[Chem. Pharm. Bull. 12 (1) 77 ~ 86]

UDC 547.92.07 : 577.176

12. Masao Shimizu, Genkichi Ohta, Katsujiro Ueno, and Toshio Takegoshi : Investigations on Steroids. I. Synthesis of Androstano[3,2-*b*]pyridine.[1]

(*Central Research Laboratory, Daiichi Seiyaku Co., Ltd.**1)

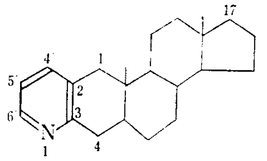
In recent years the search for modified steroidhormones possessing heterocycles fused to ring A of steroids has been markedly intensified. The effect on biological activities produced by fusion of pyrazole ring to 2,3-positions of androstanes and 19-norandrostanes was first announced by Clinton, *et al.*[2] Later, syntheses of similarly substituted isoxazole-,[2c,3] thiazole-,[3c,4] pyrimidine-,[2c,3c] triazole-,[5] pyrrole-,[6] indole-,[6] quinoline-,[7] and oxazine-[8] derivatives were reported. Among them steroidal pyrazoles, isoxazoles, thiazoles, and oxazines were found to have interesting activities. In view of these facts our interest was focused on steroidal pyridine derivatives, and this paper describes the preparation of androstano[3,2-*b*]pyridines for biological studies.

The formation of pyridine ring was carried out by condensation of 2-hydroxymethylene-3-oxoandrostanes with cyanoacetamide or its derivatives. From the results of analogous reactions, it was assumed that this method of preparation would not give androstano-[2,3-*c*] pyridine but [3,2-*b*] pyridine, and later experiments proved this view correct. Reaction of 2-hydroxymethylene-17β-hydroxyandrostan-3-one (Ia) and its 17α-methyl compound (Ib) with cyanoacetamide in ethanolic triethylamine solution under reflux gave 6'-oxo-17β-hydroxy-1',6'-dihydroandrostano[3,2-*b*]pyridine-5'-carbonitrile (IIIa) and its 17α-methyl derivative (IIIb), respectively. In the presence of sodium ethoxide or Triton B instead of triethylamine the reaction failed, and by an attempted use of piperidine as catalyst, the 2-piperidinomethylene-3-oxo compound (V) was solely obtained from Ia.

---

*1 Minamifunabori-cho, Edogawa-ku, Tokyo (清水正夫，太田元吉，上野勝次郎，竹越敏夫).

[1] In this paper simple nomenclature and numbering system are adopted, because formal nomenclature of the heterocycle-fused steroid is complicated.



androstano[3,2-*b*]pyridine

[2] *a*) R.O. Clinton, A.J. Manson, F.W. Stonner, A.L. Beyler, G.O. Potts, A. Arnold : J. Am. Chem. Soc., **81**, 1513 (1959); *b*) R.O. Clinton, A.J. Manson, F.W. Stonner, H.C. Neumann, R.G. Christiansen, R.L. Clarke, J.H. Ackerman, D.F. Page, J.W. Dean, W.B. Dickinson, C. Carabateas: *Ibid.*, **83**, 1478 (1961); cf. *c*) P. Ruggieri, C. Gandolfi, D. Chiaramonti : Gazz. chim. ital., **92**, 768 (1962).

[3] *a*) R.O. Clinton, A.J. Manson, F.W. Stonner, R.G. Christiansen, A.L. Beyler, G.O. Potts, A. Arnold : J. Org. Chem., **26**, 279 (1961); *b*) A.J. Manson, F.W. Stonner, H.C. Neumann, R.G. Christiansen, R.L. Clarke, J.H. Ackerman, D.F. Page, J.W. Dean, D.K. Phillips, G.O. Potts, A. Arnold, A.L. Beyler, R.O. Clinton : J. Med. Chem., **6**, 1 (1963); *c*) J.A. Zderic, O. Halpern, H. Carpio, A. Ruiz, D.C. Limon, L. Magana, H. Jimenez, A. Bowers, H.J. Ringold : Chem. & Ind. (London), **1960**, 1625; *d*) E. Marchetti, P. Donini : Gazz. chim. ital., **91**, 1133 (1961); *e*) E. Caspi, D.M. Piatak : Chem. & Ind. (London), **1962**, 1984.

[4] *a*) N.J. Doorenbos, C.P. Dorn, Jr. : J. Pharm. Science, **50**, 271 (1961); *b*) *Idem* : *Ibid.*, **51**, 414 (1962); *c*) J.A. Zderic, H. Carpio, A. Ruiz, D.C. Limon, F. Kincl, H.J. Fingold : J. Med. Chem., **6**, 195 (1963).

[5] G. Nathansohn, E. Testa, N. DiMola : Experientia, **18**, 57 (1962).

[6] a) J.C. Orr, A. Bowers : U.S.P. 3,032,551 (1961); b) E. W. Warnhoff, P. Nanonggai : J. Org. Chem. **27**, 1186 (1962).

[7] A. Hassner, M.J. Haddadin : J. Org. Chem., **27**, 1911 (1962).

[8] *a*) M.E. Kuehne, E.A. Konopka, B.F. Lambert : J. Med. Chem., **5**, 281 (1962); *b*) M.E. Kuehne: U.S.P. 3,033,860 (1962).

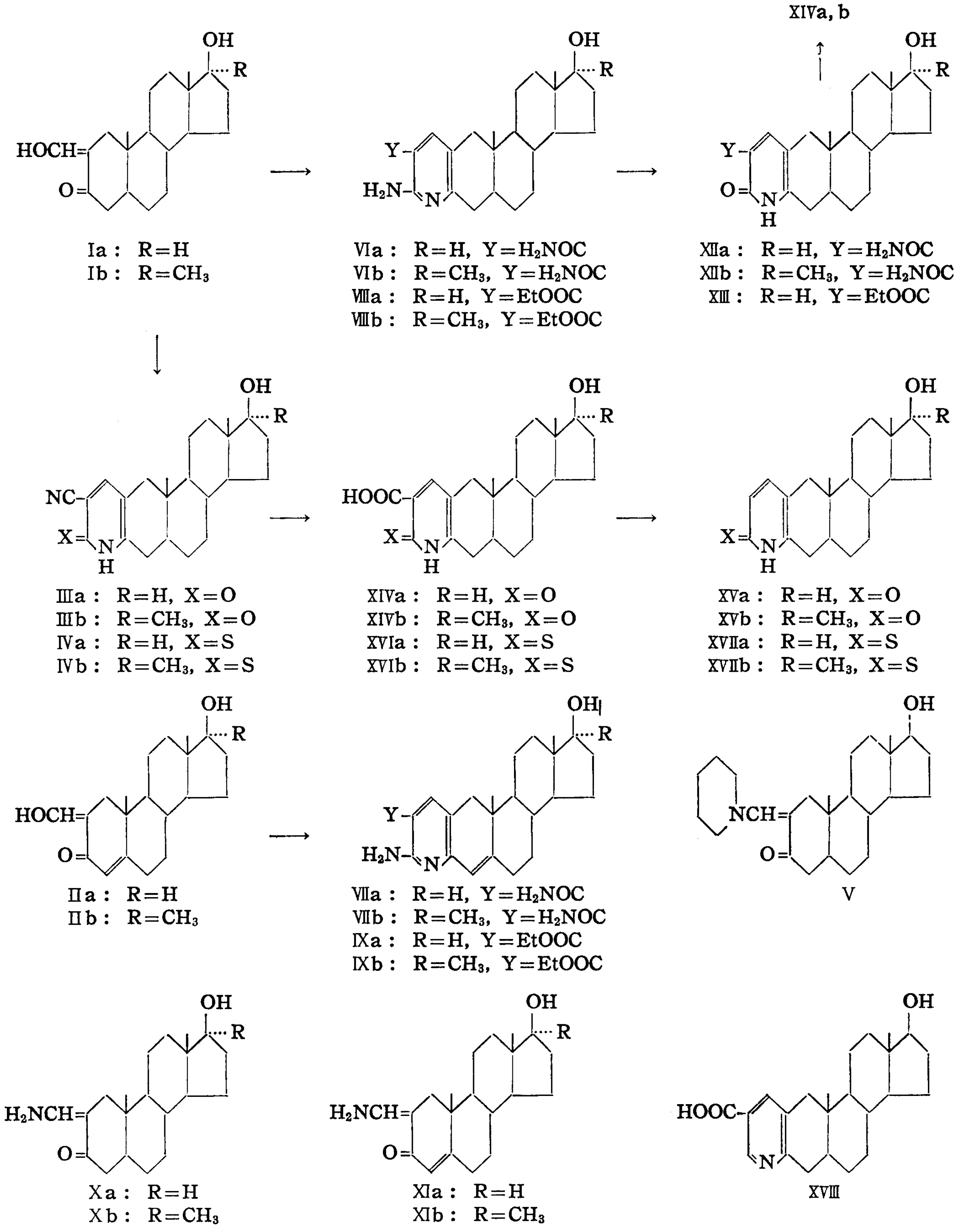


Chart 1.

The same reaction at 180° without solvent and catalyst resulted in the formation of an unexpected compound, which showed no characteristic infrared band corresponding to a nitrile group and was identified as pyridone-carboxamide derivative (XIIa). An authentic sample was prepared by another method, *vide infra*. The pyridone (IIIa) was also obtained in low yields by refluxing the ethanolic solution of the 2-hydroxymethylene-3-ketone (Ia) and malononitrile without catalyst.

Condensation of the 2-hydroxymethylene-3-oxo compounds (Ia, b) with cyanothioacetamide in methanol in the presence of either triethylamine or piperidine proceeded smoothly, and the thiopyridones (IVa, b) were obtained in good yields. The reaction with cyanothioacetamide was faster than that with cyanoacetamide. From the 2-hydroxymethylene-3-oxo steroids (II) containing a double bond at the 4-position, neither pyridones nor thiopyridones were obtained.

By treatment of the 2-hydroxymethylene-3-oxo derivatives, with or without a double bond at the 4-position, with malonamideamidine in ethanol, there was obtained the corresponding 6′-aminopyridine-5′-carboxamide derivatives (VI and VII). The yields were 40~60% in 5*α*-series and 20~30% in Δ^4-series.

According to the method of Dornow, *et al.*,[9] 2-hydroxymethylene-3-ketones (I and II) were condensed with two equivalents of ethyl 3-amino-3-ethoxyacrylate in hot dioxane to furnish the 5′-ethoxycarbonyl-6′-aminopyridines (VIII and IX) in 20~35% yields, accompanied by considerable amounts of 2-aminomethylene derivatives (X and XI). The latter compounds were identified by comparison with authentic samples prepared by known methods. The condensation was not effected by direct fusion at 100° nor by the use of ethanol as solvent. It is interesting that the 2-hydroxymethylene-Δ^4-3-ketones (IIa, b) were condensed with malonamideamidine or with ethyl 3-amino-3-ethoxyacrylate to form the pyridine ring, whereas they were not available in the reaction with cyanoacetamide or with cyanothioacetamide.*[2]

That the identical ring system occurred in the above androstanopyridones (III) and aminopyridines (VII and VIII) was shown by converting these compounds into the pyridone-carboxylic acid derivatives (XIV). Diazotization of aminopyridinecarboxamides (VI) with sodium nitrite and hydrochloric acid in aqueous acetic acid at room temperature and concomitant decomposition of diazo group furnished the pyridonecarboxamides (XIII), which were hydrolyzed at 140° with potassium hydroxide in ethanolic solution under pressure to give pyridone-carboxylic acids (XIV). Similarly, diazotization of 5′-ethoxycarbonyl-6′-aminopyridine(VIIIa), followed by hydrolysis gave the same pyridone-carboxylic acid (XIVa), which was also obtained by hydrolysis of pyridone-carbonitrile (IIIa).

The pyridone-carboxylic acids (XIV) thus obtained were decarboxylated by heating at 300° in vacuum, and the pyridone derivatives (XVa, b) were obtained as sublimates in good yields. Pyridinethionecarbonitriles (IVa, b) were hydrolyzed similarly to the corresponding thiopyridonecarboxylic acids (XVI). Decarboxylation of the carboxyl compound (XVIa) which has no 17*α*-methyl group also gave the thiopyridone (XVIIa). While, in the pyrolysis of 17*α*-methyl derivative, *i.e.*, 6′-thioxo-17*α*-methyl-17*β*-hydroxy-1′,6′-dihydroandrostano[3,2-*b*]pyridine-5′-carboxylic acid (XVIb), heating the compound at 300° in vacuum caused decarboxylation and, in part, concurrent elimination of the tertiary 17*β*-hydroxyl group. Evidence for this was afforded by the observation that the sublimed reaction product contained a material having no characteristic infrared absorption of a hydroxyl group. As the attempted purification of the thiopyridone (XVIIb) was not successful, the crude material was used in the next reaction. Further studies on the dehydrated products will be reported later.

Desulfurization of the pyridinethione-carboxylic acid (XVIa) with Raney nickel in ethanol-dimethylformamide solution gave the 17*β*-hydroxyandrostano[3,2-*b*]pyridine-5′-carboxylic acid (XVIII), which was not decarboxylated by the usual pyrolytic reaction. The ketone or thione group in the 6′-position seems to facilitate the decarboxylation.

Treatment of 17*β*-acetoxyandrostano[3,2-*b*]pyrid-6′(1′*H*)-one (XX) with phosphorus pentasulfide in refluxing pyridine provided in 33% yield, 17*β*-acetoxyandrostano[3,2-*b*]-

---

*[2] The structures for androst-4-enopyridines were tentatively given by analogy to 5*α*-androstanopyridines.

[9] A. Dornow, E. Neuse: Chem. Ber., 84, 296 (1951).

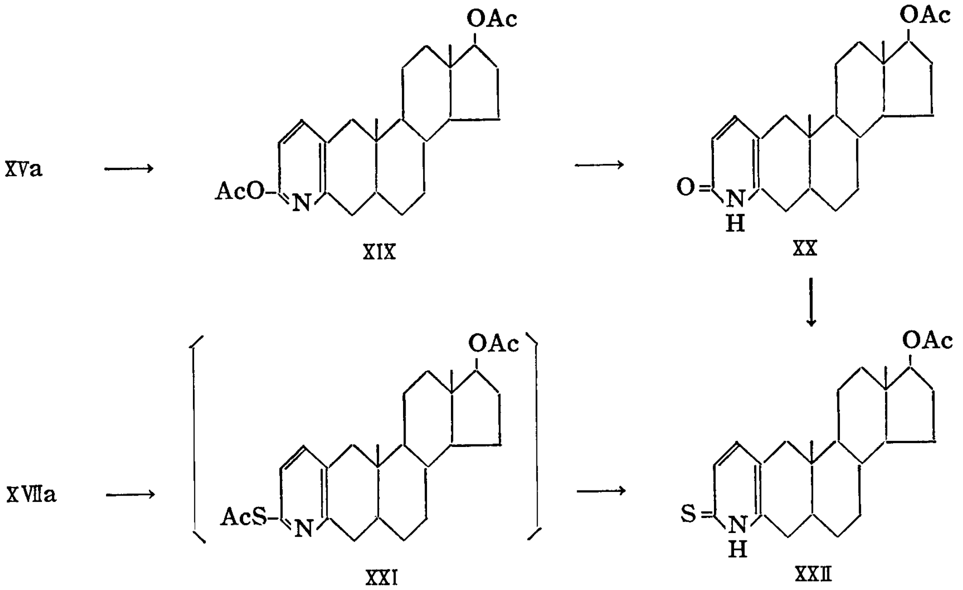


Chart 2.

pyridine-6′(1′*H*)-thione (XXII), which was identical with that obtained by acetylation of thiopyridone (XVIIa). Thus, the pyridone and the thiopyridone series were interrelated.

While preparing the 17*β*-acetoxyl compound (XX), formation of an unstable 6′,17-diacetate (XIX) was observed. Acetylation of the pyridone (XVa) with acetic anhydride and pyridine, followed by careful separation of the product afforded the diacetate (XIX), which exhibited in cyclohexane solution a maximal absorption at 270 mμ with neighboring inflexions, characteristic of pyridine ring but not of pyridone ring. The infrared spectrum shows a strong band at 1767 cm^{-1} indicative of the 6′-acetoxyl group. Upon being dissolved in warm methanol or adsorbed on alumina, the diacetate (XIX) was easily deacetylated at the 6′-position to furnish 17-acetoxy-pyridone (XX).

Likewise, a crude oily product obtained by acetylation of the thiopyridone (XVIIa) seemed to consist of 6′,17-diacetate (XXI), because it revealed in cyclohexane solution

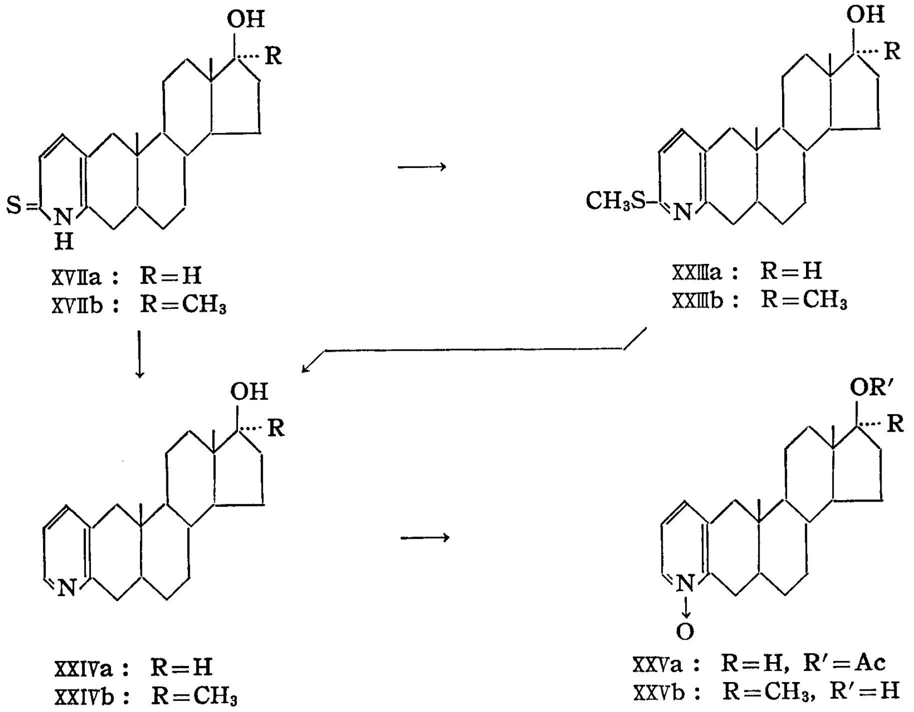


Chart 3.

a maximal absorption at 281 mμ but no further absorptions at longer wave lengths, which seemed to indicate the acetylthiopyridine structure. On the other hand, the oily product was readily converted by treatment with methanol into the crystalline 17-acetoxy-pyridinethione (XXII), which showed absorptions at 281 and 373 mμ in ethanolic solution. These bands are characteristic of 2(1*H*)-pyridinethione ring. A comparison of the spectral data of the related compounds will be reported in the following paper.

Methylation of the pyridinethione (XVIIa) with dimethyl sulfate in aqueous methanolic potassium hydroxide solution yielded the corresponding methylthiopyridine (XXIIIa). Desulfurization of the thiopyridone (XVIIa) or the methylmercaptopyridine (XXIIIa) with Raney nickel in hot ethanol-dimethylformamide solution afforded 17β-hydroxyandrostano[3,2-*b*]-pyridine (XXIVa) in excellent yield. Acetylation of XXIVa, followed by treatment with hydrogen peroxide in acetic acid gave the 17β-acetate N-oxide (XXVa). Methylation of the crude 17α-methylpyridinethione (XVIIb) again failed to give the crystalline S-methyl compound (XXIIIb). However, desulfurization of the crude 17α-methyl-pyridinethione or its S-methyl compound, followed by chromatography on alumina made available pure 17β-hydroxy-17α-methylandrostano[3,2-*b*]pyridine (XXIVb). This compound was converted into N-oxide (XXVb) under the same conditions as above.

By the above reaction sequences compounds (XXIVa and XXIVb) were obtained. The structures of these compounds and intermediates thereof were based on elemental analyses and infrared, ultraviolet and nuclear magnetic resonance spectra. The observed spectral properties will be summarized in the following paper.

A detailed description of the biological activities of the compounds will be given elsewhere, but interim results are offered. When used parenterally, compound (XXIVb) has favorable myotrophic/androgenic ratio, although its activities are weak as compared with testosterone propionate.

Experimental

Melting points are uncorrected. Unless otherwise specified, UV spectra were taken in EtOH, IR spectra in KBr disc. The identification was carried out by mixed melting point determination and comparison of UV and IR spectra.

6′-Oxo-17β-hydroxy-1′,6′-dihydroandrostano[3,2-*b*]pyridine-5′-carbonitrile (IIIa)——i) To a solution of 2-hydroxymethylene-17β-hydroxyandrostan-3-one (Ia)[2b] (3.0 g.) and cyanoacetamide (1.5 g.) in EtOH (100 ml.) was added triethylamine (7.0 ml.) and the mixture was refluxed for 9 hr. After standing at room temperature the precipitated product was filtered. Concentration of the filtrate gave a second crop. Recrystallization of the crude product (total 1.69 g.) of m.p. >300° from MeOH and then from AcOEt afforded an analytical sample of IIIa, pale yellow crystals, m.p. >300°, $[\alpha]_D$ +83° (c=0.84, pyridine). UV λ_{max} mμ (ε): 237~238 (8,350), 347 (11,660). IR ν_{max} cm^{-1}: 3440, 3150, 2240, 1680, 1620, 1572. *Anal.* Calcd. for $C_{23}H_{30}O_2N_2$: C, 75.37; H, 8.25; N, 7.64. Found: C, 74.88; H, 8.06; N, 7.78.

ii) A solution of Ia (100 mg.) and malononitrile (30 mg.) in EtOH (20 ml.) was refluxed for 11 hr. and then evaporated to dryness. The product was washed with H_2O, and recrystallized from AcOEt to give tan crystals of IIIa (15 mg.), m.p. >300°, identical with the product obtained above.

6′-Oxo-17α-methyl-17β-hydroxy-1′,6′-dihydroandrostano[3,2-*b*]pyridine-5′-carbonitrile (IIIb)——A solution of 2-hydroxymethylene-17α-methyl-17β-hydroxyandrostan-3-one (Ib)[2b] (400 mg.), cyanoacetamide (200 mg.), and triethylamine (1.0 ml.) in EtOH (20 ml.) was refluxed for 9 hr. Working-up in the same manner as described for IIIa gave pale yellow crystals of IIIb of m.p. >300°, $[\alpha]_D$ +80° (c=0.86, pyridine). UV λ_{max} mμ (ε): 237~238 (7,900), 347 (11,800). IR ν_{max} cm^{-1}: 3420, 3130, 2220, 1670, 1611, 1565. *Anal.* Calcd. for $C_{24}H_{32}O_2N_2$: C, 75.75; H, 8.48; N, 7.36. Found: C, 76.13; H, 8.42; N, 7.09.

6′-Thioxo-17β-hydroxy-1′,6′-dihydroandrostano[3,2-*b*]pyridine-5′-carbonitrile (IVa)——To a solution of Ia (3.0 g.) and cyanothioacetamide[10] (1.5 g.) in EtOH (100 ml.) was added triethylamine (1.5 ml.) and the mixture was refluxed for 30 min. After ice-cooling the deposited product was filtered (2.3 g., m.p. >300°). Crystallization from MeOH afforded brightly yellow crystals of IVa, m.p. >300°, $[\alpha]_D$ +160° (c=0.70, pyridine). UV λ_{max} mμ (ε): 309 (19,800), 410 (4,870); shoulder 240~242 (6,120). IR ν_{max} cm^{-1}:

---

10) E.G. Howard: U.S.P. 2,733,260 (1956).

3430, 3190, 3110, 2225, 1603. *Anal.* Calcd. for $C_{23}H_{30}ON_2S$: C, 72.21; H, 7.90; N, 7.32. Found : C, 72.36; H, 8.01; N, 7.34.

The use of piperidine instead of triethylamine as catalyst gave analogous result.

6′-Thioxo-17α-methyl-17β-hydroxy-1′,6′-dihydroandrostano[3,2-*b*]pyridine-5′-carbonitrile (IVb)——A mixture of Ib (20.0 g.), cyanothioacetamide (8.0 g.), MeOH (400 ml.), and triethylamine (4.0 ml.) was refluxed for 30 min., cooled in ice and filtered. A crude product (15.9 g.) of m.p. >300° was obtained. Crystallization from MeOH gave an analytical sample of IVb, m.p. >300°, $[\alpha]_D$ +141° (c=1.05, pyridine). UV λ_{max} mμ (ε) : 310 (21,600), 410 (5,570); shoulder 241 (7,160). IR ν_{max} cm^{-1} : 3440, 3190, 3120, 2235, 1605. *Anal.* Calcd. for $C_{24}H_{32}ON_2S$: C, 72.68; H, 8.13; N, 7.06. Found : C, 72.18; H, 8.32; N, 6.97.

2-Piperidinomethylene-17β-hydroxyandrostan-3-one (V)——i) A solution of Ia (350 mg.) and piperidine (470 mg.) in EtOH (15 ml.) was refluxed for 30 min. The solvent was evaporated and the residue, after chromatography in benzene-$CHCl_3$ solution on Al_2O_3, was recrystallized from AcOEt to yield V, m.p. 219~223°, $[\alpha]_D$ −260° (c=0.73, $CHCl_3$). (reported m.p. 219~221°, $[\alpha]_D$ −256°[4c]). UV : λ_{max} 334 mμ (ε 21,500). IR ν_{max} cm^{-1} : 3380, 1635, 1516. *Anal.* Calcd. for $C_{25}H_{39}O_2N$: C, 77.87; H, 10.20; N, 3.63. Found : C, 77.86; H, 10.22; N, 3.85.

ii) Ia (100 mg.) and cyanoacetamide (40 mg.) were dissolved in EtOH (10 ml.) and piperidine (4 drops) was added. The solution was heated under reflux for 40 min. and the solvent was evaporated to give a red oily residue, which exhibited no characteristic UV spectrum of pyridone. Chromatography in benzene-$CHCl_3$ solution on Al_2O_3, followed by recrystallization from AcOEt yielded V, m.p. 217~221°, identical with the product obtained above.

6′-Amino-17β-hydroxyandrostano[3,2-*b*]pyridine-5′-carboxamide (VIa)——Malonamideamidine·HCl[11] (2.24 g.) was added to a solution of NaOEt in EtOH (0.29 g. of Na in 100 ml.) and thoroughly mixed. A solution of Ia (4.00 g.) in EtOH (140 ml.) was added and the mixture was refluxed for 2 hr. After removal of inorganic salt by filtration, the filtrate was evaporated in vacuum, and the residue was washed with H_2O to give amorphous powder (5.5 g.). Trituration of this product with MeOH gave crystals of m.p. 254~258° (2.5 g.). Crystallization from MeOH afforded pale yellow methanolated crystals of VIa, m.p. 258~261°. *Anal.* Calcd. for $C_{23}H_{33}O_2N_3\cdot CH_3OH$: C, 69.36; H, 8.97; N, 10.11. Found: C, 69.10; H, 9.08; N, 9.82.

Drying in vacuum at 100° for 3 hr. caused loss of the solvated MeOH, m.p. 259~264°, $[\alpha]_D$ +43° (c=0.82, pyridine). UV λ_{max} mμ (ε) : 252 (11,400), 338 (7,500). IR ν_{max} cm^{-1} : 3440, 3340, 3130, 1664, 1621, 1580, 1546. *Anal.* Calcd. for $C_{23}H_{33}O_2N_3$: C, 72.02; H, 8.67; N, 10.96. Found : C, 71.87; H, 8.98; N, 11.18.

6′-Amino-17α-methyl-17β-hydroxyandrostano[3,2-*b*]pyridine-5′-carboxamide (VIb)——By using Ib (4.00 g.), malonamideamidine·HCl (1.78 g.), and NaOEt solution (0.28 g. of Na in 150 ml. of EtOH), the reaction was carried out in the same manner as described for VIa. The resultant amorphous product was dissolved in $CHCl_3$ and chromatographed on Al_2O_3 (80 g.). Fractions eluted with $CHCl_3$ and $CHCl_3$-AcOEt (9:1) were evaporated and the residue was crystallized from AcOEt to give VIb (2.20 g.) of m.p. 240~245°. Further crystallization from the same solvent afforded an analytical sample, pale yellow crystals, m.p. 250~252°, $[\alpha]_D$ +49° (c=1.37, MeOH), +58° (c=1.24, pyridine). UV λ_{max} mμ (ε) : 252 (11,300), 338 (7,500). IR ν_{max} cm^{-1} : 3380, 3320, 3120, 1726, 1656, 1620, 1576, 1543. *Anal.* Calcd. for $C_{24}H_{35}O_2N_3\cdot\frac{1}{2}CH_3COOC_2H_5$: C, 70.71; H, 8.90; N, 9.52. Found : C, 70.32; H, 8.68; N, 9.51.

6′-Amino-17β-hydroxyandrost-4-eno[3,2-*b*]pyridine-5′-carboxamide (VIIa)——Malonamideamidine·HCl (0.99 g.) was added to an ethanolic solution of NaOEt (130 mg. of Na in 40 ml.) and thoroughly mixed. To this solution 2-hydroxymethylene-17β-hydroxyandrost-4-en-3-one (IIa)[2b] (1.75 g.) in EtOH (90 ml.) was added and the mixture was heated under reflux for 2 hr. After removal of inorganic salt by filtration, the dark brown filtrate was concentrated and treated with H_2O. The precipitated amorphous powder was separated and extracted with hot AcOEt (500 ml.). The extract was concentrated (to 150 ml.), adsorbed on Al_2O_3 (40 g.) and eluted with AcOEt and AcOEt-MeOH. The residue obtained from AcOEt-MeOH (40:1 and 10:1) fractions was crystallized from MeOH to separate VIIa (880 mg.) of m.p. 190~193/272~275°. Further crystallization from the same solvent gave yellow plates, m.p. 274~276° (decomp.), $[\alpha]_D$ +35° (c=0.97, pyridine). UV λ_{max} mμ (ε) : 223 (20,700), 242 (18,500), 258.5 (19,000), 370 (12,800); shoulder 283.5 (9,700). IR ν_{max} cm^{-1} : 3400, 3350, 3200, 1657, 1605, 1583, 1547, 1528. *Anal.* Calcd. for $C_{23}H_{31}O_2N_3\cdot\frac{1}{2}CH_3OH$: C, 71.00; H, 8.37; N, 10.57. Found : C, 71.14; H, 8.04; N, 10.77.

6′-Amino-17α-methyl-17β-hydroxyandrost-4-eno[3,2-*b*]pyridine-5′-carboxamide (VIIb)——VIIb was prepared in the same manner as described for VIIa. By using 2-hydroxymethylene-17α-methyl-17β-hydroxyandrost-4-en-3-one (IIb)[2b] (3.30 g.) and malonamideamidine·HCl (1.80 g.), crude product (2.00 g.) of m.p. 195~198/253~258° (decomp.) was obtained. Crystallization from AcOEt afforded yellow needles, m.p. 196~197/276~280° (decomp.), $[\alpha]_D$ +39° (c=0.80, pyridine). UV λ_{max} mμ (ε) : 224 (21,300), 242 (19,300), 258.5 (19,700), 370 (13,400); shoulder 284 (9,500). IR ν_{max} cm^{-1} : 3410, 3340, 1725, 1650, 1611, 1583, 1527. *Anal.* Calcd. for $C_{24}H_{33}O_2N_3\cdot CH_3COOC_2H_5$: C, 69.53; H, 8.55; N, 8.69. Found : C, 69.42; H, 8.16; N, 9.08.

---

[11] E. Shaw, D.W. Woolley : J. Biol. Chem., **181**, 89 (1949).

Ethyl 6′-Amino-17β-hydroxyandrostano[3,2-*b*]pyridine-5′-carboxylate(VIIIa)——A solution of Ia (3.00 g.) and ethyl 3-amino-3-ethoxyacrylate[12] (4.5 g.) in dioxane (100 ml.) was refluxed for 3 hr. The mixture was evaporated in vacuum, treated with H_2O and extracted with AcOEt. Chromatography of the extract and crystallization from MeOH yielded VIIIa (1.22 g.) of m.p. 135~140° (decomp.), which was further recrystallized from MeOH to give pale yellow needles, m.p. 139° (decomp.), $[\alpha]_D$ +54° (c=1.08, $CHCl_3$). UV λ_{max} mμ (ε): 252 (11,100), 342 (9,760). IR ν_{max} cm^{-1}: 3430, 3360, 1710, 1633, 1616, 1590, 1563, 1550. *Anal.* Calcd. for $C_{25}H_{36}O_3N_2 \cdot CH_3OH$: C, 70.23; H, 9.07; N, 6.30. Found: C, 70.66; H, 9.07; N, 6.56.

Ethyl 6′-Amino-17α-methyl-17β-hydroxyandrostano[3,2-*b*]pyridine-5′-carboxylate (VIIIb) and 2-Aminomethylene-17α-methyl-17β-hydroxyandrostan-3-one (Xb)——A solution of Ib (1.00 g.) and ethyl 3-amino-3-ethoxyacrylate (2.0 g.) in dioxane (30 ml.) was refluxed for 1 hr. The mixture was evaporated in vacuum, treated with H_2O and extracted with AcOEt (50 ml.). The extract was washed with H_2O, dried, and concentrated to a volume of about 30 ml., giving a precipitate of aminomethylene compound (Xb) which was filtered off. The filtrate was passed through a column of Al_2O_3 and evaporated. Crystallization of the residue from MeOH yielded the pyridine (VIIIb) (280 mg.) as colorless needles, m.p. 179~180/195°, unchanged by further recrystallization, $[\alpha]_D$ +50° (c=1.01, $CHCl_3$). UV λ_{max} mμ (ε): 252 (9,750), 342 (8,510). IR ν_{max} cm^{-1}: 3410, 3280, 3150, 1704, 1644, 1613, 1591, 1553. *Anal.* Calcd. for $C_{26}H_{38}O_3N_2$: C, 73.20; H, 8.98; N, 6.57. Found: C, 73.33; H, 8.95; N, 6.68.

The crude aminomethylene compound (Xb) (150 mg.) was recrystallized from MeOH to give yellow needles, m.p. 261° (decomp.), identical with an authentic sample of Xb. $[\alpha]_D$ +46° (c=0.74, pyridine). *Anal.* Calcd. for $C_{21}H_{33}O_2N$: C, 76.09; H, 10.03; N, 4.23. Found: C, 76.15; H, 10.03; N, 3.94.

Ethyl 6′-Amino-17β-hydroxyandrost-4-eno[3,2-*b*]pyridine-5′-carboxylate (IXa) and 2-Aminomethylene-17β-hydroxyandrost-4-en-3-one(XIa)——A solution of IIa (4.06 g.) and ethyl 3-amino-3-ethoxyacrylate (8.0 g.) in dioxane (120 ml.) was refluxed for 3 hr., evaporated to dryness, treated with H_2O and extracted with AcOEt. The AcOEt solution was chromatographed over Al_2O_3. Fractions eluted with AcOEt were evaporated and the residue was crystallized from MeOH to give IXa (1.64 g.), m.p. 100~110° (decomp.), which was further recrystallized to yellow needles of m.p. 125~130° (decomp.), $[\alpha]_D$ +26° (c=2.19, $CHCl_3$). UV λ_{max} mμ (ε): 224~225 (17,960), 258~259 (18,090), 370~371 (13,030); shoulder 242 (15,100), 282 (11,760). IR ν_{max} cm^{-1}: 3470, 3370, 3280, 1687, 1630, 1608, 1589, 1533. *Anal.* Calcd. for $C_{25}H_{34}O_3N_2 \cdot CH_3OH$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.15; H, 8.58; N, 6.35.

The product eluted with AcOEt-MeOH (40:1) was rechromatographed and crystallized from AcOEt to furnish aminomethylene compound (XIa) (120 mg.), m.p. 225° (decomp.). Recrystallization from MeOH gave yellow needles of m.p. 228° (decomp.), identical with an authentic sample of XIa. *Anal.* Calcd. for $C_{20}H_{29}O_2N$: C, 76.15; H, 9.27; N, 4.44. Found: C, 76.37; H, 9.03; N, 4.54.

Ethyl 6′-Amino-17α-methyl-17β-hydroxyandrost-4-eno[3,2-*b*]pyridine-5′-carboxylate (IXb) and 2-Aminomethylene-17α-methyl-17β-hydroxyandrost-4-en-3-one (XIb)——Reaction of IIb (1.00 g.) with ethyl 3-amino-3-ethoxyacrylate (2.00 g.) was carried out as described in the preceding paragraph. On treatment of the reaction product with AcOEt, insoluble aminomethylene compound (200 mg.), m.p. 250° (decomp.) was separated. From the mother liquor, after chromatography and crystallization from MeOH, there was obtained the pyridine (IXb) (460 mg.), m.p. 183~187° (decomp.), unchanged by further recrystallization, $[\alpha]_D$ −4° (c=2.42, $CHCl_3$). UV λ_{max} mμ (ε): 225 (19,300), 259 (19,600), 370~371 (14,000); shoulder 242.5 (15,800), 282 (13,100). IR ν_{max} cm^{-1}: 3605, 3505, 3375, 3230, 1690~1667 (broad), 1631, 1607, 1589, 1530. *Anal.* Calcd. for $C_{26}H_{36}O_3N_2 \cdot CH_3OH$: C, 71.02; H, 8.83; N, 6.14. Found: C, 70.73; H, 8.63; N, 6.43.

Recrystallization of the above crude aminomethylene compound gave yellow needles of XIb, m.p. 260° (decomp.), $[\alpha]_D$ −25° (c=0.89, pyridine), identical with an authentic sample of XIb. *Anal.* Calcd. for $C_{21}H_{31}O_2N$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.41; H, 9.50; N, 4.01.

2-Aminomethylene-17β-hydroxyandrostan-3-one (Xa)——Ia (3.5 g.) in 10% ethanolic ammonia solution (100 ml.) was heated under reflux for 40 min. The solvent was removed and the residue was crystallized from AcOEt-MeOH to separate Xa (2.0 g.) of m.p. 242~243° (decomp.). Recrystallization from the same solvent afforded a pure sample as yellow crystals, m.p. 246~247° (decomp.), $[\alpha]_D$ +43° (c=0.91, pyridine). UV λ_{max}: 316 mμ (ε 15,760). IR ν_{max} cm^{-1}: 3315, 1641, 1530. *Anal.* Calcd. for $C_{20}H_{31}O_2N$: C, 75.67; H, 9.84; N, 4.41. Found: C, 75.41; H, 9.68; N, 4.47.

2-Aminomethylene-17α-methyl-17β-hydroxyandrostan-3-one (Xb)——Xb was prepared in the same way. Yellow crystals (from MeOH), m.p. 266~267° (decomp.), $[\alpha]_D$ +54° (c=1.06, pyridine). UV λ_{max}: 314~315 mμ (ε 15,960). IR ν_{max} cm^{-1}: 3285, 3160, 1645, 1611, 1532. [reported m.p. 288~290°, $[\alpha]_D$ +35° (pyridine), λ_{max} 316 mμ (log ε 4.20)[4c]].

2-Aminomethylene-17β-hydroxyandrost-4-en-3-one (XIa)——XIa was prepared essentially by the procedure described for Xa. Yellow crystals (from MeOH), m.p. 243~244° (decomp.), $[\alpha]_D$ −15° (c=1.17, pyridine). UV λ_{max} mμ (ε): 245 (15,380), 354 (10,840). IR ν_{max} cm^{-1}: 3350, 3260, 1649, 1629, 1551, 1503.

---

[12] S.A. Glickman, A.C. Cope: J. Am. Chem. Soc., **67**, 1019 (1945).

2-Aminomethylene-17α-methyl-17β-hydroxyandrost-4-en-3-one (XIb)——XIb was prepared similarly. Yellow crystals (from MeOH), m.p. 267~268°(decomp.), $[\alpha]_D$ −18°(c=1.35, pyridine). UV λ_{max} mμ (ε): 246 (13,580), 353 (10,130). IR ν_{max} cm^{-1}: 3315, 3225, 1649, 1603, 1541. [reported m.p. 277.5~279°, $[\alpha]_D$ −77°(EtOH), UV λ_{max} mμ (ε): 245 (14,600), 352 (10,400)[13)]].

6′-Oxo-17β-hydroxy-1′,6′-dihydroandrostano[3,2-*b*]pyridine-5′-carboxamide (XIIa)——i) To a solution of VIa (2.08 g.) in AcOH (80 ml.) was added 10% HCl (10 ml.) and aq. $NaNO_2$ solution (520 mg. in 10 ml.) and the mixture was kept at room temperature overnight. Evaporation in vacuum at 40~50° gave a crystalline residue, which was washed with H_2O to give XIIa (1.98 g.), m.p. >300°. Recrystallization from MeOH afforded a pure sample as pale yellow needles, m.p. >300°. UV λ_{max} mμ (ε): 239 (9,450), 340 (13,050). IR ν_{max} cm^{-1}: 3420, 3310, 3140, 1713, 1679, 1615, 1567. *Anal.* Calcd. for $C_{23}H_{32}O_3N_2\cdot½CH_3COOH$: C, 69.53; H, 8.27; N, 6.76. Found: C, 69.66; H, 7.87; N, 7.05.

ii) A mixture of Ia (100 mg.) and cyanoacetamide (50 mg.) was heated at 160~180° for 10 min. After cooling the mixture was triturated with H_2O to separate a solid. Recrystallization from MeOH and then from AcOEt containing a drop of AcOH gave crystals of XIIa (15 mg.), m.p. >300°, identical with an authentic sample obtained above.

6′-Oxo-17α-methyl-17β-hydroxy-1′,6′-dihydroandrostano[3,2-*b*]pyridine-5′-carboxamide (XIIb)——By the same procedure as described above, VIb (1.83 g.) was converted into XIIb. The crude product (1.33 g.) of m.p. >300° was recrystallized from MeOH to give a pure sample as pale yellow needles, m.p. >300°. UV λ_{max} mμ (ε): 239 (8,660), 339~340 (12,280). IR ν_{max} cm^{-1}: 3450, 3240, 3130, 1680, 1665, 1609, 1563. *Anal.* Calcd. for $C_{24}H_{34}O_3N_2\cdot CH_3OH$: C, 69.73; H, 8.90; N, 6.51. Found: C, 69.77; H, 8.73; N, 6.61.

Ethyl 6′-Oxo-17β-hydroxy-1′,6′-dihydroandrostano[3,2-*b*]pyridine-5′-carboxylate (XIII)——To a solution of VIIIa (670 mg.) in AcOH (60 ml.) was added 10% HCl (6.0 ml.) and aq. $NaNO_2$ solution (415 mg. in 6 ml.), and the mixture was kept at room temperature for 3 days. Evaporation in vacuum below 50° gave a residue which after trituration with H_2O was filtered and crystallized from MeOH to afford XIII (370 mg.), 210~215°. Recrystallization from MeOH-AcOEt yielded prisms of m.p. 261~263° (decomp.), $[\alpha]_D$ +73° (c=0.95, pyridine). UV λ_{max} mμ (ε): 241 (7,650), 345~346 (10,900). IR ν_{max} cm^{-1}: 3460~3420, 3240, 3090, 1734, 1692, 1661, 1603, 1564. *Anal.* Calcd. for $C_{25}H_{35}O_4N\cdot½CH_3COOH$: C, 70.40; H, 8.41; N, 3.16. Found: C, 70.60; H, 8.18; N, 2.92.

6′-Oxo-17β-hydroxy-1′,6′-dihydroandrostano[3,2-*b*]pyridine-5′-carboxylic Acid (XIVa)——i) IIIa (800 mg.) was heated in an autoclave with KOH (1.5 g.) in 90% EtOH (15 ml.) under pressure at 130~140° for 10 hr. The mixture was evaporated, neutralized with dil. HCl to give a precipitate, which was filtered and washed with H_2O (720 mg., m.p. >260°). Crystallization from MeOH furnished pale yellow needles of XIVa decomposing at 310°, $[\alpha]_D$ +82°(c=0.72, pyridine). UV λ_{max} mμ (ε): 236~237 (7,840), 342~343 (9,900). IR ν_{max} cm^{-1}: 3510, 3420, 2800~2400, 1726, 1644, 1616, 1564, 1522. *Anal.* Calcd. for $C_{23}H_{31}O_4N$: C, 71.66; H, 8.11; N, 3.63. Found: C, 71.43; H, 8.01; N, 3.73.

ii) By the same procedure as above, XIIa (2.05 g.) was hydrolyzed. The crude product (1.80 g.) of m.p. 270~275°(decomp.) was crystallized from MeOH to give XIVa as needles, m.p. 309°(decomp.), $[\alpha]_D$ +83°(c=1.09, pyridine), identical with that obtained above. *Anal.* Calcd. for $C_{23}H_{31}O_4N$: C, 71.66; H, 8.11; N, 3.63. Found: C, 71.28; H, 7.97; N, 3.88.

iii) Hydrolysis of XIII (150 mg.) in the same manner as in i) gave XIVa (130 mg.) of m.p. 286~287° (decomp.). Crystallization from MeOH afforded pale yellow needles, m.p. 308° (decomp.), $[\alpha]_D$ +80° (c=1.11, pyridine), identical with that obtained above.

6′-Oxo-17α-methyl-17β-hydroxy-1′,6′-dihydroandrostano[3,2-*b*]pyridine-5′-carboxylic Acid (XIVb)——XIIb (850 mg.) was heated in an autoclave with KOH (2.0 g.) in 90% EtOH (20 ml.) under pressure at 140~160° for 6 hr. After cooling, precipitated potassium salt was filtered, neutralized with dil. HCl to give XIVb (550 mg.). Working-up of the mother liquor afforded a second crop of XIVb (220 mg.). Crystallization from MeOH yielded needles, m.p. 300° (decomp.). UV λ_{max} mμ (ε): 236 (6,950), 340 (7,860). IR ν_{max} cm^{-1}: 3400, 3320, 3145, 1713, 1674, 1639, 1607, 1567. *Anal.* Calcd. for $C_{24}H_{33}O_4N$: C, 72.15; H, 8.33; N, 3.51. Found: C, 71.95; H, 8.18; N, 3.86.

17β-Hydroxyandrostano[3,2-*b*]pyrid-6′(1′*H*)-one (XVa)——XIVa (200 mg.) was heated in a sublimation apparatus at 300~310° under diminished pressure (1 mmHg). Vigorous gas evolution was observed and XVa was obtained as sublimate (150 mg.) which was recrystallized from MeOH to give needles, m.p. >300°. UV λ_{max}^{EtOH} mμ (ε): 230 (9,070), 316 (9,050); $\lambda_{max}^{0.1N\ KOH\ in\ 60\%\ EtOH}$ mμ (ε): 233 (10,650), 306~307 (7,910); $\lambda_{max}^{0.1N\ HCl\ in\ 95\%\ EtOH}$ mμ (ε): 219 (5,570), 297 (10,500). IR ν_{max} cm^{-1}: 3390~3300 (broad), 3130, 1661, 1622, 1553. *Anal.* Calcd. for $C_{22}H_{31}O_2N\cdot CH_3OH$: C, 73.95; H, 9.45; N, 3.75. Found: C, 73.90; H, 9.03; N, 3.96.

17α-Methyl-17β-hydroxyandrostano[3,2-*b*]pyrid-6′(1′*H*)-one (XVb)——XIVb (190 mg.) was decarboxylated as above under diminished pressure (20 mmHg) to afford XVb (150 mg.) as sublimate, m.p. >300°.

---

13) R.O. Clinton, A.J. Manson, F.W. Stonner, R.L. Clarke, K.F. Jennings, P.E. Shaw: J. Org. Chem., 27, 1148 (1962).

Recrystallization from AcOEt gave an analytical sample as needles, m.p. >300°. UV λ_{max} mμ (ε): 230~231 (8,600), 316 (8,320). IR ν_{max} cm^{-1}: 3380, 3110, 1665, 1624, 1555. *Anal.* Calcd. for $C_{23}H_{33}O_2N\cdot \frac{1}{2}H_2O$: C, 75.78; H, 9.40; N, 3.84. Found: C, 75.31; H, 9.53; N, 3.85.

6′-Thioxo-17β-hydroxy-1′,6′-dihydroandrostano[3,2-*b*]pyridine-5′-carboxylic Acid (XVIa)——IVa (5.4 g.) was heated in an autoclave with KOH (5.0 g.) in 90% EtOH (50 ml.) under pressure at 140~160° for 9 hr. After cooling, precipitated potassium salt was filtered, neutralized with dil. HCl to give a solid (4.9 g.) of m.p. 300° (decomp.). Crystallization from MeOH afforded XVIa, yellow crystals of m.p. 307~308° (decomp.), $[\alpha]_D$ +132° (c=0.63, pyridine). UV λ_{max} mμ (ε): 305 (19,950), 392~396 (5,950); shoulder 242 (4,420). IR ν_{max} cm^{-1}: 3420, 3210, 3145, 3060, 1703, 1596. *Anal.* Calcd. for $C_{23}H_{31}O_3NS\cdot \frac{1}{2}CH_3OH$: C, 67.59; H, 7.97; N, 3.35. Found: C, 67.71; H, 7.57; N, 3.30.

6′-Thioxo-17α-methyl-17β-hydroxy-1′,6′-dihydroandrostano[3,2-*b*]pyridine-5′-carboylic Acid (XVIb)—By the same procedure as above, IVb (8.0 g.) was hydrolyzed. The product (7.0 g.) of m.p. >300° was crystallized from MeOH to give a pure sample of XVIb as yellow crystals, m.p. >310°, $[\alpha]_D$ +127° (c=0.88, pyridine). UV λ_{max} mμ (ε): 303 (17,450), 392 (5,320); shoulder 244 (5,500). IR ν_{max} cm^{-1}: 3450, 3205, 3140, 3050, 1704, 1643, 1593. *Anal.* Calcd. for $C_{24}H_{33}O_3NS\cdot \frac{1}{2}CH_3OH$: C, 68.18; H, 8.17; N, 3.25. Found: C, 67.81; H, 7.88; N, 3.46.

17β-Hydroxyandostano[3,2-*b*]pyridine-6′(1′*H*)-thione (XVIIa)——XVIa (300 mg.) was heated in a sublimation apparatus at 300~310° under diminished pressure (1 mmHg) and the decarboxylated product was obtained as sublimate (150 mg.), m.p. 260~270° (decomp.). Chromatography on Al_2O_3, followed by crystallization from AcOEt gave yellow prisms of XVIIa, m.p. 265~280° (decomp.), $[\alpha]_D$ +109° (c=0.62, pyridine). UV λ_{max} mμ (ε): 282 (12,850), 372~373 (6,780). IR ν_{max} cm^{-1}: 3350, 1735, 1617, 1586, 1493. *Anal.* Calcd. for $C_{22}H_{31}ONS\cdot 2CH_3COOC_2H_5$: C, 67.50; H, 8.88; N, 2.62. Found: C, 67.51; H, 8.47; N, 3.02.

17α-Methyl-17β-hydroxyandrostano[3,2-*b*]pyridine-6′(1′*H*)-thione (XVIIb)——Decarboxylation of XVIb (250 mg.) in the same manner as above afforded a pale orange-yellow sublimate (160 mg.), m.p. *ca.* 240°. UV λ_{max} mμ: 282, 373. Purification of this material was unsuccessful.

17β-Hydroxyandrostano[3,2-*b*]pyridine-5′-carboxylic Acid (XVIII)——To a solution of XVIa (500 mg.) in EtOH-dimethylformamide (1:1, 70 ml.) was added Raney Ni W-4 (6 ml.) and the mixture was refluxed for 2 hr. The reducing agent was filtered off and the filtrate was concentrated to give a residue which was mixed thoroughly with dil. AcOH and filtered. Crystallization of the product (220 mg.) of m.p. 270~280° (decomp.) from MeOH afforded XVIII as needles, m.p. 286° (decomp.), $[\alpha]_D$ +56° (c=0.90, pyridine). UV λ_{max} mμ (ε): 275~276 (6,400), 283 (5,600). IR ν_{max} cm^{-1}: 3400, 1712, 1602. *Anal.* Calcd. for $C_{23}H_{31}O_3N\cdot CH_3OH$: C, 71.79; H, 8.79; N, 3.49. Found: C, 71.78; H, 8.43; N, 3.52.

6′,17β-Diacetoxyandrostano[3,2-*b*]pyridine (XIX)——XVa (200 mg.) was dissolved in Ac_2O (4 ml.) and pyridine (4 ml.) and the solution was left standing overnight. Evaporation in vacuum afforded a residue which was crystallized from cyclohexane to give XIX as needles, m.p. 208~212°, $[\alpha]_D$ +29° (c=1.40, $CHCl_3$). UV $\lambda_{max}^{cyclohexane}$ mμ (ε): 270 (5,390); shoulder 265 (4,650), 273 (5,310), 278 (4,170). *Anal.* Calcd. for $C_{26}H_{35}O_4N$: C, 73.38; H, 8.29; N, 3.29. Found: C, 72.80; H, 8.17; N, 3.54.

17β-Hydroxyandrostano[3,2-*b*]pyrid-6′(1′*H*)-one 17-Acetate (XX)——By heating in MeOH or aq. MeOH for a few minutes the crude diacetate (XIX) was converted into monoacetate (XX) quantitatively. Recrystallization from MeOH afforded needles, m.p. >300°. UV λ_{max} mμ (ε): 231 (8,510), 316 (8,430). IR ν_{max} cm^{-1}: 3090, 1735, 1660, 1621, 1553, 1243. *Anal.* Calcd. for $C_{24}H_{33}O_3N$: C, 75.16; H, 8.67; N, 3.65. Found: C, 75.34; H, 8.72; N, 3.57.

17β-Hydroxyandrostano[3,2-*b*]pyridine-6′(1′*H*)-thione 17-Acetate (XXII)——i) XVIIa (300 mg.) was dissolved in Ac_2O (3 ml.) and pyridine (4 ml.) and the solution was set aside overnight. Evaporation in vacuum afforded a dark orange oil (XXI), $\lambda_{max}^{cyclohexane}$ 281 mμ, which was treated with MeOH to give yellow crystals (150 mg.), m.p. 270~280° (decomp.). Crystallization from MeOH-AcOEt furnished XXII as yellow crystals, m.p. 270~285° (decomp.), $[\alpha]_D$ +100° (c=0.82, $CHCl_3$). UV λ_{max} mμ (ε): 281 (10,620), 373 (6,260). IR ν_{max} cm^{-1}: 3170, 3090, 1733, 1623, 1602, 1542, 1500, 1243. *Anal.* Calcd. for $C_{24}H_{33}O_2NS$: C, 72.14; H, 8.32; N, 3.51; S, 8.02. Found: C, 71.78; H, 8.07; N, 3.50; S, 7.73.

ii) A solution of XX (60 mg.) in pyridine (10 ml.) was refluxed for 7 hr., during which P_2S_5 (240 mg.) was added in three portions. The reaction mixture was evaporated in vacuum, treated with H_2O and extracted with $CHCl_3$. The extract was washed with H_2O and passed through a column of Al_2O_3 (1.8 g.). Evaporation of $CHCl_3$ eluate and crystallization from MeOH afforded yellow crystals (20 mg.), m.p. 265~280° (decomp.), identical with the product (XXII) obtained above.

6′-Methylthio-17β-hydroxyandrostano[3,2-*b*]pyridine (XXIIIa)——XVIIa (360 mg.) was dissolved in a mixture of MeOH (20 ml.) and aq. KOH (170 mg. in 2 ml.). After addition of Me_2SO_4 (380 mg.) the solution was stirred for 10 min. and then diluted with H_2O to give colorless precipitate (290 mg.), m.p. 115~120/192~195°. Chromatography on Al_2O_3 in $CHCl_3$ solution followed by crystallization from benzene-Et_2O afforded an analytical sample of XXIIIa, m.p. 201~204°. UV λ_{max} mμ (ε): 249 (11,160), 302~304 (7,250). IR ν_{max} cm^{-1}: 3610, 3500, 1578, 1555. *Anal.* Calcd. for $C_{23}H_{33}ONS$: C, 74.34; H, 8.95; N, 3.77. Found: C, 74.77; H, 8.94; N, 3.36.

6′-Methylthio-17α-methyl-17β-hydroxyandrostano[3,2-*b*]pyridine (**XXIIIb**)——By the procedure described for XXIIIa, crude XVIIb (600 mg.) was methylated to afford a product (560 mg.) of m.p. 120~130°, λ_{max} 250 and 303 mμ, which was dissolved in $CHCl_3$, and chromatographed on Al_2O_3. The less polar fractions afforded a semi-crystalline dehydrated mixture (160 mg.) which showed no absorptions in 3500 cm^{-1} range of its IR spectrum. From the more polar fractions a resinous material XXIIIb was obtained. Purification of this material was unsuccessful.

17β-Hydroxyandrostano[3,2-*b*]pyridine (**XXIVa**)——i) To a solution of XVIIa (1.00 g.) in EtOH-dimethylformamide (1:1, 70 ml.) was added Raney Ni W-4 (7.0 ml.) and the mixture was refluxed for 1 hr. After removal of the reducing agent by filtration the solution was evaporated in vacuum and the residue, dissolved in benzene, was chromatographed over Al_2O_3 (15 g.). Elution with benzene-$CHCl_3$ (2:1 and 1:1) gave a product (690 mg.) of m.p. 233~236° which was recrystallized from benzene. The pyridine (XXIVa) was separated as prisms, m.p. 236~237.5°, $[\alpha]_D$ +66°(c=1.02, $CHCl_3$). UV λ_{max} mμ (ε): 268~269 (5,670), 276.5 (4,340); shoulder 262~264 (4,680). IR ν_{max} cm^{-1}: 3225, 3045, 1583, 791, 783, 728. *Anal.* Calcd. for $C_{22}H_{31}ON$: C, 81.18; H, 9.60; N, 4.30. Found: C, 81.03; H, 9.23; N, 4.46.

ii) Desulfurization of XXIIIa (200 mg.) in the same manner afforded XXIVa (140 mg.), m.p. 233~236 identical with the product obtained above.

Acetate——XXIVa (690 mg.) was acetylated with Ac_2O-pyridine as usual to give a product (660 mg.) of m.p. 126~129°. Recrystallization from MeOH gave the acetate as needles, m.p. 131~132°, $[\alpha]_D$ +46°(c=0.90, $CHCl_3$). UV λ_{max} mμ (ε): 269 (5,630), 277 (4,470); shoulder 264 (4,820). IR ν_{max} cm^{-1}: 1732, 1586, 1574, 1231, 796, 730. *Anal.* Calcd. for $C_{24}H_{33}O_2N$: C, 78.43; H, 9.05; N, 3.81. Found: C, 78.84; H, 8.91; N, 3.72.

17α-Methyl-17β-hydroxyandrostano[3,2-*b*]pyridine (**XXIVb**)——i) A solution of crude XVIIb (2.05 g.) in EtOH-dimethylformamide (1:1, 120 ml.) was refluxed with Raney Ni W-4 (15 ml.) for 1 hr. After removal of the reducing agent the solution was evaporated in vacuum, the residual viscous oil dissolved in benzene and chromatographed on Al_2O_3 (30 g.). Elution with benzene gave the dehydrated product (550 mg.) as semi-crystalline solid. The compound eluted with benzene-$CHCl_3$ (2:1) was crystallized form AcOEt to give a product (650 mg.) of the desired XXIVb, m.p. 190~192°. Further recrystallization from Me_2CO afforded XXIVb as prisms, m.p. 192~193.5°, $[\alpha]_D$ +40°(c=0.85, $CHCl_3$). UV λ_{max} mμ (ε): 269 (5,800), 276.5~277 (4,580); shoulder 262~264 (4,300). IR ν_{max} cm^{-1}: 3260, 3055, 1580, 791, 783, 728. *Anal.* Calcd. for $C_{23}H_{33}ON$: C, 81.36; H, 9.80; N, 4.13. Found: C, 81.27; H, 9.94; N, 4.26.

ii) By the same procedure as above, crude XXIIIb (300 mg.) was converted into XXIVb (150 mg.), m.p. 191~192°, identical with the product obtained above.

17β-Hydroxyandrostano[3,2-*b*]pyridine 1′-Oxide 17-Acetate (**XXVa**)——To a solution of the acetate of XXIVa (550 mg.) in AcOH (2.80 g.) was added 30% H_2O_2 (560 mg.) and the mixture was maintained at 70~80° for 3 hr. Dilution with H_2O gave precipitate (520 mg.), m.p. 229~241° which was crystallized from AcOEt to needles of XXVa, m.p. 250~252°, $[\alpha]_D$ +58° (c=0.78, $CHCl_3$). UV λ_{max}^{EtOH} mμ (ε): 220 (27,700), 264 (12,200). $\lambda_{max}^{Et_2'}$ mμ: 225.5, 229.5, 277. IR ν_{max} cm^{-1}: 1740, 1728, 1596, 1245, 790, 702. *Anal.* Calcd. for $C_{24}H_{33}O_3N \cdot \frac{1}{2}CH_3COOC_2H_5$: C, 73.03; H, 8.72; N, 3.28. Found: C, 73.47; H, 8.64; N, 3.30.

17α-Methyl-17β-hydroxyandrostano[3,2-*b*]pyridine 1′-Oxide (**XXVb**)——By the same procedure as above, XXIVb (380 mg.) was converted into N-oxide. The crude product (340 mg.) of m.p. 237~241° was crystallized from AcOEt to give a pure sample as needles, m.p. 243~244°, $[\alpha]_D$ +54°(c=0.79, $CHCl_3$). UV λ_{max}^{EtOH} mμ (ε): 219~220 (27,200), 264.5 (11,900). $\lambda_{max}^{Et_2O}$ mμ (ε): 225.5 (24,500), 229.5 (25,050), 277 (13,660). IR ν_{max} cm^{-1}: 3240, 1597, 1242, 783, 696. *Anal.* Calcd. for $C_{23}H_{33}O_2N$: C, 77.70; H, 9.36; N, 3.94. Found: C, 77.64; H, 9.16; N, 3.59.

The authors express their deep gratitude to Dr. J. Shinoda, Chairman of the Board of Directors, and Dr. T. Ishiguro, President of this Company, for their kind encouragement. The authors are also indebted to Dr. F. Uchimaru, Mr. B. Kurihara and Miss K. Hanawa for elemental analyses.

Summary

Syntheses of 17β-hydroxyandrostano[3,2-*b*]pyridine (XXIVa) and related compounds were described. Condensation of 2-hydroxymethylene-3-oxo androstane derivatives with cyanoacetamide or its analogs afforded 5′,6′-disubstituted androstano[3,2-*b*]pyridines which were converted into pyridine-6′(1′*H*)-thiones (XVII). Desulfurization of XVII gave 5′,6′-unsubstituted androstano[3,2-*b*]pyridines (XXIV).

(Received August 24, 1963)