[Chem. Pharm. Bull. 21(11)2474—2478(1973)]

UDC 547.92.04 : 547.786.057

Syntheses of 16,17-Dihydroxy-17-methyl-5α-androstano[3,2-*c*]isoxazoles[1]

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(Received March 8, 1973)

In order to clarify the metabolic fate of 17β-hydroxy-17α-methyl-5α-androstano-[3,2-*c*]isoxazole, preparation of the titled compounds as its potential metabolites has been undertaken. Treatment of the appropriate 5α-androstan-3-ones (I, XIa, and XIb) with ethyl formate provided the 2-hydroxymethylene derivatives (II, XIIa, and XIIb), which in turn were condensed with hydroxylamine to yield the desired isoxazole fused steroids (IV, XIIIa, and XIIIb), respectively.

In recent years numerous kinds of the modified steroids have been presented for the chemotherapeutic purpose. One of these modifications involves the fusion of a hetero ring to the inherent steroidal nucleus. A heterocycle fused steroid, 17β-hydroxy-17α-methyl-5α-androstano[3,2-*c*]isoxazole (androisoxazole), has been shown to exhibit the potent anabolic activity.[3,4] However, the metabolic fate of this drug still remains unsolved. It has already been reported that the principal metabolites of the analogous steroids were the 16-oxygenated derivatives.[5,6] In addition the occurrence of epimerization at the 17α-methyl-17β-ol structure in man has recently been demonstrated.[7] These findings prompted us to synthesize the titled compounds as potential metabolites.

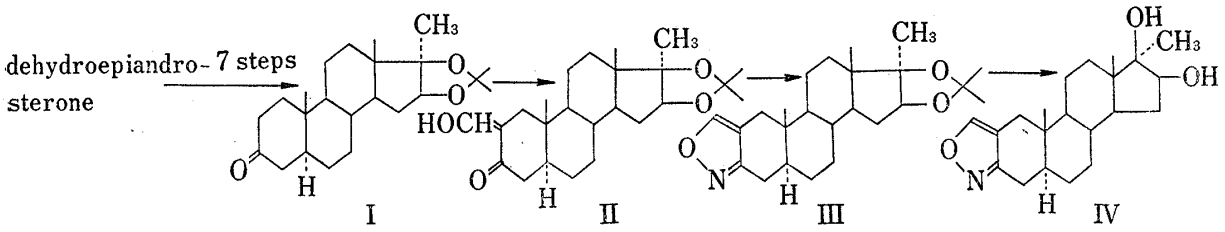

Chart 1

An initial project was focused on preparation of a compound having the 16β,17β-glycol structure. First, 16β,17β-dihydroxy-17α-methyl-5α-androstan-3-one acetonide (I),[8] obtainable from dehydroepiandrosterone in several steps, was employed as a starting material. Condensation with ethyl formate in the presence of sodium methoxide proceeded with ease yielding the 2-hydroxymethylene derivative (II). Formation of isoxazole attached to ring A was effected by refluxing with hydroxylamine in aqueous pyridine. The mode of cycliza-

1) This paper constitutes Part LXVI of the series entitled "Analytical Chemical Studies on Steroids"; Part LXV: T. Nambara, M. Ito, M. Ito, J. Mohri, J. Goto, and H. Hosoda, *Chem. Pharm. Bull.* (Tokyo), **21**, 2452 (1973).
2) Location: *Aobayama, Sendai.*
3) *a*) P. Donini and R. Montezemolo, *Farmaco Ed. Sci.*, **16**, 633 (1961); *b*) E. Marchetti and P. Donini, *Gazz. Chim. Ital.*, **91**, 1133 (1961).
4) T. Akutsu, N. Ogawa, and Y. Suzuki, *Pharmacometrics*, **4**, 789 (1970).
5) T. Watabe, S. Yagishita, and S. Hara, *Biochem. Pharmacol.*, **19**, 1485 (1970).
6) T. Takegoshi, H. Tachizawa, and G. Ohta, *Chem. Pharm. Bull.* (Tokyo), **20**, 1243 (1972).
7) B.S. Macdonald, P.J. Sykes, P.M. Adhikary, and R.A. Harkness, *Steroids*, **18**, 753 (1971).
8) T. Takegoshi, *Chem. Pharm. Bull.* (Tokyo), **20**, 1260 (1972).

tion into 5α-androstano[3,2-*c*]isoxazole under these conditions was unequivocally justified based upon the fact that the product (III) did resist the ring opening when treated with sodium methoxide.[3b] The protecting group at C-16, 17 was readily eliminated with *p*-toluenesulfonic acid to afford the desired 16β,17β-dihydroxy-17α-methyl-5α-androstano[3,2-*c*]isoxazole (IV).

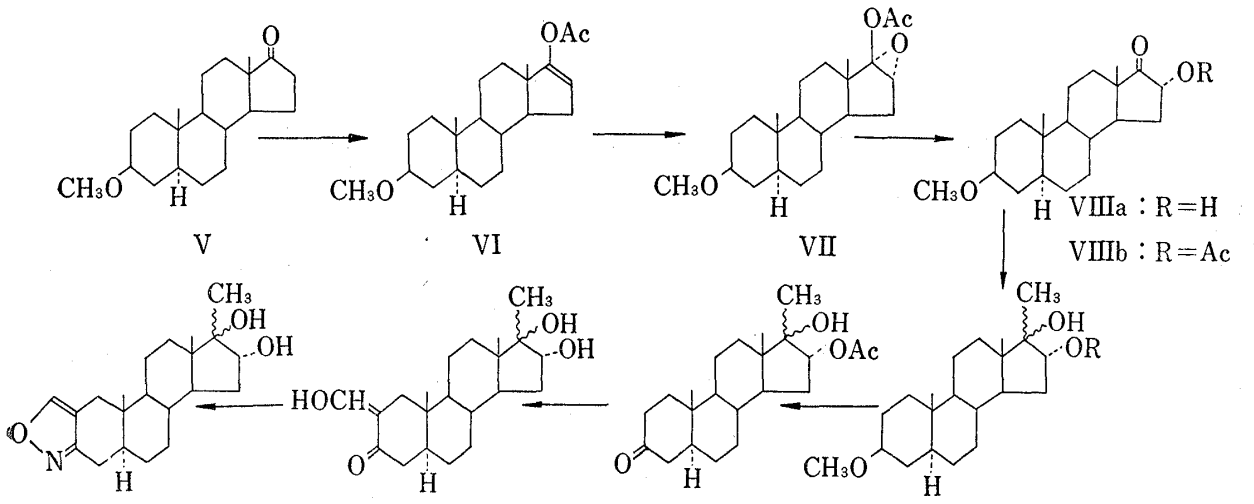

Chart 2

The preparation of C-17 epimeric 16α-hydroxyl compounds was then undertaken. Introduction of an oxygen function to C-16 was accomplished by the method worked out by Gallagher and his co-workers.[9] First, isoandrosterone 3-methyl ether (V) was transformed into the Δ^{16}-enol acetate (VI) by treatment with isopropenyl acetate and a catalytic amount of sulfuric acid in a fairly good yield. Oxidation with *m*-chloroperbenzoic acid furnished solely the 16α,17α-epoxide (VII), which on brief exposure to sulfuric acid in aqueous methanol was converted into the 16α-hydroxy-17-ketone (VIIIa). Grignard reaction of the 16-acetate (VIIIb) with methylmagnesium iodide afforded two epimeric 17-methyl-17-hydroxyl compounds (IXa, IXc) in a ratio of *ca.* 3 to 1. The *cis*-glycol structure of IXc was definitely established by leading to the 16,17-acetonide (X) in the usual manner. It is to be noted that formation of IXc reflects the influence of the steric hindrance due to the 16α-substituent.

Next effort was directed to the cleavage of the methyl ether at C-3. Concerning with this transformation chromium trioxide oxidation of 3-methoxysteroid into the formyloxy derivative has already been demonstrated.[10] Hence, the attempt was made on the utilization of this method for the subsequent elaboration. Being treated with chromium trioxide in glacial acetic acid and dry methylene chloride, 3β-methoxy-17α-methyl-5α-androstane-16α,17β-diol 16-acetate (IXb) was oxidized into the corresponding 3-oxo compound (XIa) in a satisfactory yield. It seemed very likely that the reaction might proceed in such a way that the resulting formate underwent the spontaneous hydrolysis followed by further oxidation. Reaction with ethyl formate gave rise to the 2-hydroxymethylene derivative (XIIa), which in turn was condensed with hydroxylamine to yield the desired heterocycle fused compound (XIIIa).

The synthesis of its C-17 epimer was then carried out in the same reaction sequence as described above. Oxidation of 3β-methoxy-17β-methyl-5α-androstane-16α,17α-diol 16-

9) N.S. Leeds, D.K. Fukushima, and T.F. Gallagher, *J. Am. Chem. Soc.*, **76**, 2943 (1954).
10) I.T. Harrison and S. Harrison, *Chem. Commun.*, **1966**, 752.

acetate (IXd) with chromium trioxide furnished the 3-ketone (XIb), which in turn was led to the 2-hydroxymethylene derivative (XIIb) by treatment with ethyl formate and sodium methoxide. The facile cyclization with hydroxylamine was attained to provide the isoxazole fused steroid (XIIIb) in a reasonable yield.

The 16-oxygenated compounds thus prepared will serve as useful reference for the studies on the metabolism of Androisoxazole.

Experimental[11]

16β,17β-Dihydroxy-17α-methyl-5α-androstano[3,2-*c*]isoxazole 16,17-Acetonide (III)——To a ice-cooled solution of 16β,17β-dihydroxy-17α-methyl-5α-androstan-3-one 16,17-acetonide (I)[8] (50 mg) and MeONa (143 mg) in benzene (7 ml) was added dropwise ethyl formate (2 ml) over a period of 2 hr under a N_2 gas stream and stirred at room temperature for 17 hr. The resulting solution was acidified with 15% AcOH and extracted with benzene. The organic layer was separated, washed with 5% $NaHCO_3$ and H_2O, and dried over anhydrous Na_2SO_4. Evaporation of solvent gave 2-hydroxymethylene-16β,17β-dihydroxy-17α-methyl-5α-androstan-3-one 16,17-acetonide (II) as a yellow oil. UV λ_{max}^{MeOH} nm: 285. To a solution of II (50 mg) in pyridine (3 ml) was added an aq. solution of $NH_2OH \cdot HCl$ (23 mg in 0.5 ml) and refluxed for 4 hr. The resulting solution was diluted with ether, washed with 5% HCl and H_2O, dried over anhydrous Na_2SO_4, and evaporated. An oily residue was submitted to preparative TLC using benzene–AcOEt (4: 1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.73) with AcOEt and recrystallization of the eluate from acetone–hexane gave III (25 mg) as colorless plates. mp 244.5—245°. $[\alpha]_D^{14.5}$ +29.8° (*c*=0.10). *Anal.* Calcd. for $C_{24}H_{35}O_3N$: C, 74.76; H, 9.15; N, 3.63. Found: C, 74.71; H, 9.12; N, 3.49. NMR (5% solution in $CDCl_3$) δ: 0.75 (3H, s, 19–CH_3), 0.92 (3H, s, 18–CH_3), 1.31 (3H, s, 17α–CH_3), 1.36 (3H, s, acetonide–CH_3), 1.46 (3H, s, acetonide–CH_3), 4.20 (1H, q, *J*=7, 5 Hz, 16α-H), 8.06 (1H, s, isoxazole-5-H).

16β,17β-Dihydroxy-17α-methyl-5α-androstano[3,2-*c*]isoxazole (IV)——A solution of III (38 mg) and *p*-TsOH·H_2O (6.9 mg) in 99% EtOH (3 ml) was heated at 60—70° for 45 hr. After evaporation of solvent the residue was diluted with ether–CH_2Cl_2, washed with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product was submitted to preparative TLC using benzene–AcOEt (4: 1) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.16) with AcOEt and recrystallization of the eluate from acetone–hexane gave IV (15 mg) as colorless needles. mp 232—234.5°. $[\alpha]_D^{15}$ +3.7° (*c*=0.14). *Anal.* Calcd. for $C_{21}H_{31}O_3N$: C, 73.00; H, 9.05; N, 4.05. Found: C, 72.98; H, 9.03; N, 3.85. UV λ_{max}^{MeOH} nm: 222. NMR (4% solution in $CDCl_3$) δ: 0.76 (3H, s, 19-CH_3), 0.87 (3H, s, 18-CH_3), 1.12 (3H, s, 17α-CH_3), 3.70 (1H, q, *J*=6, 4 Hz, 16-αH), 8.06 (1H, s, isoxazole-5-H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1616 (C=N).

3β-Methoxy-5α-androst-16-en-17-ol Acetate (VI)——To a solution of 3β-methoxy-5α-androstan-17-one (V) (1.1 g) in isopropenyl acetate (10 ml) was added the catalyst solution (2 ml) (isopropenyl acetate (5 ml) and conc. H_2SO_4 (0.1 ml)) and refluxed for 1.5 hr. The reaction mixture was concentrated to one-half of its volume by slow distillation over a period of 1 hr. The resulting solution was diluted with ether and washed with cold 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. An oily residue was submitted to column chromatography on silica gel. Elution with hexane–benzene (4: 1 to 2: 1) and recrystallization of the eluate from MeOH gave VI (940 mg) as colorless needles. mp 102°. $[\alpha]_D^{24}$ +61.5° (*c*=0.13). *Anal.* Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.29; H, 10.00. NMR (4% solution in $CDCl_3$) δ: 0.82 (3H, s, 19-CH_3), 0.86 (3H, s, 18-CH_3), 2.11 (3H, s, 17-$OCOCH_3$), 3.30 (3H, s, 3β-OCH_3), 5.45 (1H, m, 16-H).

3β-Methoxy-16α-hydroxy-5α-androstan-17-one (VIIIa)——To a solution of VI (460 mg) in $CHCl_3$ (20 ml) was added *m*-chloroperbenzoic acid (260 mg) and allowed to stand at room temperature overnight. The resulting solution was diluted with ether, washed with 5% $Na_2S_2O_3$, 5% $NaHCO_3$ and H_2O, and dried over anhydrous Na_2SO_4. Evaporation of solvent gave 3β-methoxy-16α,17α-epoxy-5α-androstan-17β-ol acetate (VII) (460 mg) as colorless needles. To a solution of VII in MeOH (40 ml) was added 1N H_2SO_4 (3 ml) under ice-cooling and allowed to stand at room temperature for 15 min. The resulting solution was diluted with ether, washed with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization from acetone–hexane gave VIIIa (450 mg) as colorless prisms. mp 132—133°. $[\alpha]_D^{24}$ +91.6° (*c*=0.12). *Anal.* Calcd. for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 75.31; H, 10.31. NMR (5% solution in $CDCl_3$) δ: 0.80 (3H, s, 19-CH_3), 0.95 (3H, s, 18-CH_3), 3.34 (3H, s, 3β-OCH_3), 4.35 (1H, t, *J*=4.5 Hz, 16β-H).

11) All melting points were taken on a micro-hot stage apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$ unless otherwise specified. Ultraviolet (UV) and infrared (IR) spectra were run on Hitachi Model 124 and JASCO Model IR-S spectrophotometers, respectively. Nuclear magnetic resonance (NMR) spectra were recorded on Hitachi Model R-20 spectrometer at 60 MHz employing tetramethylsilane as an internal standard. Abbreviation used s=singlet, d=doublet, t=triplet, q=quartet, and m=multiplet. For preparative thin-layer chromatography (TLC) silica gel H (E. Merck AG, Darmstadt) was used as an adsorbent.

3β-Methoxy-16α-hydroxy-5α-androstan-17-one Acetate (VIIIb)——Treatment of VIIIa (450 mg) with Ac_2O (10 ml) and pyridine (10 ml) in the usual manner followed by recrystallization from MeOH gave VIIIb (439 mg) as colorless prisms. mp 154—155°. $[\alpha]_D^{19.5}$ +182.6° (c=0.08). *Anal.* Calcd. for $C_{22}H_{34}O_4$: C, 72.81; H, 9.45. Found: C, 72.81; H, 9.53. NMR (6% solution in $CDCl_3$) δ: 0.82 (3H, s, 19-CH_3), 0.96 (3H, s, 18-CH_3), 2.09 (3H, s, 16α-$OCOCH_3$), 3.12 (3H, s, 3β-OCH_3), 5.40 (1H, q, J=6.8, 3 Hz, 16β-H).

3β-Methoxy-17α-methyl-5α-androstane-16α,17β-diol (IXa), 3β-Methoxy-17β-methyl-5α-androstane-16α, 17α-diol (IXc)——To an ethereal solution of MeMgI, freshly prepared from Mg ribbon (7 g) and MeI (43 g) in ether (150 ml) was added a solution of VIIIb (2 g) in benzene (200 ml) under ice-cooling and stirred at room temperature for 8 hr. To the resulting solution were added moist ether, ice–water and 5% HCl, successively and extracted with AcOEt. The organic layer was separated, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. An oily residue was submitted to column chromatography on silica gel. Elution with benzene–AcOEt (2: 1) and recrystallization of the eluate from acetone–hexane gave IXc (400 mg) as colorless needles. mp 199—200°. $[\alpha]_D^{18}$ −0.2° (c=0.25). *Anal.* Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 75.08; H, 10.83. NMR (4.5% solution in $CDCl_3$) δ: 0.69 (3H, s, 18-CH_3), 0.80 (3H, s, 19-CH_3), 1.16 (3H, s, 17β-CH_3), 3.32 (3H, s, 3β-OCH_3), 4.05 (1H, q, J=3, 9 Hz, 16β-H). Further elution with benzene–AcOEt (2:1) and recrystallization of the eluate from acetone–hexane gave IXa (1.4 g) as colorless needles. mp 179—180°. $[\alpha]_D^{19}$ −3.4° (c=0.22). *Anal.* Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.90; H, 10.73. NMR (5% solution in $CDCl_3$) δ: 0.78 (3H, s, 19-CH_3), 0.83 (3H, s, 18-CH_3), 1.13 (3H, s, 17α-CH_3), 3.30 (3H, s, 3β-OCH_3), 4.22 (1H, m, 16β-H).

3β-Methoxy-17α-methyl-5α-androstane-16α,17β-diol 16-Acetate (IXb)——Treatment of IXa with Ac_2O and pyridine in the usual manner followed by recrystallization from MeOH gave IXb as colorless needles. mp 153—154°. $[\alpha]_D^{21}$ +3.7° (c=0.14). *Anal.* Calcd. for $C_{22}H_{38}O_4$: C, 72.97; H, 10.12. Found: C, 73.15; H, 9.94. NMR (4.5% solution in $CDCl_3$) δ: 0.81 (3H, s, 19-CH_3), 0.92 (3H, s, 18-CH_3), 1.05 (3H, s, 17α-CH_3), 2.08 (3H, s, 16α-$OCOCH_3$), 3.31 (3H, s, 3β-OCH_3), 5.05 (1H, m, 16β-H).

3β-Methoxy-17β-methyl-5α-androstane-16α,17α-diol 16-Acetate (IXd)——Treatment of IXc with Ac_2O and pyridine in the usual manner followed by recrystallization from MeOH gave IXd as colorless needles. mp 196—197.5°. $[\alpha]_D^{19.5}$ +18.3° (c=0.08). *Anal.* Calcd. for $C_{23}H_{38}O_4$: C, 72.97; H, 10.12. Found: C, 72.86; H, 10.20. NMR (3.4% solution in $CDCl_3$) δ: 0.72 (3H, s, 18-CH_3), 0.81 (3H, s, 19-CH_3), 1.14 (3H, s, 17β-CH_3), 2.11 (3H, s, 16α-$OCOCH_3$), 3.33 (3H, s, 3β-OCH_3), 5.05 (1H, m, 16β-H).

3β-Methoxy-17β-methyl-5α-androstane-16α,17α-diol 16,17-Acetonide (X)——To a solution of IXc (140 mg) in acetone (8 ml) was added 2 drops of 70% $HClO_4$ under ice-cooling and stirred at room temperature for 1 hr. The resulting solution was poured into ice water and extracted with AcOEt. The organic layer was separated, washed with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. An oily residue was submitted to preparative TLC using benzene–AcOEt (15: 1) as developing solvent. Elution of the adsorbent corresponding to the spot (^2Rf 0.41) with AcOEt and recrystallization of the eluate from MeOH gave X (71 mg) as colorless needles. mp 120—120.5°. $[\alpha]_D^{19}$ −15.9° (c=0.13). *Anal.* Calcd. for $C_{24}H_{40}O_3$: C, 76.55; H, 10.71. Found: C, 76.64; H, 10.81. NMR (4% solution in $CDCl_3$) δ: 0.66 (3H, s, 18-CH_3), 0.80 (3H, s, 19-CH_3), 1.31 (3H, s, 17β-CH_3), 2.42 (6H, s, $-C(CH_3)_2$), 3.33 (3H, s, 3β-OCH_3), 4.34 (1H, broad d, J=4.5 Hz, 16β-H).

16α,17β-Dihydroxy-17α-methyl-5α-androstan-3-one 16-Acetate (XIa)——To a suspended solution of CrO_3 (120 mg) in AcOH (6 ml)–anhydrous CH_2Cl_2 (1 ml) was added dropwise a solution of IXb (100 mg) in anhydrous CH_2Cl_2 (5 ml) under ice-cooling over a period of 30 min and then stirred at room temperature for 1.5 hr. After careful addition of 5% Na_2SO_3 to decompose the excess reagent the resulting solution was extracted with ether. The organic layer was separated, washed with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. An oily residue was submitted to preparative TLC using benzene–AcOEt (4: 1) as developing solvent. Elution of the adsorbent corresponding to the spot (Rf 0.26) and recrystallization of the eluate from MeOH gave XIa (30 mg) as colorless needles. mp 202—204°. $[\alpha]_D^{21}$ +47.6° (c=0.10). *Anal.* Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.39; H, 9.37. NMR (4% solution in $CDCl_3$) δ: 0.96 (3H, s, 18-CH_3), 1.03 (3H, s, 19-CH_3), 1.05 (3H, s, 17α-CH_3), 2.09 (3H, s, 16α-$OCOCH_3$), 5.01 (1H, q, J=6, 3 Hz, 16β-H).

16α,17α-Dihydroxy-17β-methyl-5α-androstan-3-one 16-Acetate (XIb)——To a suspended solution of CrO_3 (630 mg) in AcOH (6 ml)–anhydrous CH_2Cl_2 (3 ml) was added a solution of IXd (140 mg) in ahnydrous CH_2Cl_2 (2 ml) under ice-cooling over a period of 30 min and then stirred at room temperature for 1.5 hr. After careful addition of 5% Na_2SO_3 to decompose the excess reagent the resulting solution was extracted with ether. The organic layer was separated, washed with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization from MeOH gave XIb (80 mg) as colorless needles. mp 206.5—208°. $[\alpha]_D^{20}$ −71.7° (c=0.02). *Anal.* Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.82; H, 9.46. NMR (4.5% solution in $CDCl_3$)δ: 0.75 (3H, s, 18-CH_3), 1.02 (3H, s, 19-CH_3), 1.14 (3H, s, 17β-CH_3), 2.09 (3H, s, 16α-$OCOCH_3$), 5.00 (1H, q, J=9.3, 2.7 Hz, 16β-H).

16α,17β-Dihydroxy-17α-methyl-5α-androstano[3,2-*c*]isoxazole (XIIIa)——To an ice-cooled solution of XIa (58 mg) and MeONa (115 mg) in benzene (5 ml) was added ethyl formate (2 ml) and stirred at room temperature for 2 hr. The resulting solution was acidified with 5% HCl and extracted with AcOEt. The organic layer was separated, washed with H_2O, and dried over anhydrous Na_2SO_4. Evaporation of solvent

gave 2-hydroxymethylene-16α,17β-dihydroxy-17α-methyl-5α-androstan-3-one (XIIa) (52 mg) as a yellow oil. UV λ_{max}^{MeOH} nm: 285. To a solution of XIIa (52 mg) in pyridine (10 ml) was added an aq. solution of NH_2-OH·HCl (40 mg in 0.2 ml) and refluxed for 4 hr. The resulting solution was diluted with AcOEt, washed with 5% HCl and H_2O, dried over anhydrous Na_2SO_4, and evaporated. An oily residue was submitted to preparative TLC using benzene–AcOEt (1: 2) as developing solvent. Elution of the adsorbent corresponding to the spot (*Rf* 0.21) with AcOEt and recrystallization of the eluate from acetone–hexane gave XIIIa (17 mg) as colorless leaflets. mp 216—218°. $[\alpha]_D^{17}$ −0.03° (c=0.13). *Anal.* Calcd. for $C_{21}H_{31}O_3N$: C, 73.00; H, 9.05; N, 4.05. Found: C, 72.98; H, 9.16; N, 4.35. UV λ_{max}^{MeOH} nm: 222. NMR (3.5% solution in $CDCl_3$) δ: 0.76 (3H, s, 19-CH_3), 0.90 (3H, s, 18-CH_3), 1.20 (3H, s, 17α-CH_3), 4.30 (1H, q, J=3, 9 Hz, 16β-H), 8.11 (1H, s, isoxazole-5-H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1616 (C=N).

16α,17α-Dihydroxy-17β-methyl-5α-androstano[3,2-*c*]isoxazole (XIIIb)——To an ice-cooled solution of XIb (55 mg) and MeONa (116 mg) in benzene (7 ml) was added ethyl formate (2 ml) and stirred at room temperature for 17 hr. The resulting solution was acidified with 5% HCl and extracted with benzene. The organic layer was separated, washed with H_2O and dried over anhydrous Na_2SO_4. Evaporation of solvent gave 2-hydroxymethylene-16α,17α-dihydroxy-17β-methyl-5α-androstan-3-one (XIIb) (50 mg) as a yellow oil. UV λ_{max}^{MeOH} nm: 285. To a solution of XIIb (50 mg) in pyridine (5 ml) was added an aq. solution of NH_2-OH–HCl (25 mg in 0.5 ml) and refluxed for 4 hr. The resulting solution was diluted with ether, washed with 5% HCl and H_2O, dried over anhydrous Na_2SO_4, and evaporated. An oily residue was submitted to preparative TLC using benzene–AcOEt (4: 1) as developing solvent. Elution of the adsorbent corresponding to the spot (^2Rf 0.21) with AcOEt and recrystallization of the eluate from acetone–hexane gave XIIIb (24 mg) as colorless needles. mp 202—203°. $[\alpha]_D^{25}$ −23.7° (c=0.08). *Anal.* Calcd. for $C_{21}H_{31}O_3N$: C, 73.00; H, 9.05; N, 4.05. Found: C, 73.21; H, 8.98; N, 4.05. UV λ_{max}^{MeOH} nm: 222. NMR (4% solution in $CDCl_3$) δ: 0.72 (3H, s, 18-CH_3), 0.75 (3H, s, 19-CH_3), 1.18 (3H, s, 17β-CH_3), 4.05 (1H, q, J=7, 2.7 Hz, 16β-H), 8.05 (1H, s, isoxazole-5-H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1616 (C=N).

Acknowledgement The authors are indebted to all the staffs of central analytical laboratory of this Institute for elemental analyses and spectral measurements.