturally scarce substances, the synthesis of samandarine and its analogues has been pursued by several groups. A multistep synthesis of samandarine was first reported by a Japanese group.[4] A few other attempts to synthesize samandarine and the ring system have also been reported.[5]

Since there are several established ways to introduce an oxygen function at C-16, the major problem inherent in the synthesis of these alkaloids is in the construction of the bridged oxazolidine system with the correct stereochemistry.

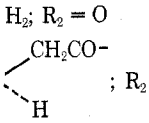
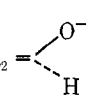
In this paper, the author reports a general procedure for the preparation of the bridged oxazolidines from α,β-unsaturated cyclic ketones and a facile, stereoselective formal synthesis of samandarine (1).



1, $R_1 = H_2$; R_2 = 

21, R_1 =  ; $R_2 = H_2$

22, $R_1 = H_2$; $R_2 = O$

23, R_1 =  ; R_2 = 

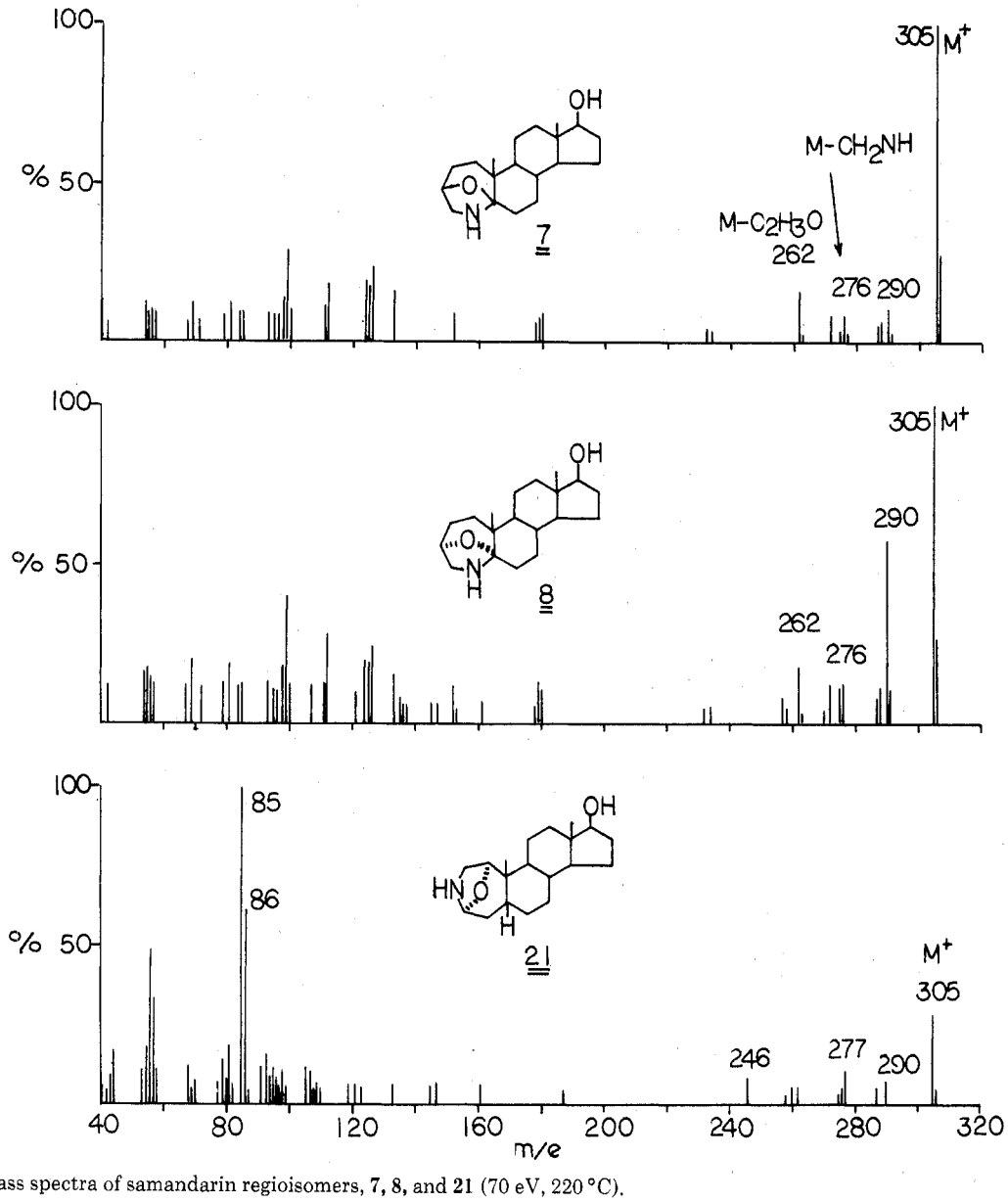
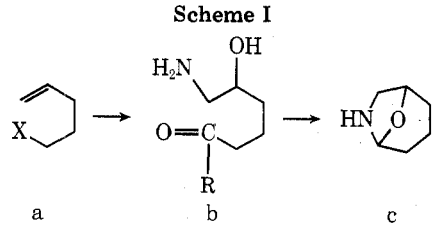


Figure 1. EI mass spectra of samandarin regioisomers, **7**, **8**, and **21** (70 eV, 220 °C).

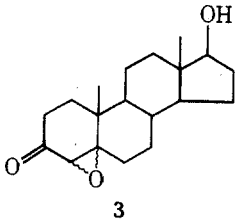
The 6-aza-8-oxabicyclo[3.2.1]octane ring system is essentially the hemiaminoacetal (ketal) of the amino alcohol (b) formed by an intramolecular condensation. Therefore, it seemed to be an easy approach to synthesize a δ,ϵ-unsaturated compound of type a and to functionalize the double bond and the group X in an appropriate manner to effect subsequent cyclization (Scheme I). In order to test this approach, the

Scheme I

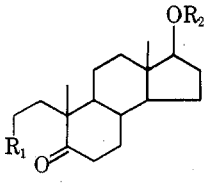


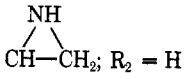
synthesis of 3,5-epoxy-4a-aza-*A*-homoandrostan-17β-ol, a regioisomer of samandarine, was first attempted.

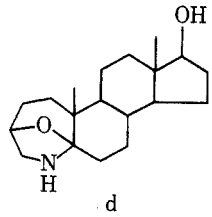
A mixture of testosterone α- and β-exoxides (**3**), which can be obtained in a high yield by H_2O_2–NaOH treatment of testosterone (**2**), was allowed to react with *p*-toluenesulfonylhydrazine in a mixture of methylene chloride and acetic acid.[6] The acetylene derivative (**4**) was obtained in a 70% overall yield from testosterone. Partial hydrogenation of the



3



4, R_1 = C≡CH; R_2 = H
5, R_1 = CH=CH_2; R_2 = Ac
6, R_1 =  ; R_2 = H

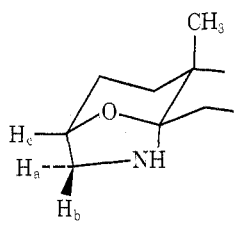


d
7, **8**

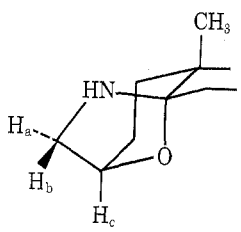
acetylene group of **4** with Lindler catalyst and subsequent acetylation gave the seco olefin (**5**) in a ca. 80% yield. Reaction of **5** with *N,N*-dichlorourethane followed by bisulfite and alkali treatment[7] gave a stereoisomeric mixture of the aziridine derivative (**6**) (ν_{NH} 3300 cm^{-1}). When the isomeric mixture (**6**) was heated in 2 NH_2SO_4 on a steam bath for 2 h, it afforded two isomeric chloroform-soluble products, **7**, mp 70–73 °C (hydrate), and **8**, mp 221–222 °C, with identical compositions of $C_{19}H_{33}NO_2$. Both **7** and **8** show typical absorptions for oxazolidines (1050–800 cm^{-1}), no carbonyl absorption in the ir spectra, and almost identical ^1H NMR and mass spectra (Figure 1) except for the difference in the chemical shifts of the 19-methyl groups. The ABX system seen around δ 3.0 is fully compatible with the structure d. The alternative structure in which the nitrogen and oxygen atom are interchanged was ruled out because the chemical shifts indicate that the methylene group is linked to the nitrogen atom. It was fully expected that the aziridine opens in the non-Markownikoff manner. The combined yield of **7** and **8** was ca. 40%. The rest of the products were very polar, and were not extracted with chloroform. This fraction probably consisted of the isomeric carbinolamines, which apparently do not cyclize under the employed condition.[8]

The structures A and B are tentatively assigned to **7** and **8** respectively, for the following reasons. The lower chemical shift of the 19-methyl group of **8** may be explained by the anisotropic effect of the β-oriented nitrogen group in the structure B. The compound **8** has a bigger coupling constant, J_{H_b,H_c}, than the isomer **7** in accordance with the implication of the model examination (Table I), although this argument may not be so reliable owing to the uncertain influence of the heteroatoms.

Table I. Expected and Observed ^1H NMR Data for **7** and **8**



A



B

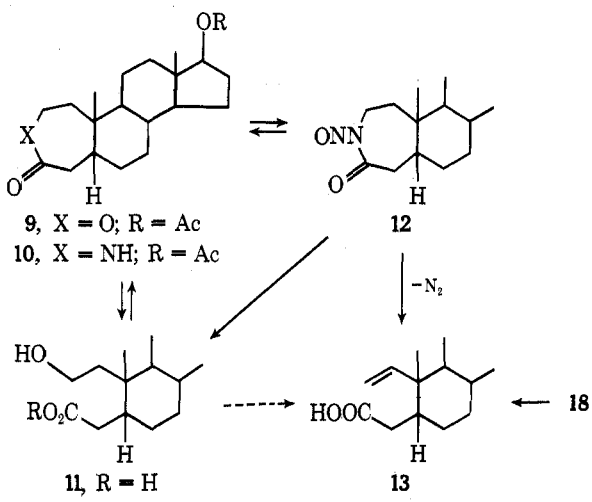
	Dihedral angles obtained from the models	Expected *J*, Hz	Observed *J*, Hz	19-CH_3, ppm
Structure A	H_b, H_c = 35°	6.5 7	6.0	
	H_a, H_c = 85°	0	0	0.90
Structure B	H_b, H_c = 25°	8.0 8	7.0	
	H_a, H_c = 95°	0	0	1.07

For the synthesis of samandarine itself, the same procedure used for the synthesis of **7** and **8** could be applied. However, the preparation of the desired starting compounds, Δ^2-1-ones in the A/B cis steroids, is lengthy if not unattainable. Consequently, alternative routes to the Δ^1-2,3-seco compound with an appropriate function at C-3 were investigated.

Attempts to convert easily obtainable 2,3-seco steroids,[9] lactone **9** or lactam **10**, to the desired Δ^1-2,3-seco compound proved to be futile. Dehydration of the seco hydroxy acid **11** and its esters, which can be obtained easily by Baeyer–Villiger oxidation of 17β-hydroxy-5β-androst-3-one, by various methods failed owing to their easy conversion to the seven-membered lactone **9**.

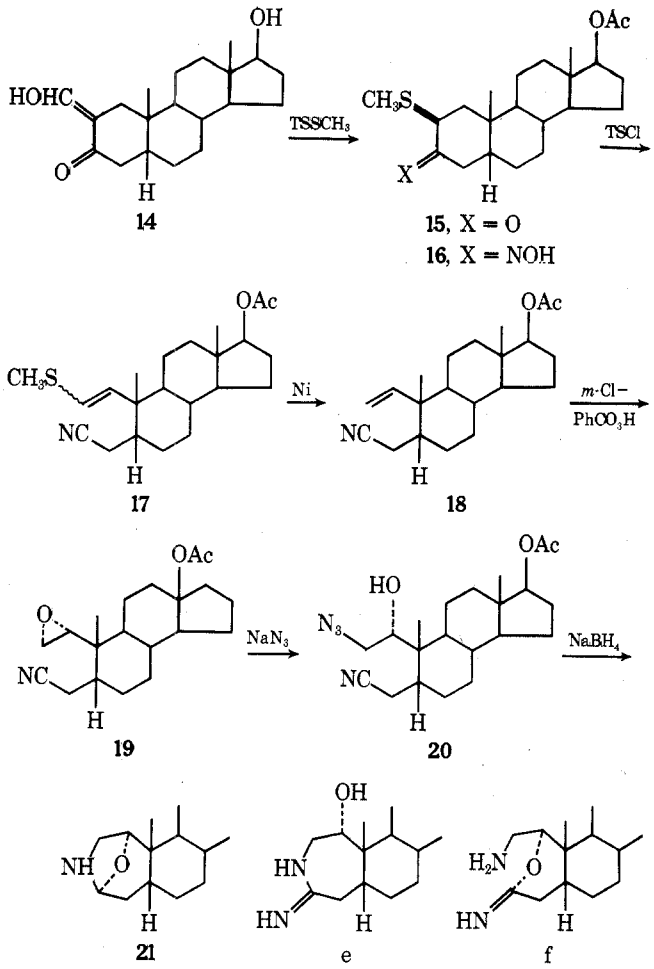
Huisgen reported that under selected conditions, the decomposition of *N*-nitroso lactams yields ω-unsaturated acids in addition to the corresponding lactones or hydroxy acids.[10] The stable *N*-nitroso compound **12**, which was prepared by the treatment of the lactam **10**[11] with sodium nitrite in acetic acid, was subjected to decomposition under various conditions (Scheme II). The major reaction product was always the lactone **9**, or the hydroxy acid **11** if the reaction was carried out under a basic condition. When the decomposition was done in dimethyl sulfoxide, less than a 5% yield of the desired methylene acid (**13**) was obtained. Meanwhile, successful ring cleavage to construct the 2,3-seco-5β-androstane skeleton of samandarine was accomplished by the procedure which Autrey and Scullard had used for the synthesis of corynantheine.[12] The hydroxymethylene derivative (**14**)[13] was treated with 1.3 mol of methyl *p*-toluenethiosulfate in the presence of potassium acetate in boiling ethanol.[14] The product isolated after acetylation, in 80% yield, was 17β-acetoxy-2β-methylthioandrostan-3-one (**15**) (Scheme III). The equatorial 2β configuration was expected for the introduced methylmercapto group, and it was confirmed by the appearance of the axial C-2 hydrogen signal in the ^1H NMR spectrum, δ 3,46 (q, J = 6, 13 Hz). The reaction of **15** with hydroxylamine chloride in pyridine afforded the oxime **16**, in a quantitative yield. The treatment of **16** with *p*-toluenesulfonyl chloride in refluxing pyridine for 30 min gave a seco nitrile product, **17**, in 65% yield as the sole product.[15] It is known that steroidal 3-ketones afford about 1:1 mixtures of the syn and anti oximes, which upon Beckmann rearrangement give the corresponding isomeric lactams, respectively. It seemed improbable that the presence of the 2β-methylmercapto group occasions the exclusive formation of one isomer, and indeed, the TLC examination showed the presence of two oximes. The apparent loss of directional influence in the Beckmann rearrangement (fragmentation) may be explained either by the equilibration of the oximes under the conditions employed or by a highly favored fragmentation due to the electron-donating methylmercapto group.[16] Removal of the methylmercapto group in **17** without affecting the double bond or nitrile group was accomplished by treatment with Levin's deactivated Raney Ni.[17] The methylene nitrile (**18**) was obtained in 40–65% yields. The poor yields resulted from the formation of the corresponding saturated nitrile derivative which seemed unavoidable even under highly controlled conditions.

Scheme II



Treatment of **18** with *m*-chloroperbenzoic acid gave preferentially one epoxide, **19**. In prior model examination, the desired 1*R* epoxide was expected to be the major product,[18] and this assumption was supported by subsequent successful conversion of **19** to the final product. The non-Markownikoff opening of the epoxide with NaN_3 in refluxing methylcello-

Scheme III



solve gave the azide **20** in a quantitative yield. The conversion of **20** to the final product, oxazolidine **21**, which involves the partial reduction of the nitrile to the aldehyde level, reduction of the azide group to the amine, and hydrolysis of the 17-acetyl moiety, was accomplished in one step by reduction with $NaBH_4$ in refluxing 2-propanol.[19] Extraction of the reaction mixture with chloroform gave almost pure crystals of **21** in about 60% yield. Recrystallization from acetone gave a specimen, mp 191–193 °C, ir 852 and 834 cm^{-1} (oxazolidine), which was identified with the authentic sample[4] by mixture melting point, ir, and TLC. The mass spectrum of **21** was practically identical with that of samandarine[20] (Figure 1). Although a nitrile group is not a normal target of $NaBH_4$ reduction, the outcome of the reaction was not entirely unexpected. Under the basic condition in the reduction, the nitrile group formed either cyclic amidine (e) or imino ester (f) which is subject to $NaBH_4$ reduction, and concomitant cyclization to the rigid oxazolidine ring prevented further reduction.[21]

Since **21** had already been converted to samandarine (**1**), which was further modified to samandarone (**22**) and a samandaridine (**23**), this work formally represents a new stereoselective synthesis of these alkaloids.

Experimental Section

All melting points were measured on a Kofler block and are uncorrected. Infrared spectra were taken with a Perkin-Elmer Model 458 in specified phases. Mass spectra were taken with a CEC Model 104. NMR spectra were measured with a JEOL HR 60 model.

17β-Acetoxy-4,5-secoandrost-3-en-5-one (5) 17β-Hydroxy-4,5-secoandrost-3-yn-5-one (4,[6] 160 mg) was dissolved in benzene (10 ml) and shaken under H_2 in the presence of Lindler catalyst (25 mg) and 1 drop of quinoline. After the uptake of 1 mol of H_2, the catalyst was filtered off and the solution was washed with dilute HCl, dried over Na_2SO_4, and evaporated to dryness. The residue was dissolved in a mixture of pyridine and acetic anhydride (2:1) and was left at room temperature for 12 h. The mixture was poured onto ice and extracted with ether. The ethereal extract was washed with dilute HCl, $NaHCO_3$ solution, and water, and dried over Na_2SO_4. Evaporation of the ether gave a crystalline residue which was crystallized from petroleum ether to prisms (**5**): mp 73–75 °C; ir (Nujol) 1740 (CH_3CO), 1700 (C=O), 1638 and 910 cm^{-1} (C=CH_2); yield 136 mg.

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.68; H, 9.70. Found: C, 76.04; H, 9.64.

17β-Hydroxy-3,4-imino-4,5-secoandrostan-5-one (6). To a solution of 17β-acetoxy-4,5-secoandrost-3-en-5-one (**5**, 1.03 g) in dry benzene (10 ml) was added *N,N*-dichlorourethane (0.49 g) and the solution was refluxed for 2 h. After cooling, the mixture was diluted with ether and washed with 5% $NaHSO_3$ solution. After evaporation of the solvent, the residue (1.1 g) was redissolved in a 5% alcoholic KOH solution and heated on a steam bath for 1 h. The reaction mixture was diluted with ether and extracted with 2% HCl solution. Basification of the HCl extract with a 5% NaOH solution liberated an oily substance which was extracted with chloroform. Evaporation of the chloroform layer afforded a colorless, resinous residue **6** (80 mg), *m/e* 305 (M^+), ir (neat) 3500 (OH), 3300 cm^{-1} (NH).

3,5-Epoxy-4-aza-*A*-homoandrostan-17-ol (7) and 8. 17β-Hydroxy-3,4-imino-4,5-secoandrostan-5-one (**6**, 400 mg) was dissolved in 2 N H_2SO_4 (10 ml) and heated at 80 °C for 2 h. The cooled solution was basified with a 5% NaOH solution and extracted with chloroform (50 ml × 3). Evaporation of the chloroform extract left a residue (85 mg), only two spots on TLC (silica gel, 5% MeOH in $CHCl_3$), which was chromatographed on a silica gel column. Elution with 5% methanol–chloroform afforded two pure compounds, **7** and **8** in the order of elution. **7:** crystals from methanol–water; mp 70–73 °C (hydrated crystals); ir (Nujol) 3450, 3300, 1047, 1018, and 895 cm^{-1}; ^1H NMR δ ($CDCl_3$) 0.74 (3 H, s, 18-CH_3), 0.90 (3 H, s, 19-CH_3), 2.79 (1 H, d, J = 10 Hz), 3.16 (1 H, q, J = 6, 10 Hz), 3.64 (1 H, t, 17-H), and 4.42 ppm (1 H, m); mass spectrum (Figure 1).

Anal. Calcd for $C_{19}H_{31}NO_2 \cdot H_2O$: C, 70.55; H, 10.28; N, 4.33. Found C, 70.55; H, 10.70; N, 4.37.

8: from $CHCl_3$; mp 221–222 °C; ir (Nujol) 3460, 3310, 1020, 1005, 900, and 878 cm^{-1}; ^1H NMR δ ($CDCl_3$) 0.74 (3 H, s, 18-CH_3), 1.07 (3 H, s, 19-CH_3), 2.75 (1 H, d, J = 10 Hz), 3.14 (1 H, q, J = 7, 10 Hz), 3.61 (1 H, t), and 4.44 ppm (1 H, m); mass spectrum (Figure 1).

Anal. Calcd for $C_{19}H_{31}NO_2$: C, 74.71; H, 10.23; N, 4.59. Found: C, 74.65; H, 10.06; N, 4.34.

17β-Acetoxy-*N*-nitroso-3-aza-*A*-homo-5β-androstan-4-one (12). 17β-Acetoxy-3-aza-*A*-homo-5β-androst-4-one (**11**, 1 g) was dissolved in an 1:1 mixture of acetic anhydride and acetic acid (50 ml), and $NaNO_2$ (300 mg) was added to the mixture under stirring at 0 °C. After stirring for 2 h, the mixture was poured onto ice, and the yellow, crystalline precipitate was collected by filtration and washed with water. Recrystallization from CH_2Cl_2–2-propanol gave a yellow prism: mp 146–148 °C; ir (Nujol) 1745 (acetate), 1710 (C=O), 1540 cm^{-1} (NO); yield 920 mg.

Anal. Calcd for $C_{21}H_{32}N_2O_4$: C, 67.71; H, 8.66; N, 15.04. Found: C, 67.54; H, 8.55; N, 15.00.

17β-Hydroxy-2,3-seco-5β-androst-1-en-3-oic Acid (13). The nitrosolactam **12** (500 mg) was dissolved in dimethyl sulfoxide (50 ml) and heated at 80 °C for 2 h. Evolution of nitrogen was observed during this period. The reaction mixture was diluted with ether and washed thoroughly with water, and then extracted with 5% $NaHCO_3$ solution. After acidification with dilute HCl, the acidic compound was extracted with ethyl acetate. Evaporation of the solvent left an acidic fraction (21 mg), which was saponified with 5% NaOH solution. After usual workup, the hydroxycarboxylic acid, **13**, was obtained and recrystallized from ethyl acetate, mp 183–186 °C, ir (Nujol) 3400 (OH), 1700 (–COOH), and 910 cm^{-1} (C=CH_2), which was identical with a specimen obtained by hydrolysis of **18**.

17β-Acetoxy-2β-methylthio-5β-androstan-3-one (15). To a boiling solution of 17β-hydroxy-2-hydroxymethylene-5β-androst-3-one (**14**, 1.0 g) in 10 ml of ethanol containing KOAc (1.0 g) was added a solution of methyl *p*-toluenethiosulfate (635 mg) in ethanol (10 ml). The solution was heated for an additional 10 min. After addition of water, the mixture was reduced in volume under vacuum and extracted with ether. The ethereal solution was washed with dilute NaOH solution and water, dried, and evaporated to dryness. The glassy residue was then acetylated by the usual method. Recrystallization of the acetate from methanol gave prisms of **15**: mp190–192 °C; ir (KBr) 1735, 1248 (acetate), 1690 cm^{-1} (3CO); ^1H NMR ($CDCl_3$) δ 0.82 (3 H, s) 1.04 (3 H, s), 2.04 (3 H, s) 2.10 (3 H, s), 3.46 (1 H, q, J = 6, 12 Hz), 4.60 ppm (1 H, m).

Anal. Calcd for $C_{22}H_{34}O_3S$: C, 69.79; H, 9.05; S, 8.39. Found: C, 70.07; H, 9.12; S, 8.63.

17β-Acetoxy-2β-methylthio-5β-androstane-3-ketoxime (16). 17β-Hydroxy-2β-methylthio-5β-androstan-3-one (**15**, 150 mg) was heated with hydroxylamine hydrochloride (200 mg) in pyridine on a steam bath for 1 h. After addition of water to the mixture, precipitated crystals were collected and recrystallized from methanol–water to prisms, **16**: mp180–183 °C; ir (KBr) 3270 (NO–H), 1730 (acetate), 1660 cm^{-1} (C≡N); yield 137 mg.

Anal. Calcd for $C_{22}H_{35}O_3NS$: C, 67.13; H, 8.96; N, 3.56; S, 8.14. Found: C, 67.05; H, 8.98, N, 3.42; S, 8.34.

17β-Acetoxy-2-methylthio-2,3-seco-5β-androst-1-ene-3-nitrile (17). The oxime **16** (300 mg) was dissolved in pyridine (6 ml) containing *p*-toluenesulfonyl chloride (450 mg). The solution was refluxed for 30 min under N_2. The resulting reaction mixture was diluted with ether and washed with water. Evaporation afforded a residue (280 mg) which was chromatographed on silica gel (17 g). Elution with CH_2Cl_2 gave crystals (185 mg), which were recrystallized from methanol, **17**: mp 105–107 °C; ir (Nujol) 2250 (C≡N), 1730 (acetate), 1570 cm^{-1} (–SC=C).

Anal. Calcd for $C_{22}H_{33}NO_2S$: C, 70.36; H, 8.86; N, 3.73; S, 8.54. Found: C, 70.44; H, 8.95; N, 3.41; S, 8.71.

17β-Acetoxy-2,3-seco-5β-androst-1-ene-3-nitrile (18). The thioenol ether **17** (130 mg) was heated with deactivated Raney Ni[17] (1.3 ml) in methanol (30 ml) under reflux for 1.5 h. The catalyst was removed by filtration and the filtrate was evaporated to dryness. Crystallization from isopropyl ether gave needles: mp 147–148 °C; ir (Nujol) 2250 (C≡N), 1740 (acetate), 1640, 924 cm^{-1} (C=CH_2).

Anal. Calcd for $C_{21}H_{31}O_2N$: C, 76.55; H, 9.48; N, 4.25. Found: C, 74.54; H, 9.30; N, 4.12.

(1*R*)-1,2-Epoxy-17β-acetoxy-2,3-seco-5β-androstane-3-nitrile (19). The seco olefin **17** (100 mg) was dissolved in $CHCl_3$ (5 ml) containing *m*-chloroperbenzoic acid (200 mg, 70% pure) and was left at room temperature for 48 h. The reaction mixture was diluted with sodium sulfite solution, $NaHCO_3$, and water. Evaporation of ether gave a crystalline residue, which was recrystallized from methanol and H_2O to needles: mp 134–135 °C; ir (Nujol) 2250 (C≡N), 1750 (acetate), 1060, and 1030 cm^{-1}; yield 81 mg.

Anal. Calcd for $C_{21}H_{31}NO_3$: C, 73.00; H, 9.05; N, 4.05. Found: C, 73.02; H, 9.21; N, 3.85.

17β-Acetoxy-2-azido-1-hydroxy-2,3-seco-5β-androstane-3-nitrile (20). The epoxide **19** (100 mg) was dissolved in methyl Cellosolve (5 ml) containing H_2O (0.3 ml), NaN_3 (150 mg), and NH_4Cl (8.5 mg). The mixture was heated under reflux for 1.5 h. Dilution of the mixture with H_2O separated crystals (101 mg), which were recrystallized from ether–isopropyl ether to prisms (**20**): mp 191 °C (sinters at 178 °C); ir (Nujol) 3480 (OH), 2770 (C≡N), 2110 (–N_3), and 1735 cm^{-1} (acetate).

Anal. Calcd for $C_{21}H_{32}N_4O_3$: C, 65.26; H, 7.82; N, 14.50. Found: C, 65.46; H, 7.90; N, 14.49.

1,4-Epoxy-3-azahomo-5β-androstan-17β-ol (21). To a solution of the azide **20** (20 mg) in 2-propanol (1 ml) was added $NaBH_4$ (10 mg) and the mixture was heated at 90 °C under N_2 for 16 h. After evaporation of the solvent, the residue was dissolved in 5 ml of water and extracted with $CHCl_3$ several times. Evaporation of the extract gave a crystalline mass which showed only one spot on TLC (silica gel, 15% MeOH–H_2O). Recrystallization from methanol gave prisms [mp 191–193 °C; ir (KBr) 3420 (OH), 3320 (NH), 1115, 1060, 1015, 852, 834 cm^{-1}; ^1H NMR δ $CDCl_3$) 0.76 (3 H, s), 0.86 (3, H, s), 3.00 (3 H, m), 3.66 (1 H, t), and 4.19 ppm (1 H, q)], which was identified with an authentic sample sent by Dr. Oka by mixture melting point, TLC, ir, and mass spectra (Figure 1).

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Registry No.—**1**, 467-51-6; **4**, 17541-44-5; **5**, 58673-15-7; **6**, 58673-16-8; **7**, 58673-17-9; **8**, 58673-18-0; **11**, 21522-17-8; **12**, 58673-19-1; **13**, 58673-20-4; **14**, 52129-23-4; **15**, 58673-21-5; **16**, 38623-74-4; **17**, 38623-75-5; **18**, 38623-76-6; **19**, 38623-77-7; **20**, 38623-78-8; **21**, 25484-32-6.

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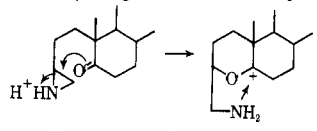

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