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13. Genkichi Ohta, Katsujiro Ueno, and Masao Shimizu : Investigations on Steroids. II.[1] Spectral Properties of Androstano[3,2-*b*]pyridine.[2]

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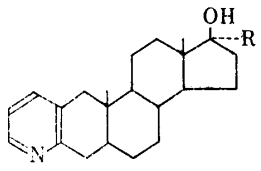
In the preceding paper the syntheses of 17β-hydroxyandrostano[3,2-*b*]pyridine (Ia) and its 17α-methyl derivative (Ib) were described. The formation of the extended pyridine ring was accomplished by reaction of 2-hydroxymethylene-3-keto steroids with cyanoacetamide or its derivatives, and in spite of the difference in the functional groups of cyanoacetamide derivatives the pyridine ring was shown to be fused to ring A in the same manner. The structure [3,2-*b*]pyridine was tentatively assigned to this ring fusion by analogy to similar reactions in the literature;[3] however, the [2,3-*c*]pyridine structure was not excluded. Evidence for the former structure and other related information have been obtained by spectral investigations which are reported herein.

Alkylpyridines are effectively characterized by the intense infrared absorption bands below 900 cm^{-1} associated with C-H out-of-plane bending vibrations, and the influence

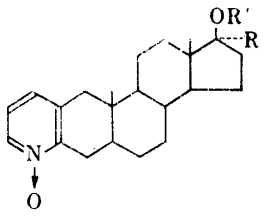
Table I.

Substances	UV λ_{max} mμ		IR δ_{C-H} cm^{-1} in CS_2	
17β-Hydroxyandrostano[3,2-*b*]pyridine (Ia)	269[a]	268~269[b]	782	729
17α-Methylandrostano[3,2-*b*]pyridin-17β-ol (Ib)		269[b]	782	728
2,3-Dimethylpyridine	265[a]	266[c]	784	726
5,6,7,8-Tetrahydroquinoline	268[a]	268[c]	782	728
3,4-Dimethylpyridine	260[a]		818	724
17β-Hydroxyandrostano[3,2-*b*]pyridine N-oxide 17-acetate (IIa)	264[b]	277[d]	777	698
17α-Methyl-17β-hydroxyandrostano[3,2-*b*]pyridine N-oxide (IIb)	264.5[b]	263.5[c] 277[d]	775	696
2,3-Dimethylpyridine N-oxide		261.5[c] 276.5~277[d]	777	694

a) in C_6H_{12} *b*) in EtOH *c*) in 95% EtOH *d*) in Et_2O



Ia : R=H
Ib : R=CH_3



IIa : R=H, R'=Ac
IIb : R=CH_3, R'=H

Chart 1.

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1) Part I. This Bulletin, **12**, 77 (1964).

2) For the nomenclature, cf. Part I of this series.

3) A. Dornow, E. Neuse : Chem. Ber., **84**, 296 (1951); Org. Syntheses, **32**, 32 (1952).

of the molecular structure on the position of these bands has been studied.[4] Also, the effect of alkyl groups on ultraviolet absorption has been reported.[5] In Table I the infrared and ultraviolet absorptions of androstano-pyridines are compared with those of 2,3- and 3,4-dimethylpyridines[4,5] and 5,6,7,8-tetrahydroquinoline,[6] published in the literature.

In the infrared region the androstano-pyridines (I) exhibit bands at 782 and 728~729 cm^{-1} which are in good agreement with those of 2,3-dimethylpyridine and 5,6,7,8-tetrahydroquinoline and quite distinct from those of 3,4-dimethylpyridine, thus excluding the [2,3-*c*]pyridine structure. The positions of the absorptions of the androstano-pyridine N-oxides (II) coincide with those of 2,3-dimethylpyridine N-oxide.

In the ultraviolet spectrum the difference between the absorption maximum of 3,4-dimethylpyridine and that of 2,3-dimethylpyridine is rather small (5 mμ). The difference (4 mμ) between the androstano[3,2-*b*]pyridine (I) series and 2,3-dimethylpyridine seems to be effected by ring strain. A similar effect has been pointed out by Godar, *et al.*[6] The position of maximal absorption of androstano[3,2-*b*]pyridine N-oxides (II) agreed well with that of 2,3-dimethylpyridine N-oxide. It was also observed that the androstano-[3,2-*b*]pyridines (I) contain more prominent fine structure near the main peak than 2,3-dimethylpyridine. The fine structure is absent in the spectrum of the N-oxide derivatives.

The nuclear magnetic resonance data for compound Ib also supports the [3,2-*b*]-pyridine structure. The spectrum shows at low field ABX type signals (1.73, 2.73, and 3.06 τ, centers of quartets; area ratio: *ca.* 1:1:1) characteristic of the three vicinal protons on the heterocyclic ring. As far as the aromatic proton region is concerned, the positions, intensities, line-shapes of the signals as well as the coupling constants and the chemical shifts between the protons are all consistent with the published data of 2,3-dimethylpyridine.[7] In the spectrum of Ib the singlets, each equivalent to 3 protons,

Table II.

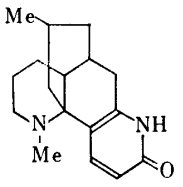
17β-Hydroxyandrostano-[3,2-*b*]pyridine	λ_{max}^{EtOH} mμ		5,6-Dimethyl-	λ_{max}^{EtOH} mμ	
6′-thioxo-1′,6′-dihydro-5′-carbonitrile (III)	309	410	2-thioxo-1,2-dihydro-3-pyridinecarbonitrile (XXIII)	311	405~410
6′-thioxo-1′,6′-dihydro-5′-carboxylic acid (IV)	305	392~396	2-thioxo-1,2-dihydro-3-pyridinecarboxylic acid (XXIV)	305	390
6′(1′*H*)-thione (V)	282	372~373	2(1*H*)-pyridinethione (XVIII)	283	371
6′-amino-5′-carboxamide (VI)	252	338	2-amino-3-pyridinecarboxamide (XIV)	251	337
6′-oxo-1′,6′-dihydro-5′-carbonitrile (VII)	237~238	347			
6′-oxo-1′,6′-dihydro-5′-carboxamide (VIII)	239	340	2-oxo-1,2-dihydro-3-pyridine-carboxamide (XV)	239	340
6′-oxo-1′,6′-dihydro-5′-carboxylic acid (IX)	236~237	342~343	2-oxo-1,2-dihydro-3-pyridine-carboxylic acid (XVI)	237~238	341
6′-oxo-1′,6′-dihydro-5′-carboxylic acid ethylester (X)	241	345~346			
6′(1′*H*)-one (XI)	230	316	2(1*H*)-pyridone (XVII)	232	315
6′(1′*H*)-one 17-acetate (XII)	231	316			
6′-hydroxy diacetate (XIII)	270	(C_6H_{12})			

4) K. Tsuda, M. Maruyama: This Bulletin, **1**, 146 (1953); H. Shindo, N. Ikekawa: *Ibid.*, **4**, 192 (1956); H. Shindo: *Ibid.*, **4**, 460 (1956).
5) N. Ikekawa, M. Maruyama, Y. Sato: *Ibid.*, **2**, 209 (1954); N. Ikekawa, Y. Sato: *Ibid.*, **2**, 400 (1954).
6) E. Godar, R.P. Mariella: J. Am. Chem. Soc., **79**, 1402 (1957).
7) H.J. Bernstein, J.A. Pople, W.G. Schneider: Canad. J. Chem., **35**, 65 (1957).

at 9.22, 9.13, and 8.76 τ are assignable to the C_{18} methyl, C_{19} methyl, and the methyl group at the 17-position, respectively on the basis of comparison with known steroids.

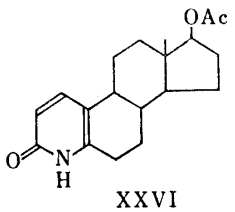
In the series of reactions by which androstano[3,2-*b*]pyridin-17β-ol (Ia) and its 17α-methyl compound (Ib) were synthesized, the ultraviolet absorptions were found to be a useful tool in characterizing the intermediate compounds. Dimethylpyridine derivatives were referred to as model compounds. The results are summarized in Table II.

α-Pyridones and α-aminopyridines containing an electron-attracting group at the β-position exhibit similar ultraviolet spectra in which peaks are present in the range of 235~250 and of 335~350 mμ. Elimination of β-substituted grouping of α-pyridone causes a large hypsochomic shift. On the contrary, androstano[3,2-*b*]pyridine-6',17β-diol diacetate (XIII) shows only one peak at 270 mμ with neighboring fine structure, and its spectrum resembles that of a polyalkylpyridine. α-Pyridinethiones, whether or not they are substituted at the β-position, exhibit a prominent band at 370~410 mμ.



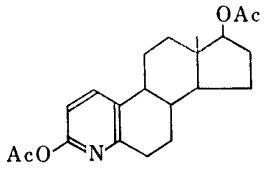
XXV

λ_{max} 230, 315 mμ



XXVI

λ_{max} 220, 288 mμ



XXVII

λ_{max} 212, 254 mμ

Chart 2.

In the literature a few comparable pyridone compounds have been reported. β-Obscurine,[8] a kind of Lycopodium alkaloid, is represented as XXV and its absorption maxima are consistent with those of 5,6-dimethyl-2(1*H*)-pyridone (XVII) and of androstano[3,2-*b*]pyrid-6'(1'*H*)-one derivatives. However, discrepancies are observed between two compounds of 4-azasteroid series[9] and the corresponding compounds of the present work. The positions of the absorption maxima of 17β-acetoxy-4-azaestra-1,5(10)-dien-3-one (XXVI) did not agree with those of 5,6-dimethyl-2(1*H*)-pyridone (XVII) or those of androstano[3,2-*b*]pyrid-6'(1'*H*)-ones (XI and XII).*2 Moreover, the absorption spectrum of the 3,17-diacetate (XXVII) is not consistent with that of androstano[3,2-*b*]pyridine-6',17β-diol diacetate (XIII),*3 which exhibits a characteristic ultraviolet absorption of a fully aromatic pyridine ring. Therefore, doubts remain on the structures assigned for these 4-azasteroids.

5,6-Dimethylpyridine derivatives used as model compounds were synthesized by sequences shown in Chart 3. Compound (XIV) was prepared by the method of Dornow, *et al.*[3] Diazotization of XIV gave XV, which was hydrolyzed with hydrochloric acid to XVI. Decarboxylation of XVI furnished pyridone (XVII), which was treated with phosphorus pentasulfide to afford a 2-thione (XVIII). Tracy, *et al.*[10] have reported the reaction of

*2 The ultraviolet spectrum of XI[1] taken in acidic or basic solution also did not correspond to that of XXVI[9] in the same solution.

*3 That α-acetoxypyridine is readily deacetylated to α-pyridone is well known; cf. A.E. Tschitschibabin, P.G. Szokow: Ber., **58**, 2651 (1925). The reported stability of XXVII in acidic or basic medium[9] is rather exceptional. As mentioned earlier,[1] compound (XIII) (IR ν_{max} cm^{-1}: 1767 (6'-OAc), 1726 (17-OAc), 1581, 1243, 1186) is not stable in MeOH but in cyclohexane. When XIII was dissolved in MeOH, the ultraviolet maximum of XIII at 271~272 mμ was gradually diminished and new bands of XII at 231 and 316 mμ appeared. In acidic medium (0.1*N* HCl in 95% EtOH) the change was more rapid (λ_{max} 285 → 297 mμ) and in basic medium (0.1*N* KOH in 60% EtOH) only the maxima corresponding to XII at 232 and 307 mμ were observed.

8) W.A. Ayer, J-A. Berezowsky, G.G. Iverach: Tetrahedron, **18**, 567 (1962).
9) M. Uskokovic, V. Toome, M. Gut: J. Org. Chem., **27**, 643 (1962).
10) A.H. Tracy, R.C. Elderfield: *Ibid.*, **6**, 63 (1941).

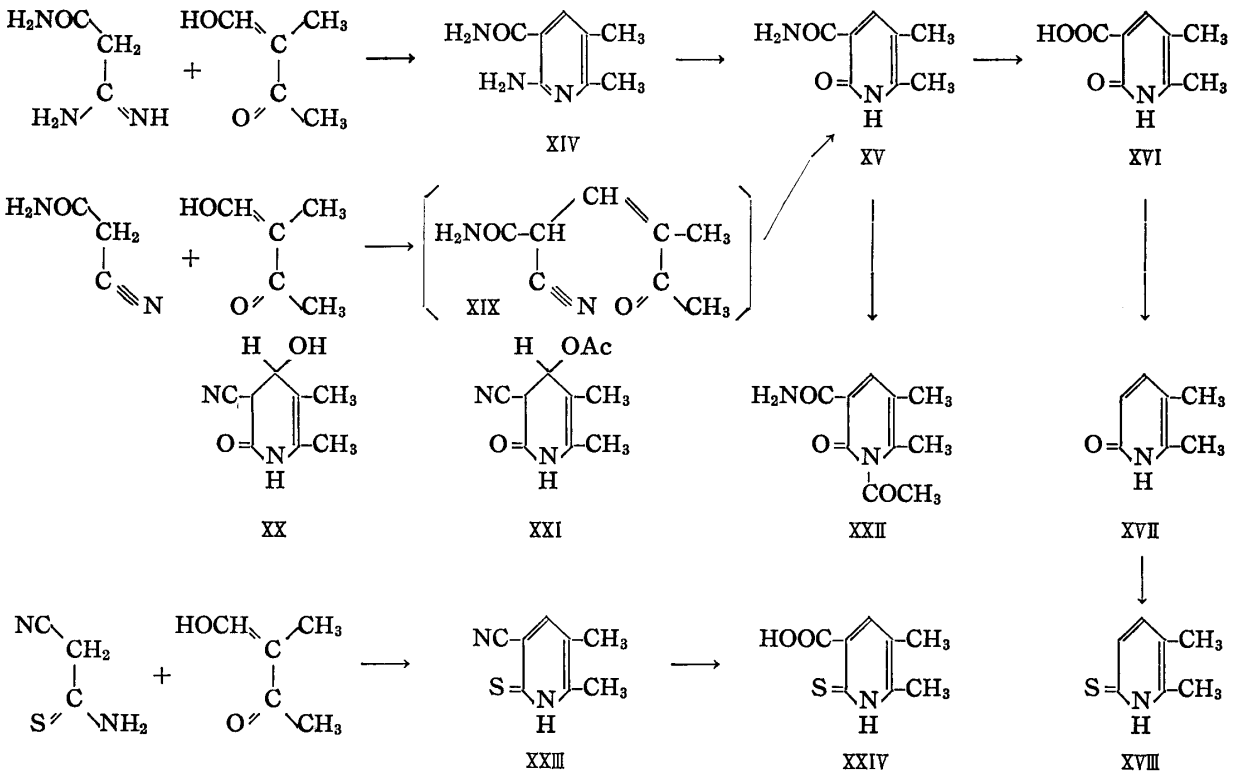


Chart 3.

3-hydroxymethylene-2-butanone with cyanoacetamide for preparing dimethylpyridine derivatives. The structure of the reaction product has been assigned as XX on the basis of its chemical behaviors. The compound obtained by this reaction, however, showed no characteristic infrared absorption of a nitrile group. Its ultraviolet absorptions (maxima at 239 and 340 mμ) indicated the presence of pyridone ring. By direct comparison, this compound was proved to be identical with XV described above. The acetate of this compound is stable to dilute alkali and shows no characteristic ultraviolet bands of a fully aromatic pyridine ring, indicating that the acetyl group is present as N-acetate in place of O-acetate. The infrared spectrum also lacked bands characteristic of an O-acetyl group. Therefore, the structure of the acetate shown as XXI by the above authors, should be revised as XXII. In this reaction the pyridone-carboxamide (XV) appears to have resulted from the cyclization between a cyano group and a carbonyl group of the intermediate (XIX), since under the reaction conditions it would not be expected that the cyano group once formed at the β-position of the pyridone ring underwent hydrolysis to a carboxamide. Similar results have been observed in the reactions of androstano[3,2-*b*]pyridine series reported in Part I. Condensation of 3-hydroxymethylene-2-butanone with cyanothioacetamide furnished 2-thioxo-5,6-dimethyl-1,2-dihydro-3-pyridinecarbonitrile (XXIII). The reaction proceeded in the same way as in androstanopyridine series. Hydrolysis of XXIII with hydrochloric acid gave XXIV.

Experimental

Melting points are uncorrected. IR spectra were taken in a KBr disc, UV spectra in EtOH. NMR spectrum was taken on a JNM C. 60 spectrometer (Japan Electron Optics Laboratory Co., Ltd.) at 60 Mc. using 8% solution in deuterochloroform. Tetramethylsilane was used as an internal standard.

2-Oxo-5,6-dimethyl-1,2-dihydro-3-pyridinecarboxamide (XV)——i) Sodium salt of 3-hydroxymethylene-2-butanone (21.9 g.) was dissolved in cold H_2O, carefully acidified with dil. HCl and extracted with Et_2O. Crude 3-hydroxymethylene-2-butanone thus obtained and cyanoacetamide (15 g.) were dissolved in MeOH (150 ml.), and after addition of piperidine (9.5 ml.) the solution was heated under

reflux for 20 min. and cooled. The crystalline deposites were filtered and the mother liquor was again refluxed with piperidine (2.0 ml.) for 4.5 hr. and cooled to separate a second crop. The total yield of the crude product was 5.0 g. Recrystallization from AcOH afforded XV, as pale yellow prisms, m.p. >300° (reported m.p. 347°[10]). This substance was soluble in dil. NaOH and precipitated by addition of HCl. UV λ_{max} mμ (ε): 239 (8,740), 340 (11,000). IR ν_{max} cm^{-1}: 3330, 3160, 1665, 1617, 1562. *Anal.* Calcd. for $C_8H_{10}O_2N_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.62; H, 6.15; N, 16.88.

ii) To a solution of 2-amino-5,6-dimethyl-3-pyridinecarboxamide[3] (XIV) (290 mg.) in 2% HCl (10 ml.) was added dropwise aq. $NaNO_2$ solution (122 mg. in 1 ml.) and the mixture was set aside at room temperature for 2 hr. to precipitate yellow crystals (170 mg.). Recrystallization from AcOH gave XV as prisms, m.p. >300°, which was identified with the product described above by comparison of IR and UV spectra.

Hydrolysis of XV with conc. HCl, by the procedure of Tracy, *et al.*,[10] furnished 2-oxo-5,6-dimethyl-1,2-dihydro-3-pyridinecarboxylic acid (XVI), separated as needles from H_2O, m.p. 303° (decomp.) (reported m.p. 310~312° (decomp.)[10]). UV λ_{max} mμ (ε): 237~238 (7,270), 341 (9,180). IR ν_{max} cm^{-1}: 3430, 3145, 3040, 1712, 1647, 1603, 1554, 1514. *Anal.* Calcd. for $C_8H_9O_3N$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.30; H, 5.35; N, 8.71.

1-Acetyl-2-oxo-5,6-dimethyl-1,2-dihydro-3-pyridinecarboxamide (XXII)——XV (500 mg.) was refluxed with Ac_2O (10 ml.) for 5 hr., during which the solid gradually went into solution. The cooled solution was diluted with H_2O and the precipitate was recrystallized from AcOH to give pale yellow needles, m.p. 281° (decomp.) (reported m.p. 283~285° (decomp.)[10]). UV λ_{max} mμ (ε): 356 (12,800); shoulder 240 (7,880). IR ν_{max} cm^{-1}: 3200, 1708, 1686, 1638, 1603, 1560, 1510. *Anal.* Calcd. for $C_{10}H_{12}O_3N_2$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.55; H, 6.03; N, 13.63.

5,6-Dimethyl-2(1*H*)-pyridinethione (XVIII)——A mixture of XVII[10] (250 mg.), P_2S_5 (670 mg.) and pyridine (10 ml.) was refluxed for 4 hr., evaporated to dryness, diluted with H_2O and extracted with $CHCl_3$. Evaporation of the extract gave a residue (100 mg.) which was recrystallized from MeOH to afford XVIII as pale yellow plates, m.p. 218~224° (decomp.). UV λ_{max} mμ (ε): 283 (13,960), 371 (8,280); shoulder 230 (3,220). IR ν_{max} cm^{-1}: 3170, 1596, 1513. *Anal.* Calcd. for C_7H_9NS: C, 60.39; H, 6.52; N, 10.06; S, 23.03. Found: C, 60.52; H, 6.32; N, 9.82; S, 22.58.

2-Thioxo-5,6-dimethyl-1,2-dihydro-3-pyridinecarbonitrile (XXIII)——3-Hydroxymethylene-2-butanone prepared from its Na salt (7.3 g.) in the same manner as described for XV and cyanothioacetamide (6.0 g.) were dissolved in MeOH (60 ml.), and the solution was heated under reflux with piperidine (3.0 ml.) for 20 min. and cooled. The yellow precipitate (2.3 g.) was crystallized from MeOH to give XXIII, as yellow needles of m.p. 250~255° (decomp.). UV λ_{max} mμ (ε): 311 (20,110), 405~410 (4,350); shoulder 240 (5,520). IR ν_{max} cm^{-1}: 3155, 3090, 2220, 1584, 1510. *Anal.* Calcd. for $C_8H_8N_2S$: C, 58.50; H, 4.91; N, 17.06; S, 19.53. Found: C, 58.39; H, 5.38; N, 17.51; S, 19.54.

2-Thioxo-5,6-dimethyl-1,2-dihydro-3-pyridinecarboxylic Acid (XXIV)——XXIII (1.5 g.) in conc. HCl (30 ml.) was heated under reflux for 3 hr. and diluted with H_2O to separate a solid (1.0 g.). Recrystallization from MeOH gave XXIV as yellow needles, m.p. 288~289° (decomp.). UV λ_{max} mμ (ε): 305 (18,950), 390 (4,560); shoulder 240 (3,890). IR ν_{max} cm^{-1}: 3420, 3190, 3115, 3010, 1690, 1606, 1590, 1560. *Anal.* Calcd. for $C_8H_9O_2NS$: C, 52.43; H, 4.95; N, 7.65. Found: C, 52.44; H, 4.61; N, 7.32.

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Summary

From the ultraviolet, infrared, and nuclear magnetic resonance spectra of androstano-pyridines which were previously prepared, the structure of the ring fusion was confirmed to be androstano[3,2-*b*]pyridine. Comparison of the ultraviolet absorptions of 6′-substituted and 5′,6′-disubstituted androstano[3,2-*b*]pyridines with those of the corresponding dimethylpyridine derivatives was described.

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