[Chem. Pharm. Bull. 12 (1) 92 ~ 100] UDC 547.92.07

14. Katsujiro Ueno: Investigations on Steroids. III.[1] Pyrolytic Elimination of the Tertiary 17β-Hydroxyl Group.

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

As shown in Part I[2] of this series, pyrolysis of 6′-thioxo-17α-methyl-17β-hydroxy-1′,6′-dihydroandrostano[3,2-*b*]pyridine-5′-carboxylic acid[3] (XI) afforded the corresponding decarboxylated compound, accompanied by considerable amounts of dehydrated products. This paper is concerned with the dehydration of the above thiopyridone derivative and of a model compound, 17β-hydroxy-17α-methylandrostan-3-one.

A number of studies on the elimination of the tertiary 17-hydroxyl group have been already described. Acid-catalyzed dehydration was shown to cause Wagner-Meerwein rearrangement. Tortorella, *et al.*[4] showed that 17α-methylandrostane-3β,17β-diol (V) undergoes the rearrangement to yield 17,17-dimethyl-18-norandrost-13-en-3β-ol (VI). Similarly rearranged compounds were reported in the reaction of androstano-isoxazole-,[5] 6-chloroandrostane-,[6] and estrane-[7] series. In the 11-oxygenated steroids and in some pregnane derivatives having a bulky group at the 20-position, the double bond of the rearranged product was shown to be at the 12-position.[8] In cases where phosphorus oxychloride was used as a dehydrating agent, no rearrangement was observed. For instance, Julia, *et al.*[9] isolated the 17-exomethylene and the 17-methyl-Δ^{16} derivatives from the dehydration mixture of 17α-methylandrost-5-en-3β,17β-diol 3-acetate, while Caspi, *et al.*[10] reported that the dehydration of 4,17α-dimethylestra-1,3,5(10)-trien-17β-ol afforded exclusively the 17-exomethylene compound. Julia, *et al.*[9] on acetylating 17α-methylandrost-5-en-3β,17β-diol isolated the desired diacetate, the 17-exomethylene and 17-methyl-Δ^{16} compounds and an undetermined product. The last compound was suggested to have a rearranged structure.

In the case of the pyrolytic dehydration of 17β-hydroxy-17α-methyl-androstan-3-one (I), Ruzicka, *et al.*[11] described that vacuum distillation of the compound in the presence of copper sulfate afforded the corresponding 17-exomethylene compound (IV). The purity of their product (IV) was criticized by Sondheimer, *et al.*[12] who prepared by an unambiguous method the 17-exomethylene compound (IV), different from that of the above authors.

*1 Minamifunabori-cho, Edogawa-ku, Tokyo (上野勝次郎).

1) Part II: This Bulletin, **12**, 87 (1964).
2) Part I: *Ibid.*, **12**, 77 (1964).
3) For the nomenclature, cf. Part I of this series.
4) V. Tortorella, G. Lucente, A. Romeo: Annali di Chimica, **50**, 1198 (1960).
5) *a*) E. Caspi, D. M. Piatak: Chem. & Ind., **1962**, 1984. *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).
6) A. D. Cross, H. Carpio, H. J. Ringold: J. Med. Chem., **6**, 198 (1963).
7) R. Kirdani, R. I. Dorfman, W. R. Nes: Steroids, **1**, 219 (1963).
8) *a*) H. L. Herzog, C. C. Joyner, M. J. Gentles, M. T. Hughes, E. P. Oliveto, E. B. Hershberg, D. H. R. Barton: J. Org. Chem., **22**, 1413 (1957). *b*) N. L. Wendler, R. P. Graber, G. G. Hazen: Tetrahedron, **3**, 144 (1958). *c*) H. L. Herzog, M. J. Gentles, A. Mitchell, E. B. Hershberg, L. Mandell: J. Am. Chem. Soc., **81**, 6478 (1959). *d*) E. L. Shapiro, M. Steinberg, D. Gould, M. J. Gentles, H. L. Herzog, M. Gilmore, W. Charney, E. B. Hershberg, L. Mandell: *Ibid.*, **81**, 6483 (1959). cf. *e*) V. Tortorella, A. Romeo: Gazz. chim. ital., **92**, 1118 (1962).
9) S. A. Julia, H. Hasser: Helv. Chim. Acta, **35**, 2080 (1952).
10) E. Caspi, P. K. Grover, N. Grover, E. J. Lynde: J. Chem. Soc., **1962**, 1710.
11) L. Ruzicka, P. Meister, V. Prelog: Helv. Chim. Acta, **30**, 867 (1947).
12) F. Sondheimer, R. Mechoulam: J. Am. Chem. Soc., **79**, 5029 (1957).

In view of these facts it appeared desirable to examine the pyrolysis of I, as a model experiment. Heating I at 300~310° for an hour, followed by chromatography on alumina afforded the dehydration mixture in 20~25% yield and unchanged starting material.

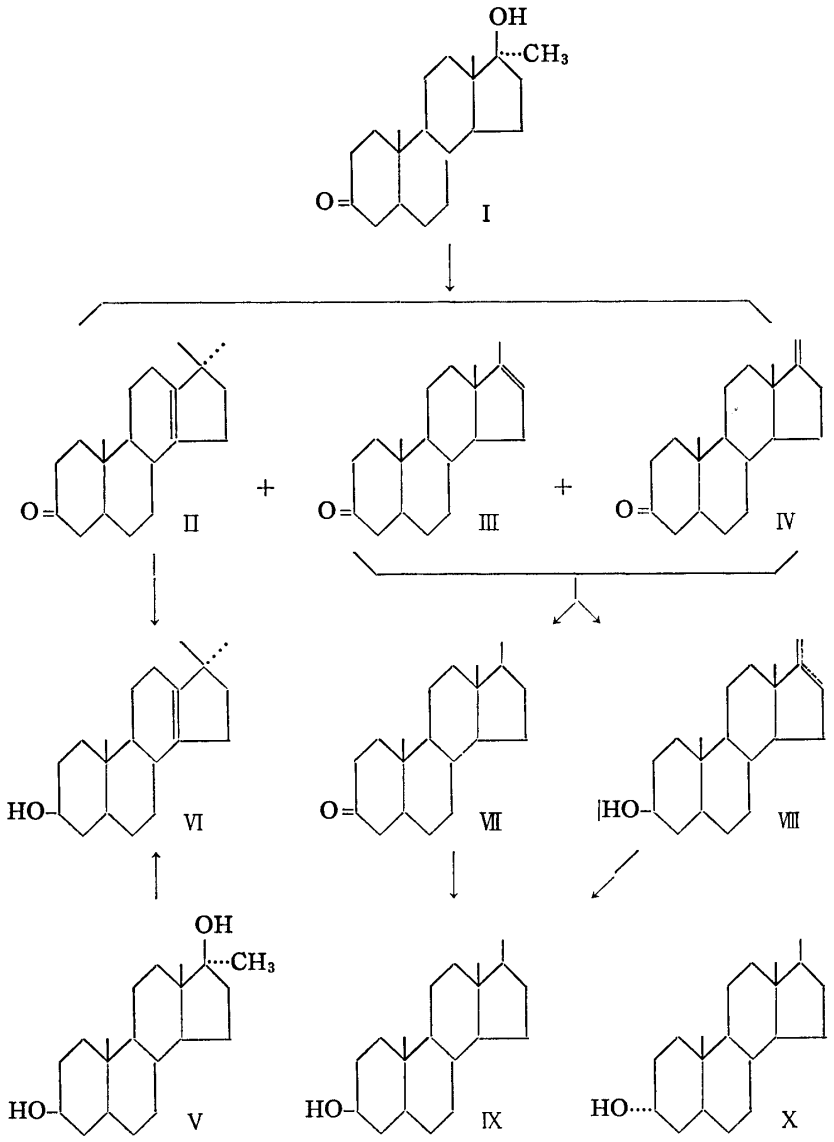


Chart 1.

The mixture was again chromatographed and two substances were isolated. The compound from the less polar fraction was proved to be 17,17-dimethyl-18-norandrost-13-en-3-one (II) in the following way. Gas chromatography of this compound indicated its homogeneity. The infrared spectrum exhibited bands at 1381 and 1355 cm^{-1} characteristic of a *gem*-dimethyl group but no band due to a di- or tri-substituted double bond. The nuclear magnetic resonance spectrum of this compound agreed well with the rearranged structure (II). In the spectrum no signal appeared in the vinyl region, which eliminated the alternative structure containing a double bond at the 12-position. The singlet equivalent to 6 protons at 9.03 τ was assigned to the *gem*-dimethyl group at the 17-position which is subjected to some deshielding because of its stereochemical relationship to the Δ^{13}-double bond. The singlet observed at 9.01 τ was assigned to the C_{19} methyl group. On catalytic hydrogenation of this compound with palladium on carbon, the unchanged material was recovered. However, after reduction with sodium borohydride, titration of

the reduced product with perbenzoic acid revealed the presence of one double bond, to which a tetrasubstituted structure was assigned. The reduced product was identified as 17,17-dimethyl-18-norandrost-13-en-3β-ol (VI) prepared by the method of Tortorella, *et al.*[4]

The apparently homogeneous product from the more polar fraction of the above chromatography was shown to be a mixture of the 17-methyl-Δ^{16} (III) and the 17-methylene (IV) compounds from the following evidence. Gas chromatography of the material indicated the presence of two components. The infrared spectrum contained bands at 3060, 1655, and 884 cm^{-1} characteristic of a terminal methylene grouping along with bands of a trisubstituted double bond at 3030, 1630, and 795 cm^{-1}. By reduction with sodium borohydride and successive hydrogenation with palladium catalyst, the mixture was converted into the known 17β-methylandrostan-3β-ol (IX), whose properties were in agreement with those reported.[9,11] A small amount of the 3α-epimer (X) was also obtained. In another experiment the mixture was first hydrogenated with palladium on carbon to 17β-methyl-3-ketone (VIII), homogeneous by gas chromatography. In the nuclear magnetic resonance spectrum of VIII two singlets, each equivalent to 3 protons, at 9.42 and 8.96 τ were assigned to the C_{18} methyl and C_{19} methyl groups respectively, and a doublet at 9.15 τ (J=4 c.p.s,) was assignable to the methyl group at the 17-position. No signal was present in vinyl region. Although the physical constants of this compound differed from those reported,[11] sodium borohydride reduction of this ketone gave the same 3β-ol (IX) as above.

Treatment of the mixture of 17-methyl-Δ^{16} (III) and 17-methylene (IV) derivatives with formic acid afforded the rearranged compound (II), indicating that this product is predominant in the acid-catalyzed reaction.

Pyrolysis in the presence of copper sulfate was also repeated. The yield of dehydrated product was increased to about 80%, and the components of the product were exactly the same as described above.

It was concluded from these results that the pyrolytic dehydration of I furnishes the rearranged compound (II),*2 17-methyl-Δ^{16} (III) and 17-methylene (IV) derivatives.

Experiments were next carried out on the androstano-thiopyridone derivative. As the pyrolysis of 6'-thioxo-17α-methyl-17β-hydroxy-1',6'-dihydroandrostano[3,2-*b*]pyridine-5'-carboxylic acid (XI) afforded an intractable decarboxylated substance, this was methylated with dimethyl sulfate in methanolic potassium hydroxide solution to give the methylthiopyridine derivative. Chromatography of the product on alumina separated the dehydration mixture from the undehydrated compound (XIII). Although the latter was not obtained in a pure crystalline state, desulfurization of the crude material with Raney nickel afforded the known 17β-hydroxy-17α-methylandrostano[3,2-*b*]pyridine (XVII), described previously.[2]

Rechromatography of the dehydration mixture and examination of the products showed analogous results as in the case of the model compound. The less polar compound exhibited infrared absorptions at 1379 and 1356 cm^{-1} characteristic of a *gem*-dimethyl group and lacked absorptions indicative of an isolated di- or tri-substituted double bond. The rearranged structure (XIV) was assigned to this compound, which was identical with that prepared by treatment of the crude undehydrated compound (XIII) with *p*-toluenesulfonic acid in acetic acid-acetic anhydride. Desulfurization of XIV with Raney nickel afforded the Δ^{13}-pyridine (XVIII).

The more polar substance was also a mixture difficult to separate. The infrared spectrum indicated the presence of both an isolated terminal methylene group (1653, 884, and 872 cm^{-1}) and an isolated trisubstituted double bond (1632, 818, and 798 cm^{-1}), showing that the mixture was composed of 17-methyl-Δ^{16} and 17-methylene derivatives (XV and

*2 For the Wagner-Meerwein rearrangement in the pyrolysis, cf. J. A. Berson. C. J. Olsen, J. S. Walia : J. Am. Chem. Soc., 84, 3337 (1962).

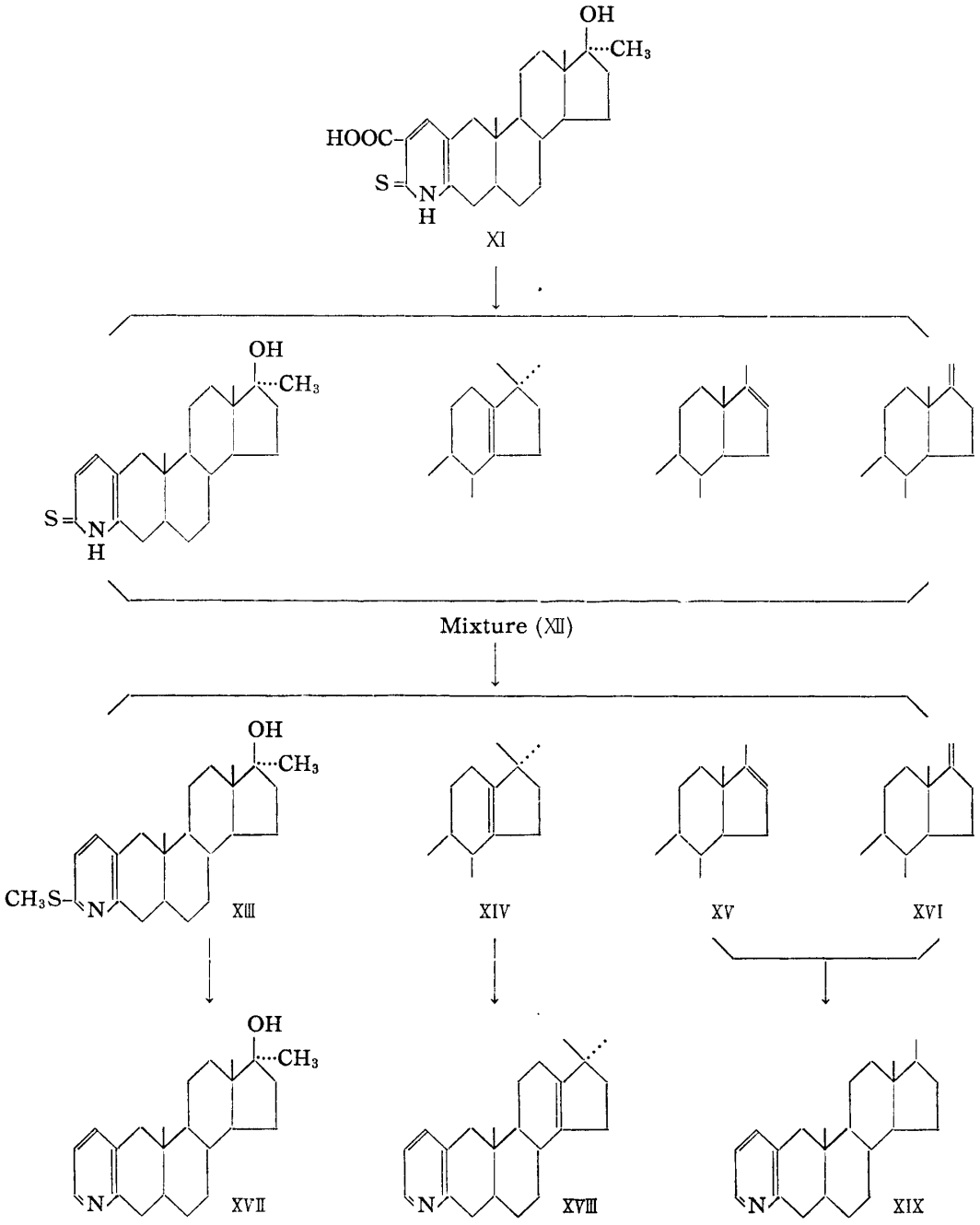


Chart 2.

XVI). Desulfurization of the mixture with Raney nickel furnished 17β-methylandrostano-[3,2-*b*]pyridine (XIX) resultant from the concurrent reduction of the isolated double bonds.

The nuclear magnetic resonance data for the two pyridines described above supported the assigned structures, XVIII and XIX. In the spectrum of XIX there were two singlets at 9.43 and 9.22 τ due to the C_{18} methyl and C_{19} methyl groups, respectively, with a doublet at 9.16 τ (J=5 c.p.s.) assignable to the methyl group at the 17-position. But, one peak of the doublet appeared at the same position as the signal of the C_{19} methyl group. Compound (XVIII) showed a spectrum distinguishable from those of XVII[2] and XIX. The spectrum contained a singlet at 9.25 τ due to the C_{19} methyl group and a strong single peak at 9.00 τ corresponding to 6 protons of the two magnetically equivalent methyl groups at the 17-position. Naturally, in all the spectra of steroidal[3,2-*b*]pyridines (XVIII, XIX) no

signal was observed in vinyl region, but these spectra exhibited at low field three characteristic signals corresponding to the three vicinal protons on the pyridine ring, which were identical with those of the pyridine (XVII).[2] Thus, it was concluded that the dehydration gave three compounds, *e.g.*, the rearranged product (XIV), 17-methyl-Δ^{16} (XV), and 17-methylene (XVI) derivatives. Analysis by gas chromatography was consistent with this result.

Table I. Ultraviolet End Absorptions of Androstane Derivatives

Substances		ε at 206 mμ in EtOH
3-Ketone series	Δ^{13} (II)	5,330
	17-methyl-Δ^{16} (III) + 17-methylene (IV)	3,790
	17β-methyl (VII)	830
3-ol series	Δ^{13} (VI)	5,200
	17-methyl-Δ^{16} + 17-methylene (VIII)	3,190
	17β-methyl (IX)	0
6′-Methylthiopyridine series	Δ^{13} (XIV)	15,300
	17-methyl-Δ^{16} (XV) + 17-methylene (XVI)	12,580
Pyridine series	Δ^{13} (XVIII)	11,430
	17β-methyl (XIX)	6,190
	17β-hydroxy-17α-methyl (XVII)	5,860

Ultraviolet end absorptions due to the double bond are compared in Table I, which provided additional support for the assigned structures. The end absorption of the Δ^{13}-compounds containing the tetrasubstituted double bond is more intense than those of mixtures of 17-methyl-Δ^{16} and 17-methylene compounds. Saturation of double bonds resulted in the decrease of intensities. In androstano-pyridine series, an additional contribution of the pyridine ring to the intensity of the end absorption is observed.

Table II.

	$[M]_D$ ($CHCl_3$) 17α-Methylandrostan-17β-ol	$[M]_D$ ($CHCl_3$) 17,17-Dimethyl-18-norandrost-13-ene	ΔM_D
[3,2-*b*]pyridine	136	0	−136
[2,3-*d*]isoxazole	119[5b]	− 23[5b]	−142
[3,2-*c*]isoxazole	108[5b]	− 31[5b]	−139
Δ^4-[2,3-*d*]isoxazole	352[5b]	121[5a]	−231
3-one	33[11]	− 25	− 58
3β-ol	− 37 (EtOH)[4]	−101	− 64
3β-ol 3-Acetate	− 63[11]	−109	− 46
Δ^5-3β-ol	−152 (EtOH)[13]	−543[4]	−391

It is of interest that the molecular rotation difference accompanied by the rearrangement of 17β-hydroxy-17α-methylandrostano[3,2-*b*]pyridine (XVII) to the Δ^{13}-compound (XVIII) is strongly negative (−136°). This shift is comparable to those observed in the corresponding androstano[2,3-*d*]isoxazole and [3,2-*c*]isoxazole compounds, respectively. On the other hand, in the case of 17β-hydroxy-17α-methylandrostane derivatives which have no heterocycles, the shift is rather small. The presence of a double bond in the 4 or 5-position causes a larger negative shift whether or not a heterocycle is fused to ring A. These results are listed in Table II.

13) K. Miescher, W. Klarer: Helv. Chim. Acta, **22**, 962 (1939).

Experimental

Melting points are uncorrected. IR spectra were taken in a KBr disc, UV spectra in EtOH. Unless otherwise stated, optical rotations were taken in $CHCl_3$ solution at ca. 20°, concn. of 1.0～1.5%. NMR spectra were measured on a JNM C.60 spectrometer (Japan Electron Optics Laboratory Co., Ltd.) at 60 Mc. using 8% solution of the compounds in deuterochloroform. Tetramethylsilane was used as an internal standard.

Gas Chromatography——Gas chromatography was carried out by using a Barber-Colman Model 10 chromatographic unit with an argon ionization detector. The U-shaped column, 6 feet × 6 mm. (int. diam.), was packed with 1% SE-30 (G.E.) silicone polymer on Anakrom ABS (70～80 mesh.). Condition A : column temperature 180°, cell temperature 180°, flash heater temperature 260°, argon gas flow rate 25 ml./min. Condition B : column temperature 200°, cell temperature 170°, flash heater temperature 270°, argon gas flow rate 110 ml./min. In condition B the relative retention times were calculated from the retention time of cholestane (25.1 min.), used as a reference compound. The results are shown in Table III.

Table III.

Compounds	Rt (Condition A) (min.)	Compounds	Rt (Condition B) (min.)	Relative Rt
I	56.18	XIV	42.95	1.71
II	23.95	Mixture XV + XVI	47.63 50.63	1.90 2.02
Mixture III + IV	28.35 30.75	XVII	31.60	1.26
VII	29.20	XVIII	14.55	0.58
		XIX	17.08	0.68

Rt : retention time

Dehydration of 17α-Methyl-17β-hydroxyandrostan-3-one (I)——i) I (1.5 g.) was placed in a 100 ml. flask equipped with an air cooler and heated in a metal bath at 300° for 1 hr. with frequent scraping of the sublimate from the inner wall. Chromatography of the reaction mixture in benzene solution over Al_2O_3 afforded the less polar dehydrated products in 18～25% yield, separated from the more polar starting material. The dehydrated products (1.48 g.) obtained by several above experiments were again adsorbed on Al_2O_3 (45 g.) and eluted with (a) petr. ether (120 ml.) and petr. ether-benzene (9:1, 110 ml.), (b) petr. ether-benzene (9:1, 190 ml. and 1:1, 50 ml.), (c) petr. ether-benzene (1:1, 140 ml.) and (d) petr. ether-benzene (1:1, 250 ml.) and benzene (100 ml.). The less polar compound (410 mg.) from fraction (b) and the more polar compound (300 mg.) from fraction (d) were collected. Compounds (690 mg.) from the middle fraction (c) were again chromatographed in a similar way, and the less polar compound (80 mg.) and the more polar compound (250 mg.) were obtained. In the chromatography the eluted substances were checked by their IR spectra.

Recrystallization of the less polar compound from Me_2CO gave 17,17-dimethyl-18-norandrost-13-en-3-one (II) as colorless needles, m.p. 135～137°, $[\alpha]_D$ −8.7°. (reported m.p. 142～143°, $[\alpha]_D$ 0°[14]). The difference from the reported value is inexplicable; however, the dehydration of I with TsOH-Ac_2O-AcOH gave the product of m.p. 137～139°, $[\alpha]_D$ −8.6°. IR ν_{max} cm^{-1} : 1716 (C=O); 1381, 1355 (*gem*-dimethyl). *Anal.* Calcd. for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found : C, 84.15; H, 10.60.

Recrystallization of the more polar compound from Me_2CO afforded needles of a mixture of 17-methylandrost-16-en-3-one (III) and 17-methyleneandrostan-3-one (IV), m.p. 138-139°, $[\alpha]_D$ +53.4°. IR ν_{max} cm^{-1} : 1715 (C=O); 3030, 1630, 795 (>C=CH-); 3060, 1655, 884 (>C=CH_2). *Anal.* Calcd. for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found : C, 84.10; H, 10.66.

ii) A mixture of I (1.0 g.) and anhyd. $CuSO_4$ (2.0 g.) was heated on a free flame under reduced pressure to reflux for about 3 min. The reaction mixture was extracted with $CHCl_3$ to give the dehydrated products in 85% yield. Chromatography of the dehydrated products in the same manner as described above afforded the crude II (270 mg.) and the crude mixture of III and IV (250 mg.), together with unseparable fraction (250 mg.). Recrystallization of the crude II from Me_2CO gave a pure sample, m.p. 136～138°. The identity was confirmed by mixed fusion, and comparison of the IR spectrum with that obtained above. *Anal.* Calcd. for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.90; H, 10.50.

Recrystallization of the crude mixture (III and IV) afforded a sample of m.p. 135～136°, $[\alpha]_D$ +54.0°. The IR spectrum of this compound was not completely identical with a sample described in i), which was attributable to different ratios of III to IV in the two samples.

14) L.H. Knox, E. Velarde, S. Berger, D. Cuadriello, A.D. Cross : Tetrahedron Letters, **1962**, 1249.

17,17-Dimethyl-18-norandrost-13-en-3β-ol (VI)——i) A solution of the 3-ketone (II) (200 mg.) obtained by dehydration without $CuSO_4$ in MeOH (5 ml.) was added to a mixture of $NaBH_4$ (40 mg.), MeOH (2 ml.), and H_2O (0.3 ml.). After standing for 30 min. at room temperature, the reaction mixture was diluted with H_2O, neutralized with AcOH, and extracted with $CHCl_3$. The extract was dried over anhyd. Na_2SO_4 and evaporated to give the crude 3β-ol (VI), which was dissolved in benzene and passed through a column of Al_2O_3. Elution with benzene-Et_2O (1:1) afforded VI, colorless plates (from Me_2CO), m.p. 133~135°. IR ν_{max} cm^{-1}: 3330, 1063, 1039 (3β-OH); 1379, 1355 (*gem*-dimethyl). *Anal.* Calcd. for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.03; H, 11.11. Acetate: m.p. 107~109°. *Anal.* Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 80.27; H, 10.63.

VI and its acetate were identified by mixed fusion and comparison of the IR spectra with an authentic sample of VI, m.p. 136~138°, $[\alpha]_D$ −35° (EtOH), and that of the acetate, m.p. 110~111°, $[\alpha]_D$ −30°, respectively, which were prepared according to the method of Tortorella, *et al.*[*2,4]

ii) The $NaBH_4$ reduction in the same manner of the ketone (II), which was obtained by the dehydration in the presence of $CuSO_4$, afforded VI, m.p. 133.5~135°, $[\alpha]_D$ −38° (EtOH). *Anal.* Calcd. for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.18; H, 11.09. Acetate: m.p. 107~109°. *Anal.* Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 80.02; H, 10.61. The 3β-ol (VI) and its acetate were identified in the same manner with samples obtained above.

17β-Methylandrostan-3-one (VII)——i) A mixture of III and IV (140 mg.), which was obtained by dehydration without $CuSO_4$, in MeOH (20 ml.) was hydrogenated over 20% Pd/C (100 mg.). After removal of the catalyst, evaporation of the solvent gave an oily residue, the IR spectrum of which did not contain any band near 1700 cm^{-1}, but exhibited four strong bands from 1200 to 1050 cm^{-1}. This indicated a ketal formation at the 3-position. The oily residue was heated under reflux in MeOH (2 ml.)-H_2O (1 ml.) in the presence of HCl (10%, 1 drop) for 30 min. to give VII, m.p. 142~143° (from Me_2CO), $[\alpha]_D$ +37°. IR ν_{max} cm^{-1}: 1716 (C=O). *Anal.* Calcd. for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.47; H, 11.03.

ii) A mixture of III and IV, obtained by the dehydration in the presence of $CuSO_4$, was reduced in the same manner to give VII, m.p. 141~142°, $[\alpha]_D$ +35°. *Anal.* Calcd. for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.31; H, 11.19.

The identity of the above two samples was confirmed by mixed melting point determination and comparison of the IR spectra. (Ruzicka, *et al.*[11] reported VII, m.p. 130~132°, $[\alpha]_D$ +31.6°).

Reduction of the Mixture (III and IV) with Sodium Borohydride. Formation of the Mixture (VIII)——i) A mixture (III and IV) (340 mg.) produced by the dehydration without $CuSO_4$ was dissolved in MeOH (10 ml.) and treated with a solution of $NaBH_4$ (80 mg.) in MeOH (10 ml.) and H_2O (0.5 ml.). After standing at room temperature for 1 hr., the solution was evaporated, and the residue was diluted with H_2O, neutralized with AcOH and extracted with $CHCl_3$. The product was chromatographed on Al_2O_3. Elution with benzene-Et_2O, followed by recrystallization from Me_2CO gave the mixture (VIII), m.p. 118~123.5°. IR ν_{max} cm^{-1}: 3320 (OH); 1077, 1039 (3β-OH); 1005 (3α-OH); 3070, 1655, 875 (17-exomethylene); 3030, 1630, 795 (Δ^{16}).

ii) A mixture (III and IV) obtained by the dehydration with $CuSO_4$ was treated in the same manner as described in i) to give the mixture (VIII), m.p. 122~127°, whose IR spectrum was almost identical with that obtained above.

17β-Methylandrostan-3β-ol (IX) and its 3α-Epimer (X)——i) A mixture (VIII) (240 mg.) described in i) of the preceding paragraph was submitted to catalytic reduction in MeOH in the presence of Pd/C. The benzene solution of the reduced mixture was passed through a column of Al_2O_3 (6.0 g.) and eluted with benzene-Et_2O (9:1). This afforded at first a small amount of 3α-ol (X) (30 mg.) and then the major product, 3β-ol (IX) (140 mg.). Recrystallization of the crude IX from Me_2CO afforded a pure sample as needles of m.p. 138~140°, $[\alpha]_D$ 0°. (reported m.p. 138~139°, $[\alpha]_D$ +5.8°;[9] m.p. 139~141°, $[\alpha]_D$ +6.2°[11]). $[\alpha]_D$ did not completely coincide with those reported. IR ν_{max} cm^{-1}: 3300, 1082, 1043, 1039 (3β-OH). *Anal.* Calcd. for $C_{20}H_{34}O$: C, 82.69; H, 11.80. Found: C, 82.51; H, 11.82.

Recrystallization of the crude X from Me_2CO gave needles, m.p. 168~171°. IR spectrum showed that this contained 3α-hydroxyl group. The m.p. was not agreed with a reported value (m.p. 184~186°[11]), but scarcity of the material prevented further examination. IR ν_{max} cm^{-1}: 3280, 1030, 1001 (3α-OH). *Anal.* Calcd. for $C_{20}H_{34}O$: C, 82.69; H, 11.80. Found: C, 82.57; H, 11.60.

ii) A mixture (VIII) (250 mg.) described in ii) of the preceding paragraph was treated in the same manner as described above to give the crude 3β-ol (IX) (120 mg.) and the crude 3α-ol (X) (20 mg.).

Purification of IX afforded needles of m.p. 139~140.5°, $[\alpha]_D$ 0°. The IR spectrum was superimposable with that of a sample obtained above. *Anal.* Calcd. for $C_{20}H_{34}O$: C, 82.69; H, 11.80. Found: C, 82.48; H, 11.87.

---

*2 Tortorella, *et al.* reported VI, m.p. 130~132°, $[\alpha]_D$ −35.9° (EtOH), but its acetate was not specified by them.

Recrystallization of the crude X gave needles of m.p. 171.5~173°. The IR spectrum was identical with that obtained above.

iii) VII (35 mg.) was reduced with $NaBH_4$ (15 mg.) in MeOH (3 ml.). After working-up in the same manner as described above, 3β-ol (IX) of m.p. 140.5~141.5° and a small amount of 3α-ol (X) of m.p. 171~173° were obtained. The identity of the two samples was confirmed, respectively, by mixed fusion and comparison of the IR spectra with the samples obtained above.

Methylation of the Decarboxylated Mixture (XII) and Separation of the Methylthiopyridine Derivatives (XIII~XVI)——6′-Thioxo-17α-methyl-17β-hydroxy-1′,6′-androstano[3,2-*b*]dihydropyridine-5′-carboxylic acid (XI) was decarboxylated as described in Part I of this series. The decarboxylated mixture (XII) (1.4 g.) was dissolved in a solution of KOH (630 mg.), MeOH (60 ml.), and H_2O (6 ml.), and treated with Me_2SO_4 (1.42 g.). After shaking for 10 min. at room temperature, H_2O (150 ml.) was added to precipitate the product, which was filtered and dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried over anhyd. Na_2SO_4, passed through a column of Al_2O_3 (90 g.), and eluted with $CHCl_3$. The earlier fractions gave the semicrystalline dehydrated mixture (XIV~XVI) (300 mg.) and the later fractions afforded the crude non-crystallizable viscous oil of XIII (1.4 g.).

The dehydrated mixture (XIV~XVI) (1.29 g.) obtained by repetition of the above reaction was dissolved in petr. ether, chromatographed on Al_2O_3 (60 g.) and eluted with petr. ether containing increasing amount of benzene.

From the petr. ether-benzene (19:1) eluate, 230 mg. of the Δ^{13}-fraction, followed by 140 mg. of a mixture (XIV, XV, XVI) was obtained. From the petr. ether-benzene (4:1) eluate, 340 mg. of a mixed fraction (XV and XVI) was gained. Further elution with petr. ether-benzene (4:1) gave also 150 mg. of an impure mixture (XV and XVI), in which the 17-methylene (XVI) appeared to be predominant.

Several recrystallization of the crude Δ^{13}-fraction from Me_2CO afforded colorless needles of 6′-methylthio-17,17-dimethyl-18-norandrost-13-eno[3,2 *b*] pyridine (XIV), m.p. 144.5~147°. UV λ_{max} mμ (ε): 249~250 (13,600), 302 (8,800). IR ν_{max} cm^{-1}: 3040, 1581, 1556, 807 (pyridine);.1379, 1356 (*gem*-dimethyl). *Anal.* Calcd. for $C_{24}H_{33}NS$: C, 78.42; H, 9.05; N, 3.81. Found: C, 78.67; H, 8.92; N, 3.97.

Recrystallization of the mixed fraction (XV and XVI) from Me_2CO gave a mixture of 6′-methylthio-17-methylandrost-16-eno[3,2-*b*]pyridine (XV) and 6′-methylthio-17-methyleneandrostano[3,2-*b*]pyridine (XVI) as colorless needles, m.p. 152~154°. UV λ_{max} mμ (ε): 249~250 (12,700), 302 (8,300). IR ν_{max} cm^{-1}: 3065, 1653, 884, 872 (>C=CH_2, XVI); 3030, 1632, 818, 798 (>C=CH-, XV); 1583, 1558, 807 (pyridine).

Preparation of 6′-Methylthio-17,17-dimethyl-18-norandrost-13-eno[3,2-*b*]pyridine (XIV) from XIII——A solution of the crude XIII (1.0 g.) in Ac_2O (75 ml.) and AcOH (45 ml.) was heated with *p*-TsOH·H_2O (600 mg.) on a water bath at 100° for 1 hr., and evaporated under reduced pressure. The residue was treated with dil. Na_2CO_3 and extracted with $CHCl_3$. The extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to dryness. Chromatography on Al_2O_3 (30 g.) in benzene solution gave pale yellow crystals of XIV (730 mg.), m.p. 125~140°. Recrystallization from Me_2CO-MeOH afforded 460 mg. of XIV as colorless needles, m.p. 144~146°, $[\alpha]_D$ +23°. The identity was confirmed by mixed melting point determination and comparison of IR and UV spectra with the product (XIV) obtained above.

17β-Hydroxy-17α-methylandrostano[3,2-*b*]pyridine (XVII)——Desulfurization of the crude oil (XIII) (1.5 g.) with Raney Ni and working-up in the usual manner gave crude crystals (740 mg.) of m.p. 190~192°, which was recrystallized to give XVII, identical with an authentic sample described previously.[2]

17,17-Dimethyl-18-norandrost-13-eno[3,2-*b*]pyridine (XVIII)——To a solution of XIV (460 mg.) in dimethylformamide (25 ml.) and EtOH (10 ml.) was added Raney Ni W-4 (6 ml.), and the mixture was heated under reflux for 1.5 hr. After removal of the reducing agent, evaporation under reduced pressure gave an oily residue, which was dissolved in petr. ether and chromatographed on Al_2O_3 (22 g.). The petr. ether-benzene (4:1) eluate gave needles of XVIII, m.p. 79.5~82°, after crystallization from cold Me_2CO, $[\alpha]_D$ 0°. UV λ_{max} mμ (ε): 268.5 (5,900), 276.5~277 (4,600). IR ν_{max} cm^{-1}: 3040, 1575, 793, 730 (pyridine); 1384, 1357 (*gem*-dimethyl). *Anal.* Calcd. for $C_{23}H_{31}N$: C, 85.92; H, 9.72; N, 4.36. Found: C, 85.85; H, 9.74; N, 4.35.

17β-Methylandrostano[3,2-*b*]pyridine (XIX)——A solution of the mixture (XV and XVI) (410 mg.) in dimethylformamide-EtOH (1:1, 40 ml.) was heated under reflux with freshly prepared Raney Ni W-4 (6 ml.) for 2 hr. Filtration of the reducing agent and evaporation of the solvent in vacuum gave a crystalline residue, which was crystallized from Me_2CO to give XIX as colorless needles of m.p. 155~157°, $[\alpha]_D$ +65°. UV λ_{max} mμ (ε): 268.5 (5,600), 276.5 (4,500). IR ν_{max} cm^{-1}: 3040, 1575, 792, 731 (pyridine). *Anal.* Calcd. for $C_{23}H_{33}N$: C, 85.39; H, 10.28; N, 4.33. Found: C, 85.09; H, 10.01; N, 4.43.

The author wishes to express his deep gratitude to Professor Dr. T. Okamoto and Dr. M. Natsume, University of Tokyo, for giving facilities for NMR spectral measurement, and to Dr. J. Shinoda, Chairman of the Board of Directors, and Dr. T. Ishiguro, President of this Company, for their kind encouragements. The author is grateful to Dr. M. Shimizu, Director, and Dr. G. Ohta of this Laboratory for their kind and unfailing guidances throughout the course of this work. The author is also

indebted to Dr. F. Uchimaru for gas chromatography, and to Mr. B. Kurihara and Miss K. Hanawa for elemental analyses.

Summary

Pyrolysis of androstane derivatives which contain 17β-hydroxy-17α-methyl grouping was shown to afford three kinds of dehydration products : 17-methyl-Δ^{16}, 17-methylene, and 17,17-dimethyl-18-nor-Δ^{13}-compounds. The last compound was formed by a Wagner-Meerwein type rearrangement.

(Received August 24, 1963)

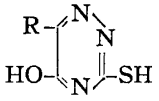
[Chem. Pharm. Bull. 12 (1) 100 ~ 103]

UDC 615.778 : 547.837

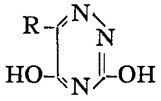
15. Takeo Ueda and Mitsuru Furukawa : Syntheses and Antiviral Effects of 3-Amino-6-alkyl-*as*-triazin-5-ol Derivatives.

(*Pharmaceutical Institute, Keio-Gijuku University*[*1])

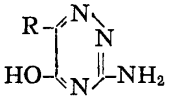
As described in the previous report,[1] our group found that several compounds of 3-mercapto-6-alkyl-*as*-triazin-5-ol (I) and 6-alkyl-*as*-triazin-3,5-diol (II) showed antiviral activities against the PR-8 strain of influenza virus.



I



II



III

From the view of the relationship between the antiviral activity and the structure of these series, it is suggested that the simultaneous existence of alkyl groups of optimum carbon length and hydroxyl or mercapto group might be necessary for the generation of antiviral activity.

On the other hand, 3-amino-*as*-triazine is known to inhibit the biosyntheses of riboflavine,[2] adenine, histidine,[3] chlorophyll[4] etc. and antagonize the activities of tyrosinase, lactoperoxidase, carboxylic acid peroxidase etc.[5] Particularly, it is of interest that this agent inhibits the incorporation of phosphate in the process of nucleic acid biosynthesis.[6] This fact suggests that this agent might be worthy to be screened as an inhibitor of virus nucleic acid synthesis. Such the action of this agent may be due to the existence of amino group at 3-position of *as*-triazine ring. This assumption prompted the authors to conceive an idea to replace hydroxyl or mercapto group at 3-position in the series of I and II with amino group.

Thus, compounds of 3-amino-6-alkyl-*as*-triazin-5-ol (III) were synthesized and examined as to their antiviral activity.

This report is concerned with the synthesis and antiviral activity of 3-amino-6-alkyl-*as*-triazin-5-ol.

---

*1 Shinano-machi, Shinjuku-ku, Tokyo (上田武雄, 古川 潮).

1) T. Ueda, I. Nakata : Yakugaku Zasshi, **80**, 1068 (1960).
2) K. A. Sund, H. N. Little : Science, **132**, 622 (1960).
3) F. W. Weyter, H. P. Broquist : Biochim. et Biophys. Acta, **40**, 567 (1960).
4) H. T. Pyform, D. Appleman, W. G. Heim : Plant Physiol, **32**, 674 (1957).
5) P. Castelfranco : Biochim. et Biophys. Acta, **41**, 485 (1960).
6) D. J. Wort, B. C. Loughman : Can. J. Botany, **39**, 339 (1961).