Sterling-Winthrop Research Institute

5α-Androstano[3,2-b]pyridines, 5α-Androstano[17,16-b]pyridines and Androst-4 and 5-eno[17,16-b]pyridines (1)

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A new synthesis of 5α-androstano[3,2-b]pyridin-17β-ol acetate (VIa) and 17-methyl-5α-androstano[3,2-b]pyridin-17β-ol (VIb), first reported by Shimizu, Ohta, Ueno, and Takegoshi, was achieved. The analogous 5α-androstano[17,16-b]pyridin-3β-ol (XII), 5α-androstano[17,16-b]pyridin-3-one (XIVa), and androst-4-eno[17,16-b]pyridin-3-one (XIVb) were also prepared. An illustration of the method follows. Condensation of 3β-hydroxy-5α-androstan-17-one (VIIa) with 3-(2-furyl)acrolein afforded 16-[3-(2-furyl)-2-propenylidene]-3β-hydroxy-5α-androstan-17-one (VIIIa), the oxime (IXa) of which was thermally cyclized to 5α-androstano[17,16-b]-6'-(2-furyl)pyridin-3β-ol (Xa). 3β-Hydroxy-5α-androstano[17,16-b]pyridine-6'-carboxylic acid (XI) was obtained by ozonolysis of Xa. Thermal decarboxylation of XI gave XII. Cinnamaldehyde was used in place of 3-(2-furyl)acrolein to give the corresponding phenylpyridines.

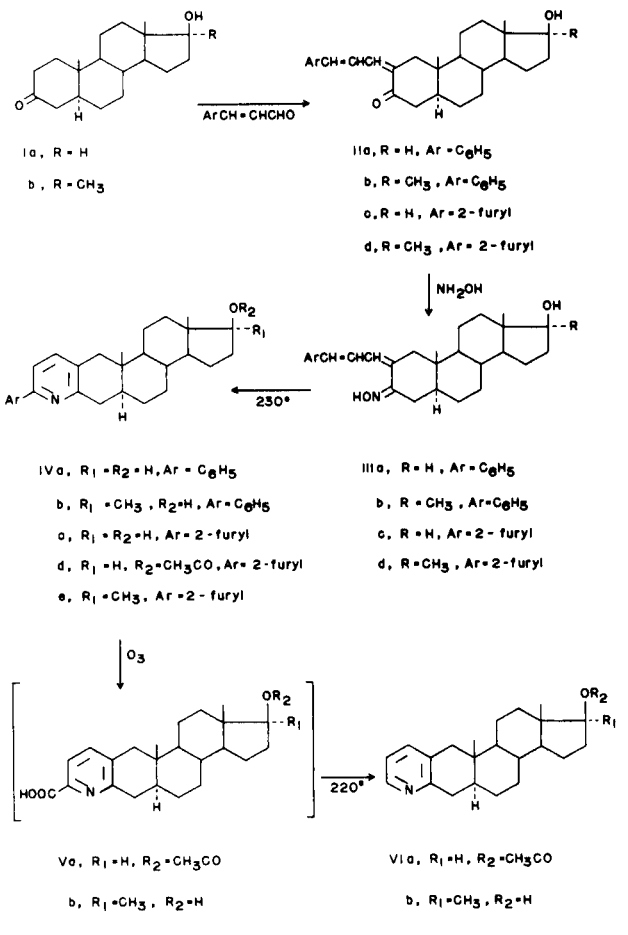
Following the discovery in these laboratories of the activity of certain 5α-androstano[3,2-c]pyrazoles (2a,b) as anabolic agents in experimental animals and the appearance of 17-methyl-5α-androstano-[3,2-c]pyrazol-17β-ol (stanozolol, Winstrol ®) as a useful anabolic drug in humans (3), the synthesis of analogous steroids with fused heterocyclic rings was undertaken in several laboratories (4).

A recent communication described the synthesis of a series of 5α-androstano[3,2-b]pyridines and their derivatives (5). The present paper reports a different synthesis of the same 5α-androstano[3,2-b]-pyridines and several analogous 5α-androstano-[17,16-b]pyridines and androsteno[17,16-b]pyridines.

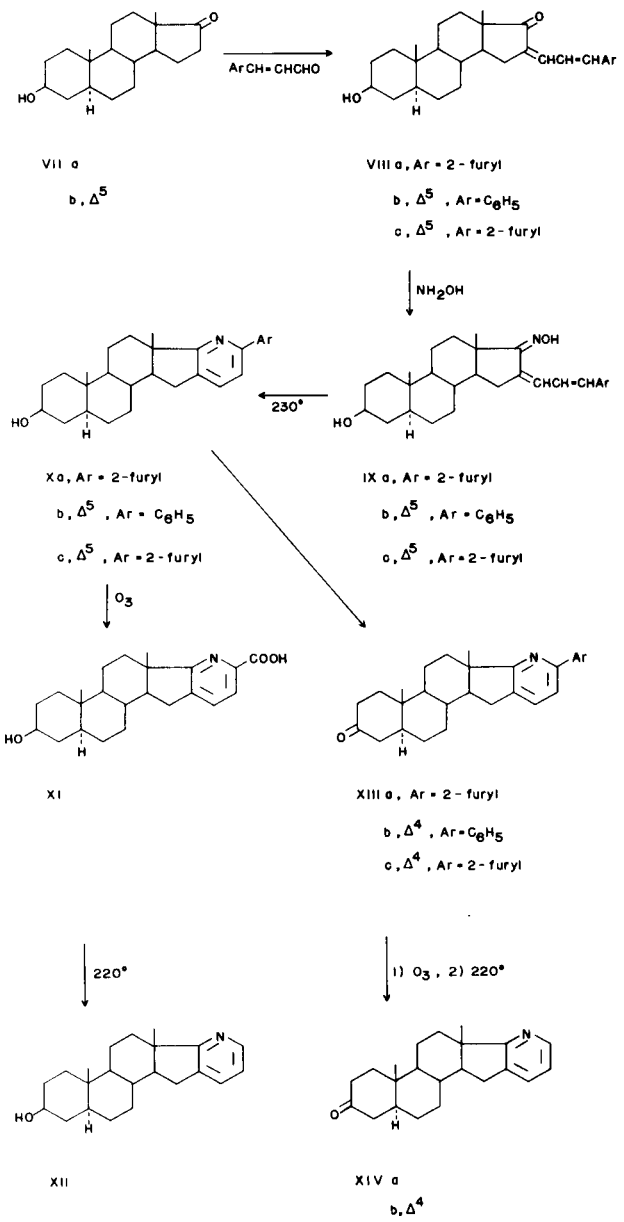
Scheme I shows the synthetic route to 5α-androstano[3,2-b]pyridin-17β-ol acetate (VIa) and 17-methyl-5α-androstano[3,2-b]pyridin-17β-ol (VIb). Both VIa and VIb corresponded closely in physical and spectral properties with the same compounds reported previously (5). The route to 5α-androstano[17,16-b]pyridin-3β-ol (XII), 5α-androstano-[17,16-b]pyridin-3-one (XIVa), and androst-4-eno-[17,16-b]pyridin-3-one (XIVb) is given in Scheme II. Preparation of the 6'-phenylpyridines (IVa-b, Xb, and XIIIb) by an old thermal cyclization (6) provided the groundwork for extention of this method to the preparation of the corresponding 6'-(2-furyl)pyridines (IVc-e, Xa, Xc, XIIIa, and XIIIc). The furyl group was then selectively removed by successive ozonolysis and decarboxylation steps to product VIa, VIb, XII, XIVa, and XIVb.

By simply dissolving the androstan(en)one (I or VII) and cinnamaldehyde or 3-(2-furyl)acrolein in methanolic potassium hydroxide and letting the solution stand at room temperature, a crystalline 2- or 16-(3-aryl-2-propenylidene)androstan(en)-3 or 17-one (II or VIII) was obtained in yields of 59-99%

SCHEME I



SCHEME II



(see Table I). That condensation occurred at C-2 and not at C-4 in the case of the 5α-androstan-3-ones was inferred by analogy to the condensation of other trans-2-decalone systems with benzaldehyde (7).

Cyclization of the corresponding oximes (III and IX; see Table II) was accomplished by heating them at 220-230° without a diluent (6). Yields of the cyclohexano[b]-6'-arylpyridines (IVa, IVc, and IVe) were somewhat higher than yields of the cyclopentano-[b]-6'-arylpyridines (Xa-c; see Table III).

Whereas the furan ring is readily cleaved by ozone, the pyridine ring is quite resistant to ozone attack (8). Picolinic acids are easily thermally decarboxylated (9). Accordingly, the 2-furyl groups of the cycloalkano[b]-6'-(2-furyl)pyridines (IVc-e, Xa, Xc, XIIIa, and XIIIc) were removed first by ozonolysis to the cycloalkano[b]pyridine-6'-carboxylic acids (Va, Vb, XI, and those from XIIIa and XIIIc) followed by thermal decarboxylation of the latter to the simple cycloalkano[b]pyridines (VIa, VIb, XII, XIVa, and XIVb; see Table IV).

In every case but one the cycloalkano[b]pyridine-6'-carboxylic acid was decarboxylated without purification by heating it at 220° without a diluent. The yield of 3β-hydroxy-5α-androstano[17,16-b]-6'-carboxylic acid (XI) in that case was 65%.

Decarboxylation of XI produced, in addition to the expected XII (41% yield), a small amount of the corresponding 3-one (XIVa, 1% yield), identical with that prepared by way of XIIIa. It is suggested that the 3-one group of XIVa was formed by oxidation of the 3β-ol group during ozone treatment of Xa (8).

The tertiary 17β-ol group of IVe was not expected to interfere with the ozonolysis and decarboxylation steps. However, VIb was obtained in only 43% yield.

An unexpectedly low yield of XIVa (8.7%), produced by combined Oppenauer oxidation, ozonolysis and decarboxylation steps starting with Xa, was realized. Attack of the 3-one group by ozone and/or oxygen might have occurred (8).

Starting with Xc combined ozonolysis and decarboxylation produced XIVb in 4.2% yield. The 4-ene-3-one group was undoubtedly attacked by ozone.

Infrared and ultraviolet spectral data for all new compounds are included in Tables I-IV and are consistent with the assigned structures. It has already been noted and is confirmed here that the [b] fusion of a saturated steroid A-ring (cyclohexane) with the pyridine nucleus produced a 12 mμ bathochromic shift in the principal absorption maximum (5,10) and that the [e] fusion of a second A-ring produced an additional 12 mμ shift (11). In this work [b] fusion of a single D-ring (XII and XIVa, cyclopentane) also produced a 12 mμ bathochromic shift. Greater exhaltation of the ε-value was observed for D-ring fusion than for A-ring fusion, however. Bathochromic shifts of 14 mμ and 13 mμ in the two absorption maxima resulted from the [e] fusion of a D-ring with picolinic acid (XI).

EXPERIMENTAL

General.

Reagent grade solvents and inorganic chemicals were used in reactions. Melting points were taken in capillaries and are uncorrected. Rotations were determined on 1% chloroform solutions. A Cary Model 11 spectrophotometer was used to record ultraviolet spectra of 95% ethanol solutions. Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer on 0.75% and 1% potassium bromide pellets.

The experimental details of the sequence Ia→IIc→IIIc→IVc→IVd→VIa follow. Also detailed below are the sequences Xa→XI→XII + XIVa and Xc→XIIIb→XIVb. Sample preparations are thus described for all of the compounds listed in Tables I-IV.

2-[3-(2-Furyl)-2-propenylidene]-17β-hydroxy-5α-androstan-3-one (IIc).

The product began crystallizing spontaneously after 10 minutes at room temperature from a solution of 17β-hydroxy-5α-androstan-3-

TABLE I

2- or 16-(3-Aryl-2-propenylidene)androstan(en)-3- or 17-ones

Compound	Formula	Anal. Calcd.	Anal. Found	Recrystallization Solvent	% Yield	M.p., °C	$[\alpha]_D^{25}$	λ max, mμ (ε)	λ max, μ
IIa	$C_{28}H_{36}O_2$	C, 83.12 H, 8.97	C, 83.26 H, 8.96	Ethyl acetate	69	178-180	+ 60°	233 (9,000), 337 (35,500)	2.93, 6.01, 6.24
IIb	Not characterized								
IIc	$C_{26}H_{34}O_3 \cdot {}^1/_2CH_3OH$	C, 77.52 H, 8.84	C, 77.71 H, 8.36	Methanol	59	192-194	+ 63°	361 (36,300)	2.88, 6.02, 6.21
IId	$C_{27}H_{36}O_3 \cdot {}^1/_2C_2H_5OH$	C, 77.92 H, 9.11	C, 77.74 H, 9.04	Ethanol	84	258-262 dec.	+ 24°	360 (35,800)	2.86, 6.01, 6.22
VIIIa	$C_{26}H_{34}O_3$	C, 79.15 H, 8.69	C, 79.18 H, 8.48	Ethyl acetate	87	226-228	-178°	361 (39,400)	2.90, 3.00, 5.92, 6.30
VIIIb (a)	$C_{28}H_{34}O_2$	C, 83.54 H, 8.51	C, 83.58 H, 8.37	Methanol	99	210-214	-198°	235 (6,100), 233 (40,100)	2.99, 5.84, 6.21, 6.28
VIIIc	$C_{26}H_{32}O_3$	C, 79.55 H, 8.22	C, 79.59 H, 8.22	Ethyl acetate	82	208-210	-233°	238 (3,250), 359 (38,200)	2.85, 2.95, 5.90, 6.28

(a) The author thanks Dr. John W. Dean for his permission to include the data on this compound, first prepared by him in these laboratories.

TABLE II

2 or 16-(3-Aryl-2-propenylidene)androstan(en)-3- or 17-one Oximes

Compound	Formula	Anal. Calcd.	Anal. Found	Recrystallization Solvent	% Yield	M.p., °C	$[\alpha]_D^{25}$	λ max, mμ (ε)	λ max, μ
IIIa	$C_{28}H_{37}NO_2 \cdot {}^1/_2CH_3OH$	C, 78.58 H, 9.02 N, 3.22	C, 78.79 H, 8.70 N, 3.27	Methanol	79	210-212		231 (10,100), 322 (36,300)	2.78, 3.07
IIIb	Not characterized								
IIIc	$C_{26}H_{35}NO_3 \cdot {}^1/_2CH_3OH$	C, 74.79 H, 8.76 N, 3.29	C, 75.09 H, 9.00 N, 3.42	Methanol	90	*ca.* 145 dec.		335 (36,000)	3.03
IIId	$C_{27}H_{37}NO_3 \cdot C_2H_5OH$	C, 74.16 H, 9.23 N, 2.98	C, 73.61 H, 9.05 N, 3.24	Ethanol	56	*ca.* 150 dec.		335 (38,900)	3.00
IXa	Not characterized								
IXb	$C_{28}H_{35}NO_2$	C, 80.53 H, 8.45 N, 3.35	C, 80.36 H, 8.26 N, 3.58	Methanol	80	266-268 dec.	-173°	233 (8,070), 329 (40,800)	2.80, 3.04
IXc	$C_{26}H_{33}NO_3$	C, 76.62 H, 8.16 N, 3.44	C, 76.64 H, 8.12 N, 3.41	Ethyl acetate	49	232-234 dec.	-212°	338 (44,300)	2.82, 3.05

TABLE III

Androstano(eno)[3,2-b] or [17,16-b]-6'-arylpyridines

Compound	Formula	Anal. Calcd.	Anal. Found	Recrystallization Solvent	% Yield	M.p., °C	$[\alpha]_D^{25}$	λ max, mμ (ε)	λ max, μ
IVa	$C_{28}H_{35}NO$	C, 83.74 H, 8.78 N, 3.49	C, 83.44 H, 8.59 N, 3.50	Ethyl acetate	36	232-234	+ 64°	248 (14,100), 287 (13,300)	2.9, 6.31, 6.40, 13.0, 13.6, 14.5
IVb	$C_{29}H_{37}NO$	C, 83.81 H, 8.97 N, 3.37	C, 83.72 H, 8.77 N, 3.45	Ethyl acetate	16 (a)	211-213	+ 43°	248 (14,400), 284 (13,400)	2.95, 6.31, 6.40, 13.0, 13.6, 14.5
IVc	$C_{26}H_{33}NO_2$	C, 79.75 H, 8.50 N, 3.58	C, 79.50 H, 8.07 N, 3.90	Acetonitrile	48	212-214	+ 73°	266 (15,800), 309 (18,600)	2.9, 6.24, 6.30, 6.43, 13.3
IVd	$C_{28}H_{35}NO_3$	C, 77.56 H, 8.14 N, 3.23	C, 77.63 H, 8.10 N, 3.42	Acetonitrile	88 (b)	214-218	+ 54°	266 (15,200), 309 (18,000)	5.77, 6.24, 6.31, 6.44, 7.97, 13.2
IVe	$C_{27}H_{35}NO_2$	C, 79.96 H, 8.70 N, 3.45	C, 79.68 H, 8.63 N, 3.44	Ethyl acetate	63	224-226	+ 49°	266 (15,100), 309 (17,600)	2.87, 6.25, 6.31, 6.44, 13.5
Xa	$C_{26}H_{33}NO_2$	C, 79.75 H, 8.50 N, 3.58	C, 79.58 H, 8.22 N, 3.85	Acetone	26	237-239	+ 95°	268 (14,700), 309 (19,000)	2.93, 6.31, 6.44, 13.4, 13.7
Xb	$C_{28}H_{33}NO$	C, 84.17 H, 8.32 N, 3.51	C, 84.06 H, 8.60 N, 3.40	Methanol	43	245-252	- 17°	249 (12,100), 289 (14,100)	2.90, 6.31, 6.37, 13.2, 13.7, 14.6
Xc	$C_{26}H_{31}NO_2$	C, 80.17 H, 8.02 N, 3.60	C, 80.19 H, 7.77 N, 3.64	Ethyl acetate	25	245-247 (e)	- 10°	268 (14,200), 309 (18,200)	2.93, 6.36, 6.44, 13.6 13.8
XIIIa	Not characterized								
XIIIb	$C_{28}H_{31}NO$	C, 84.59 H, 7.86 N, 3.52	C, 84.55 H, 7.82 N, 3.55	Methanol	71 (c)	222-224 (e)	+201°	245 (28,400), 288 (16,000)	5.97, 6.20, 6.37, 13.0, 13.5, 14.4
XIIIc	$C_{26}H_{29}NO_2$	C, 80.58 H, 7.54 N, 3.61	C, 80.63 H, 7.77 N, 3.63	Ethyl acetate	55 (d)	222-224	+222°	242 (19,500), 265 sh. (15,100), 309 (18,500)	5.98, 6.23, 6.31, 6.44, 13.3, 13.5

(a) Overall yield based on Ib. (b) Yield based on acetylation of IVc. (c) Yield based on oxidation of Xb. (d) Yield based on oxidation of Xc.
(e) Evacuated capillary.

TABLE IV

Androstano(eno)[3,2-b] or [17,16-b]pyridines

Compound	Formula	Anal. Calcd.	Anal. Found	Recrystallization Solvent	% Yield (a)	M.p., °C	$[\alpha]_D^{25}$	λ max, mμ (ε)	λ max, μ
VIa	$C_{24}H_{33}NO_2$	C, 78.43 H, 9.05 N, 3.81	C, 78.23 H, 8.93 N, 3.91	Sublimed	65	142-144 (b)	+ 44° (c)	269 (5,660), 277 (4,550) (d)	5.76, 6.33 sh 6.37, 8.1, 12.7, 13.7 (e)
VIb	$C_{23}H_{33}NO$	C, 81.36 H, 9.80 N, 4.13	C, 81.24 H, 9.47 N, 4.03	Methanol	43	197-198 (f)	+ 42° (g)	269 (5,410), 277 (4,260) (h)	3.07, 6.32, 12.8, 13.1, 13.7 (i)
XII	$C_{22}H_{31}NO$	C, 81.18 H, 9.60 N, 4.30	C, 81.41 H, 9.29 N, 4.28	Acetone	27	196-197	+ 45°	269 (6,500), 277 (4,850)	2.9, 6.26, 6.34, 12.5
XIVa	$C_{22}H_{29}NO$	C, 81.69 H, 9.04 N, 4.33	C, 81.84 H, 9.24 N, 4.39	Acetone	8.7 (j)	175-177	+ 69°	269 (6,530), 277 (4,900)	5.85, 6.26, 12.6
XIVb	$C_{22}H_{27}NO$	C, 82.20 H, 8.47 N, 4.36	C, 82.18 H, 8.55 N, 4.46	Ethyl acetate	4.2	199-201	+119°	242 (17,900), 268 (8,050), 276 (5,200)	6.04, 6.23, 6.37, 12.55, 12.63

(a) Except for XIVa, all yields are for the combined ozonolysis and decarboxylation steps. (b) Allotropic change at about 135°; compare m.p. 131-132° (from methanol, ref. 5). (c) Compare + 46° (ref. 5). (d) Compare λ max, 269 mμ (ε, 5,630) and λ max, 277 mμ (ε, 4,470) (ref. 5). (e) Compare 5.77, 6.31, 6.36, 8.13, 12.6 and 13.7 μ (ref. 5). (f) Compare m.p. 192-193.5° (ref. 5). (g) Compare + 40° (ref. 5). (h) Compare λ max, 269 mμ (ε, 5,800) and λ max, 277 mμ (ε, 4,580) (ref. 5). (i) Compare 3.07, 3.27, 6.33, 12.7, 13.7 μ (ref. 5). (j) Overall yield from Xa by Oppenauer oxidation of Xa to XIIIa, followed by ozonolysis and decarboxylation of crude XIIIa.

one (m.p. 178-181°, 2.90 g., 0.0100 mole), 3-(2-furyl)acrolein (m.p. 49-53°, 1.34 g., 0.0110 mole), and potassium hydroxide (85%, 0.7 g., 0.01 mole) in methanol (40 ml.). After being chilled for 16 hours at 5° the mixture was filtered, affording bright-yellow needles containing about one-half mole of methanol of solvation, 2.75 g., 67.1% yield, m.p. 188-192°. One recrystallization from methanol raised the m.p. to 192-194°, 2.40 g., 58.5% yield.

2-[3-(2-Furyl)-2-propenylidene]-17β-hydroxy-5α-androstan-3-one oxime (IIIc).

A solution of IIc (m.p. 192-194°; 1.29 g., 0.00327 mole) and hydroxylamine hydrochloride (0.45 g., 0.0065 mole) in pyridine (5 ml.) and 95% ethanol (20 ml.) was heated for 4 hours at reflux and quenched in water. The resulting solid crystallized from methanol as a hemimethanolate in fine, pale-yellow needles; 1.20 g., 89.7% yield.

5α-Androstano[3,2-b]-6'-(2-furyl)pyridin-17β-ol (IVc).

Heating IIIc (12.00 g., 0.0282 mole) at 220-230° and 0.1 mm. of mercury in a cylindrical Pyrex glass tube gave IVc mixed with some brown tar as a sublimate on the sides of the tube (6.74 g.). Two recrystallizations of part (3.14 g.) of the sublimate, first from methanol, then from acetonitrile, gave the analytical sample, pale-yellow blades, 1.24 g., m.p. 212-214°. In order to remove colored impurities the mother liquors and the rest of the sublimate were percolated through silica gel (30 g.) with 1:1 methylene dichloride-ether and recrystallized from acetonitrile; 4.04 g., m.p. 205-212°. The total yield was thus 47.9%.

5α-Androstano[3,2-b]-6'-(2-furyl)pyridin-17β-ol acetate (IVd).

Acetylation of IVc (m.p. 205-212°, 2.41 g., 0.00607 mole) by treatment with acetic anhydride (10 ml.)-pyridine (20 ml.) for 24 hours at room temperature afforded IVd after one recrystallization from acetonitrile; beige prisms, 2.32 g., 88.2% yield, m.p. 214-218°.

5α-Androstano[3,2-b]pyridin-17β-ol acetate (VIa).

Ozone (0.036 mole) was bubbled through a stirred solution of IVd (m.p. 217.5-218.5°, 3.94 g., 0.00909 mole) in glacial acetic acid (60 ml.) and ethyl acetate (30 ml.) held at -5° to 0°. The solution was bright-yellow during ozonization and changed to pale-yellow after absorption of about two molar-equivalents of ozone. Hydrogen peroxide (30%, 2 ml., 0.02 mole) was added and the solution was stirred for 17 hours at room temperature. Quenching it in water (2 l.) gave crude Va as a white solid (3.35 g.), which was heated at 200-210° and 0.1-0.5 mm. of mercury. The product (2.25 g.) sublimed and was resublimed; irregular, microscopic, colorless crystals, 2.17 g., 65.1% yield, m.p. 142-144°.

3β-Hydroxy-5α-androstano[17,16-b]pyridine-6'-carboxylic acid (XI).

Ozone (0.060 mole) was bubbled through a stirred solution of Xa (m.p. 236-237°, 7.83 g., 0.0200 mole) in glacial acetic acid (70 ml.) and ethyl acetate (35 ml.) held at 3-10°. Water (20 ml.) was added dropwise with stirring and the mixture was let stand for 15 hours at room temperature. Evaporation of the solvents under reduced pressure at 40° gave a solid, which crystallized from methanol as the hemimethanolate; microscopic colorless crystals, 5.04 g., 65.4% yield, m.p. 217-224° dec. One recrystallization gave the analytical sample, which was dried at 100° and 0.02 mm. of mercury, m.p. 223-227° dec., $[\alpha]_D^{25}$ + 84°, λ max, 233 mμ (ε, 7,000) and 277 mμ (ε, 8,100), λ max, 2.8-3.1, 5.65, 5.85, 6.28, 6.36 μ. In chloroform solution the infrared spectrum of XI showed λ max, 5.66 μ (5.78 μ, shoulder) while the spectrum of picolinic acid showed λ max 5.65 μ (5.60 μ and 5.77 μ, shoulders). The ultraviolet spectrum of picolinic acid showed λ max, 219 mμ (ε, 7,220) and λ max, 264 mμ (ε, 3,980).

Anal. Calcd. for $C_{23}H_{31}NO_3 \cdot {}^1/_2CH_3OH$: C, 73.21; H, 8.63; CH_3O, 4.03. Found: C, 73.44; H, 8.74; CH_3O, 3.85.

5α-Androstano[17,16-b]pyridin-3β-ol (XII).

Compound XI (m.p. 217-224°, 3.54 g., 0.00918 mole) was heated from 190° to 220° during 1 hour and held at 220° for 3 hours under nitrogen. The residue was chromatographed on alumina (Merck reagent-grade, 100 g.). Elution with ether afforded the product (1.44 g., 48.2% yield, m.p. 194-196°), which was recrystallized from acetone; colorless plates, 1.23 g., 41.2% yield, m.p. 196-197°.

5α-Androstano[17,16-b]pyridin-3-one (XIVa).

This compound, 0.16 g., 5.4% yield, was obtained in the early ether eluates preceding XII and was recrystallized from acetone; colorless needles, 0.04 g., 1% yield, m.p. 174-176°. It was identical by mixture melting point and infrared spectral comparisons with the XIVa prepared by Oppenauer oxidation of Xa followed by ozonolysis and decarboxylation of crude XIIIa.

Androst-4-eno[17,16-b]-6'-(2-furyl)pyridin-3-one (XIIIb).

A solution of aluminum isopropoxide (5.73 g., 0.0272 mole) in dry toluene (50 ml.) was added during 1 hour with stirring to a refluxing solution of Xc (m.p. 242-247°, evacuated capillary, 5.30 g., 0.0136 mole) in dry toluene (200 ml.) and cyclohexanone (40 ml.). Refluxing was continued for 1.5 hours, while 150 ml. of toluene was collected. The solution was cooled, saturated potassium sodium tartrate solution was added, and the mixture was steam distilled until 1.6 l. of distillate was collected. The pot residue was extracted several times with methylene dichloride. The combined extracts (about 80 ml.) were washed with water, dried over sodium sulfate, filtered and evaporated. Two recrystallizations of the residue from ethyl acetate afforded the product as tan needles; 2.91 g., 55% yield, m.p. 222-224° (evacuated capillary).

Androst-4-eno[17,16-b]pyridin-3-one (XIVb).

Ozone (0.040 mole) was bubbled with stirring through a solution of XIIIc (m.p. 215-222°, evacuated capillary, 7.81 g., 0.0202 mole) in glacial acetic acid (70 ml.) and ethyl acetate (35 ml.) cooled by an ice-salt bath. Water (20 ml.) was added dropwise, then hydrogen peroxide (30%, 4.6 ml., 0.040 mole). After standing for 24 hours, the solution was concentrated on the steam bath under reduced pressure to an amorphous, yellow solid which was heated at 220-230° for 3 hours. A solution of the resulting brown glass was chromatographed on silica gel (Davison Chemical Co., 100-200 mesh, 200 g.). The product was obtained as a semi-solid in the ether eluates. Two recrystallizations from ethyl acetate gave pale-yellow prisms, 0.27 g., 4.2% yield, m.p. 199-201°.

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