Steroidal Imidazopyridines and Lactam Imidazopyridines

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Condensation of 17β-acetoxy-2α-bromo-5α-androstan-3-one with unsubstituted and substituted aminopyridines, gives the corresponding 17β-acetoxy-5α-androstanimidazo[1,2-*a*]pyridines.

Treatment of 16α-bromo-3-aza-A-homo-4α-androsten-4,17-dione with 2-aminopyridine or methyl-2-aminopyridine produces the corresponding 3-aza-A-homo-4α-androsten[16,17:2',3']imidazo[1,2-*a*]pyridines. Similarly, from 2α-bromo-17β-acetamido-5α-androstan-3-one and methylaminopyridine the 17β-acetamido-5α-androstan[2,3:2',3']imidazo[1,2-*a*]methylpyridine has been obtained.

The structure of the compounds was apparent from their chemical properties and spectral data (ir, uv and nmr).

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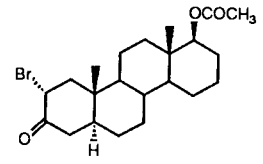
Chemistry.

The reaction of α-haloketones with 2-aminopyridines is known as the Chichibabin reaction [1]. Extension of this reaction to steroidal 16α-bromo-17-ketones and the 21-bromo-20-ketone with substituted 2-aminopyridines in xylene gives the corresponding imidazopyridines [2-3]. Condensation of 17β-acetoxy-2α-bromo-5α-androstan-3-one (**I**) with unsubstituted and substituted 2-aminopyridine gives the corresponding 17β-acetoxy-5α-androstanimidazo[1,2-α]-pyridines **II**. The 17β-acetoxy-5α-androstan[2,3:2',3']imidazo[1,2-*a*]pyridine has also been obtained by the action of pyridine and hydroxylamine on the 17β-acetoxy-2α-bromo-5α-androstan-3-one according to the method of Gaglioti and co-workers [4].



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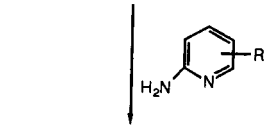
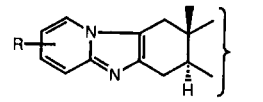




II

The structure of **II** was confirmed by physical and spectral data. The compounds prepared are reported in Table I and their spectral data in Tables II, III and IV.

Given that steroidal lactams present specific biological interest [5-6] and that no information exists on the synthesis and pharmacological properties of homo-aza-steroidal imidazopyridines, we decided to prepare some compounds of this type with the hope that in the near future we will investigate their pharmacological action.

The indroduction of the heterocyclic nucleus in the D-ring of the modified steroid can be effected by treating 16α-bromo-3-aza-A-homo-4α-androstene-4,17-dione (**III**) [7] with 2-aminopyridine or substituted 2-aminopyridine in xylene.

Table I

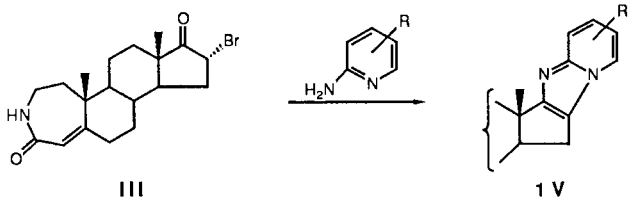
17β-Acetoxy-5α-androstan[2,3:2',3']imidazo[1,2-*a*]pyridines **II**

Compound No.	R	Formula	M.p.°C	Recryst. Solvent	Analysis Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
IIa	H	$C_{26}H_{34}N_2O_2$	221-223	CH_3OH	76.85	77.22	8.27	8.12	6.90	7.21
IIb	6'-CH_3	$C_{27}H_{36}N_2O_2$	243-245	CH_3OH	77.11	76.95	8.63	8.62	6.66	6.82
IIc	7'-CH_3	$C_{27}H_{36}N_2O_2$	242-244	CH_3OH-$CH_3COOC_2H_5$	77.11	77.15	8.63	8.58	6.66	6.62
IId	8'-CH_3	$C_{27}H_{36}N_2O_2$	260-261	CH_3OH-$CH_3COOC_2H_5$	77.11	77.31	8.63	8.71	6.66	6.38

Table II

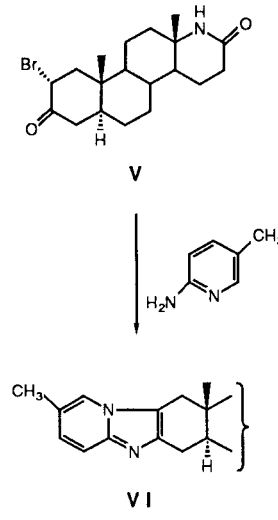
IR of 17β-Acetoxy-5α-androstan[2,3:2′,3′]imidazo[1,2-*a*]pyridines **II**

Compound No.	(-OCOCH$_3$) Stretching Vibration (cm^{-1})	(Ar) Stretching Vibration (cm^{-1})
IIa	1728, 1240	750, 730
IIb	1730, 1250	795, 760
IIc	1725, 1245	770, 750
IIc	1728, 1240	770, 740



III IV

Structure assignment of the compounds **IV** obtained was based on physical and spectral (ir, uv and nmr) data which are reported in Tables V, VI, VII and VIII.



V VI

Table III

UV of 17β-Acetoxy-5α-androstan[2,3:2′,3′]imidazo[1,2-*a*]pyridines **II**

Compound No.	λ mμ	ε
IIa	214, 228.1, 235.6, 269.4, 281.6	16444, 20355, 20266, 3733, 4133
IIb	215.1, 230.1, 238.9, 273 284.1	22386, 23798, 24403, 4668, 4739
IIc	215.6, 229.1, 235.1, 269.9, 282.2	19935, 24082, 19137, 5101, 5170
IId	215.2, 229.2, 237.3, 272.1, 283.2	20676, 22338, 19846, 4784, 4915

Table IV

NMR of 17β-Acetoxy-5α-androstan[2,3:2′,3′]imidazo[1,2-*a*]pyridines **(II)**

Compound No.	5′-H	6′-H	7′-H	8′-H	CHOCOCH$_3$	Ar-CH$_3$	ROCOCH$_3$	19-CH$_3$	18-CH$_3$
II	7.8	6.76	7.12	7.54	4.62	—	2.06	0.88	0.84
IIa	7.6	—	6.95	7.44	4.64	2.32	2.04	0.86	0.86
IIb	7.83	6.75	—	7.44	4.64	2.38	2.06	0.84	0.84
IIc	7.58	6.96	7.34	—	4.66	2.36	2.10	0.84	0.84

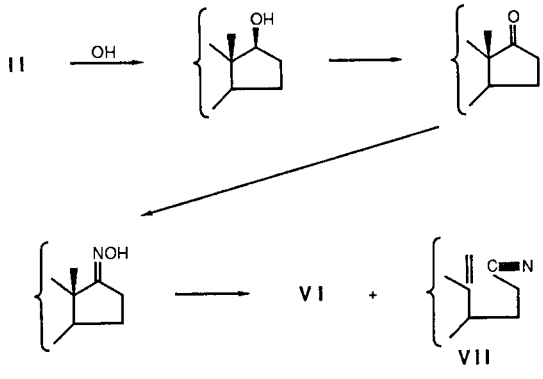
Table V

3-Aza-A-homo-4α-androsten[16,17:2′,3′]imidazo[1,2-*a*]pyridines **IV**

Compound No.	R	Formula	Yield %	Mp °C	Recrystallization Solvent	Carbon Calcd.	Carbon Found	Analysis Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
IV	H	$C_{24}H_{29}N_3O$	90	>300	CH$_3$OH	76.50	76.39	7.87	7.81	11.20	10.95
IVb	6′-CH$_3$	$C_{25}H_{31}N_3O$	85	>300	CH$_3$OH	77.12	77.11	7.96	8.25	10.79	10.82
IVc	7′-CH$_3$	$C_{25}H_{31}N_3O$	87	>300	CH$_3$OH	77.12	77.45	7.96	8.20	10.79	10.51
IVd	8′-CH$_3$	$C_{25}H_{31}N_3O$	65	>300	CH OH	77.12	76.92	7.96	8.16	10.79	10.39

An alternative method has been also used for the synthesis of compound **IVa**, using as starting material 16α-bromo-3-aza-A-homo-4α-androstene-4,17-dione in pyridine-hydroxylamine hydrochloride mixture.

Using as starting material 2α-bromo-3-oxo-13α-amino-13,17-seco-5α-androstan-17-oic-13,17-lactam (**V**) and 2-amino-5-methylpyridine, we have obtained the 17α-aza-D-homo-5α-androstan [2,3:2',3']imidazo[1,2-*a*]-6'-methylpyridine (**VI**).



Compound **VI** was also synthesized by an alternative method using compound **II** as starting material. Specifically, compound **II** was hydrolyzed and its 17β-OH group was oxidized to the corresponding ketone. The ketone was subsequently transformed to the corresponding oxime which generated compound **VI** and the unsaturated nitrile **VII** by Beckmann rearrangement. Compound **VI** and **VII** were separated by column chromatography.

For biological purposes we have synthesized compound **VIII**, which has the amide group out of the steroidal skeleton, using as starting material 17β-acetamido-2α-bromo-5α-androstan-3-one and 2-amino-5-methylpyridine. The synthesis of compound **VIII** could be also effected by reduction of the oxime of 5α-androstan[2,3:2',3']imidazo-[1,2-α]pyridin-17-one with *t*-butyl alcohol and sodium followed by acetylation.

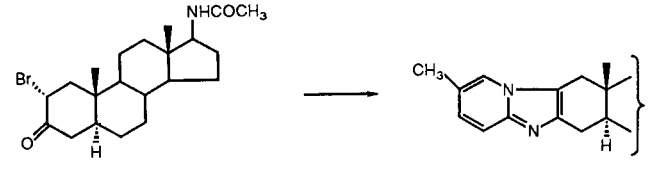


Table VI

IR of 3-Aza-A-homo-4α-androsten[16,17:2',3']imidazo[1,2-*a*]pyridines **IV**

Compound No.	(-NH-) Stretching Vibration (cm^{-1})	(-NHCO-) Stretching Vibration (cm^{-1})	(-Ar) Stretching Vibration (cm^{-1})
IVa	3300	1625, 1590	750, 730
IVb	3300	1625, 1590	800, 750
IVc	3300	1625, 1590	775, 720-740
IVd	3300	1625, 1590	770, 740

Table VII

Uv of 3-Aza-A-homo-4α-androsten[16,17:2',3']imidazo]1,2-*a*]pyridines **IV**

Compound No.	R	λ mμ	ε
IVa	H	214.3, 230, 235.5, 229.5, 281.3	16298, 17770, 18575, 3271, 3349
IVb	6'-CH_3	216.4, 230.5, 238.4, 275.5, 280.2	23735, 21498, 19739, 3404, 3696
IVc	7'-CH_3	216, 228, 236, 271, 283	38400, 39882, 41485, 11828, 12342
IVd	8'-CH_3	215, 228, 235, 269.8, 281.8	31298, 33640, 35008, 5591, 5996

Table VIII

NMR of 3-Aza-A-homo-4α-androsten[16,17:2',3']imidazo[2,3-*a*]pyridines **IV**

Compound No.	5'-H	6'-H	7'-H	8'-H	-COCH-C-	NHCO	Ar-CH_3	19-CH_3	18-CH_3
IVa	7.90	6.77	7.17	7.64	5.78	7.38	—	1.20	1.05
IVb	7.68	—	6.94	7.48	5.78	7.35	2.31	1.22	1.02
IVc	7.81	6.76	—	7.51	5.78	7.37	2.34	1.20	1.04
IVd	7.74	6.75	6.85	—	5.78	7.40	2.33	1.22	1.06

EXPERIMENTAL

Melting points were determined on a Fisher Johns melting point apparatus and are uncorrected. The ir spectra were recorded with a Perkin-Elmer 298 in solid phase potassium bromide. The uv spectra were determined with a Perkin-Elmer 551s in methanol. The nmr spectra were determined with a Jeol FX900 and with a Varian Associates XL-100 instrument using deuteriochloroform and TMS as the internal standards. Elemental analyses were performed by the analytical laboratory of the Chemistry Department "Demokritos".

17-Acetoxy-5α-adrostan[2,3:2',3']imidazo[1,2-*a*]pyridines **II**.

Method A.

To a solution of 10 mmoles of 2α-bromo-17β-acetoxy-5α-androstan-3-one in 20 ml anhydrous xylene, 2.5 × 10 mmoles of 2-aminopyridine or substituted 2-aminopyridine was added and the mixture was refluxed for 96 hours. After evaporation of the solvent under reduced pressure, the remaining residue was dissolved in chloroform and the solution was washed several times with water dried over sodium sulfate and evaporated under reduced pressure to give a residue which was chromatographed on a column of silica gel prepared with chloroform, the corresponding imidazo[1,2-*a*]pyridines were obtained. The compounds prepared and their spectral data are reported in Tables I-IV.

Method B.

A solution of 1 mmole of 2α-bromo-17β-acetoxy-5α-androstan-3-one in 30 ml of anhydrous pyridine was refluxed for 18 hours. To this solution 700 mg (2 mmoles) of hydroxylamine hydrochloride was added and the mixture was refluxed for 24 hours. After this time the solvent was evaporated under reduced pressure and the residue was extracted several times with chloroform. The solution was washed several times with water, dried over sodium sulfate and evaporated under reduced pressure. The residue was chromatographed on a column of silica gel prepared with chloroform. By eluting with chloroform, the 17β-acetoxy-5α-androstan-[2,3:2',3']imidazo[1,2-*a*]pyridine was obtained in 38% yield. Its melting point and ir spectrum were identical to the compound prepared by method A.

3-Aza-A-homo-4α-androsten[16,17:2',3']imidazo[1,2-*a*]pyridines **IV**.

Method A.

Compounds **IV** were obtained under the same reaction conditions used for the preparation of **II**. Using as starting material 16α-bromo-3-aza-A-homo-4α-androstene-4,17-dione (**III**) [7] and substituted and unsubstituted 2-aminopyridine in xylene. The physical and spectral data are reported in Tables V-VIII.

Method B.

Reaction of 16α-Bromo-3-aza-A-homo-4α-androstene-4,17-dione with Hydroxylamine in Pyridine Solution.

Under the same reaction conditions as for the synthesis of compound **IIa**, 3-aza-A-homo-4α-androsten[16,17:2',3']imidazo[1,2-*a*]pyridine (**IVa**) was obtained in 38% yield. Its melting point and ir spectrum were identical to **IVa** prepared by method A.

17α-Aza-D-homo-5α-androstan[2,3:2',3']imidazo[1,2-*a*]-6'-methylpyridin-16-one (**VI**).

Method A. From 2α-Bromo-17α-aza-D-homo-5α-androstane-3,17-dione (**V**).

To a solution of 10 mmoles of 2α-bromo-17α-aza-D-homo-5α-androstane-3,17-dione (**V**) [7] in 30 ml of anhydrous xylene, 2.5 × 10 mmoles of 2-amino-5-methyl-pyridine was added. The mixture was heated under reflux for 144 hours.

The solvent was subsequently evaporated under reduced pressure and the residue was dissolved in chloroform and washed several times with water. The chloroform solution was dried over sodium sulfate and the solvent was evaporated under reduced pressure. The residue was chromatographed from a column of silica gel (1:200) prepared with chloroform. By eluting with chloroform-methanol (98:2), the 17α-aza-D-homo-5α-androstan[2,3:2',3']imidazo[1,2-α]-6'-methylpyridine (**VI**) was obtained in 55% yield. Recrystallization from ethyl acetate gave mp >300°C; ir ν max 3200-3250 (NH), 1665, 1635 (NHCO), 800, 740 cm^{-1} (Ar); nmr: δ, 7.62 (5'-H), 7.00 (7'-H), 7.12 (8'-H), 7.52 (NHCO), 2.34 (6'-CH_3); uv: λ mμ. 215 (22810), 228.8 (24030), 236.5 (24210), 272.7 (4780), 283.8 (4920).

Anal. Calcd. for $C_{25}H_{33}N_3O$: C, 76.72; H, 8.44; N, 10.74. Found: C, 76.57; H, 8.42; N, 10.44.

Method B. From 17β-Acetoxy-5α-androstan[2,3:2',3']imidazo[1,2-*a*]-6'-methylpyridine (**II**).

To a solution of 7.2 g of 17β-acetoxy-5α-androstan[2,3:2',3']imidazo-[1,2-*a*]-6'-methylpyridine in 250 ml of methanol, 2 g of potassium hydroxide was added. The mixture was heated under reflux for 2 hours. After this time cold water was added and neutralized with acetic acid. The resulted precipitate was collected by filtration and washed several times with water. After drying over calcium chloride 6.2 g of 17β-hydroxy-5α-androstan[2,3:2',3']imidazo[1,2-*a*]-6'-methylpyridine was obtained, mp 288-290°; ir: ν max 3330-3350 (OH), 795, 745 cm^{-1} (−Ar).

5α-Androstan[2,3:2',3']imidazo[1,2-*a*]-6'-methylpyridine.

To a solution of 6.5 g of 17β-bydroxy-5α-androstan[2,3:2',3']imidazo-[1,2-*a*]-6'-methylpyridine in 1 ℓ of acetone, 15 ml of Jones reagent was dropwise added with agitation. The mixture was agitated for 20 hours at room temperature. The solvent was evaporated under reduced pressure. Water was added to the residue and the solution was extracted several times with chloroform. The chloroform solutions was washed with water, dried and evaporated. The residue was chromatographed on a column of silica gel (1:20). The desired compound was obtained in 57% yield by eluting the column with benzene-ethyl acetate (1:2) mp 280-281° (methanol); ir (potassium bromide): ν max 1730 (CO), 798, 745 cm^{-1} (−Ar).

Anal. Calcd. for $C_{25}H_{32}N_2O$: C, 79.74; H, 8.56; N, 7.44. Found: C, 79.78; H, 8.45; N, 7.39.

Beckmann Rearrangement of 5α-Androstan[2,3:2',3']imidazo[1,2-*a*]-6'-methylpyridin-17-one Oxime.

To a solution of 5α-androstan[2,3:2',3']imidazo[1,2-*a*]-6'-methylpyridin-17-one (3 g) in a mixture of ethanol (16 ml) and pyridine (16 ml), 4 g of hydroxylamine hydrochloride was added and the mixture was heated under reflux for 3.5 hours. Subsequently, the solution was added to cold water and the precipitate collected by filtration, washed with water and dried over calcium chloride to give the corresponding oxime in 85% yield, mp 300°; ir: 3300-3320 (OH), 1640 (C=N), 800, 745 cm^{-1} (−Ar).

Without further purification of the oxime, 1.5 g was dissolved in 20 ml of dry dioxane and the solution was cooled at 0°. To this solution, a solution of 2 ml of fresh distilled thionyl chloride in 8 ml of dry dioxane was added dropwise with agitation. The mixture was agitated for 5 hours at room temperature. It was poured into ice-water and extracted several times with chloroform. The solution was washed with water, dried over magnesium sulfate and the solvent was distilled under reduced pressure to give a residue of 1.2 g, which was chromatographed on a column of silica gel (200 g). Elution with chloroform gave 300 mg of ω-cyanoolefin **VII**, mp 241-243° (methanol-*n*-hexane); ir: ν max 2250 cm^{-1} (C≡N); nmr: 7.75 (5'-H), 7.00 (7'-H), 7.43 (8'-H), 4.84, 4.51 (C=CH_2), 2.37 (6'-CH_3), 2.30 (CH_2-C=CH_2), 1.26 (19-CH_3); uv: λ mμ 216.5 (22906), 231.5 (24651), 237.5 (24046), 256.0 (21674), 275.0 (8837), 282.3 (8883).

Anal. Calcd. for $C_{25}H_{31}N_3$: C, 80.38; H, 8.36; N, 11.24. Found: C, 80.02; H, 8.42; N, 10.98.

With further elution of the column with chloroform:methanol (98:2) the 17α-aza-D-homo-5α-androstan[2,3:2',3']imidazo[1,2-*a*]-6'-methylpyridin-17-one (500 mg) was obtained which had the same ir and mp with compound **VII** prepared before from **V** and 2-amino-6-methylpyridine.

17β-Acetamido-5α-androstan[2,3:2',3']imidazo[1,2-*a*]-6'-methylpyridine (**IX**).

Method A. From 5α-Androstan[2,3:2',3']imidazo[1,2-*a*]-6'-methylpyridin-17-one Oxime.

To a solution of 1 g of 5α-androstan[2,3:2',3']imidazo[1,2-*a*]-6'-methylpyridin-17-one oxime in 150 ml of butanol, 4.5 g of sodium was added. The mixture was heated under reflux for 3 hours and it was poured into ice-water. Then, it was extracted with chloroform. The solution was washed with water, dried and the solvent was evaporated under reduced pressure. The remaining residue was added in a mixture of pyridine (5 ml) and acetic anhydride, and allowed to stay at room temperature for 24 hours. Then, it was poured into ice-water and extracted with chloroform. After drying, the solvent was evaporated and the residue was chromatographed from silica gel (120 g), using chloroform:methanol (99:1) gave a reacted oxime acetate as the first fraction. Further elution with chloroform:methanol (95:5) gave the desired imidazopyridine (550 mg). Recrystallization from methanol-ethyl acetate brought mp >300°; ir: ν max 3280 (NH), 1640, 1540 (−NHCO−), 795, 745 cm^{-1} (−Ar); uv λ mμ 214.9 (22310), 229.0 (23775), 236 (24330), 273.1 (4660), 283.8 (4710); ^1H nmr: 7.57 (5'-H), 6.90 (7'-H), 7.40 (8'-H), 7.32 (NHCO), 2.32 (6'-CH_3), 0.98 (19-CH_3), 0.85 (18-CH_3).

Anal. Calcd. for $C_{27}H_{37}N_3O$: C, 77.32; H, 8.33; N, 10.02. Found: C, 77.12; H, 8.67; N, 9.85.

Method B. From 17β-Acetamido-5α-androstan-3-one.

Synthesis of 17β-Acetamido-2α-bromo-5α-androstan-3-one (**VIII**).

To a solution of 17β-acetamido-5α-androstan-3-one (5 g) in 350 ml of glacial acetic 6.3 g of pyridinium bromide perbromide was added. The mixture was agitated at room temperature for 15 hours. Subsequently, it was poured into ice-water and the precipitate was collected by filtration, washed with water and dried to produce bromoketone **VIII** in 78% yield, mp 181-183° (methanol) ir: ν max 3280 (NH), 1720 (CO), 1640, 1540 cm^{-1} (NHCO).

Anal. Calcd. for $C_{21}H_{32}BrNO_2$: C, 61.46; H, 7.80; N, 3.41. Found: C, 61.58; H, 7.90; N, 3.68.

17b-Acetamido-5α-androstan[2,3:2',3']imidazo[1,2-*a*]-6'-methylpyridine (**IX**).

To a solution of 10 × 2.5 mmoles of bromoketone **VIII** in 30 ml of anhydrousxylene, 10 × 2.5 mmoles of 2-amino-5-methylpyridine was added. The mixture was treated as usually and compound **IX** was obtained in 70% yield. Its ir spectrum and melting point were identical with the compound prepared by method A.

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