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Steroids. III. Alumina-Induced Reactions of Steroidal Oxime Acetates[1]

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An alumina-induced reaction of 6-acetoximino-3β-acetoxycholestan-5α-ol nitrite (I) is examined and affords several kinds of compounds. Among them II, III and IV are belong to the same type of compound. From the spectral data and their reactions, the structures containing 5α,6α-epoxy and 6β,7β-isonitrosoimino groups are tentatively assumed for them. V and VI are identified to be another type containing 5α-acetoxy and 6-oxo groups. The formation pathways of both types of compounds are deduced by comparison with the reaction products of the relative compounds.

Various kinds of chemical transformations are known to occur on alumina.[3] During our studies on steroids, we found a series of interesting reactions of steroidal oxime acetates on alumina under the conditions of chromatography. We now wish to report rearrangement reactions of 6-acetoximinocholestanes on alumina.

When allowed to remain on a column of neutral alumina (Grade III) for 48 hr and eluted with several kinds of solvents (see Experimental), 6-acetoximino-3β-acetoxycholestan-5α-ol nitrite (I) afforded compound (II), $C_{29}H_{46}O_4N_2$, compound (III), $C_{29}H_{46}O_4N_2$, compound (IV), $C_{27}H_{44}O_3N_2$, compound (V), $C_{31}H_{50}O_5$, and compound (VI), $C_{29}H_{48}O_4$.

V and VI were identified as 3β,5α-diacetoxycholestan-6-one[1] and 5α-acetoxycholestan-3β-ol-6-one,[1] respectively, by infrared (IR) and nuclear magnetic resonance (NMR) spectral comparison, and mixed melting point.

When allowed to stand in acetic acid at room temperature, II was quantitatively converted into an α,β-unsaturated aldehyde (VII), $C_{29}H_{46}O_3$, whose IR spectrum showed the absorptions at 2725 (CHO), 1735 (OAc), 1680 (CHO), and 1600 cm^{-1} (C=C), and NMR spectrum (CCl_4) showed the signals at δ 9.90 s (CHO), 4.67 m (W_H=24, 3α-H), 3.47 q (J=14 and 4, 4α-H), 2.00 s (3β-OAc), and 0.97 s (10β-Me). 2.4-Dinitrophenylhydrazone of VII was identified with an authentic sample of 2,4-dinitrophenylhydrazone of 3β-acetoxy-6-formyl-B-norcholest-5-ene.[4] Catalytic reduction of II over Adams' platinum in a mixed solvent of benzene and methanol, also, afforded 3β-acetoxy-6-formyl-B-norcholest-5-ene. Both reactions, in conclusion, were resulted in losing N_2O unit.

An upper part of the mass spectrum of II is recorded in Table I. The pattern of fragmentation below *m/e* 382 is the same as that of VII. This fact exhibits that the structure of II has a N_2O group, which is eliminated in the fragmentation process to remain an α,β-unsaturated aldehyde function in the B ring. The IR spectrum of II shows the absorptions at 1735 (OAc), 1690 and 1600 cm^{-1} (>N-NO). The NMR spectrum (CCl_4) of II shows the signals at δ 4.83 q (J=8 and 4, 7α-H,)[5] 4.57 m (W_H=24, 3α-H), 3.23 q (J=16 and 4, 4α-H), 2.00 s (3β-OAc), and 1.00 s (10β-Me). From these spectral data, the structure shown in Chart 1, *i.e.*, 3β-acetoxy-5α,6α-epoxy-6β,7β-isonitrosoiminocholestane, is tentatively assumed for II.

1) Part II: M. Onda and A. Azuma, *Chem. Pharm. Bull.* (Tokyo), **20**, 1467 (1972).
2) Location: *Minato-ku, Tokyo, 108, Japan.*
3) U.S. Joshi, N.P. Damadaran, and S. Dev, *Tetrahedron*, **24**, 5817 (1968) and references cited therein.
4) K. Tanabe, R. Hayashi, and R. Takasaki, *Chem. Pharm. Bull.* (Tokyo), **9**, 1 (1961); J.W. Cornforth, G.D. Hunter, and G. Popjak, *Biochem. J.*, **54**, 590 (1953).
5) Quartet splitting may be due to long range coupling with some proton.

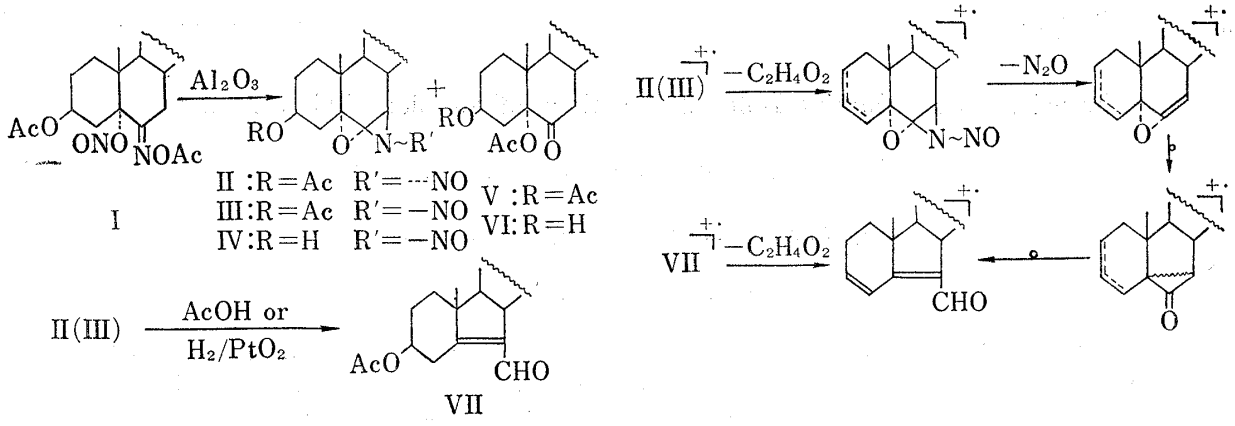

Chart 1

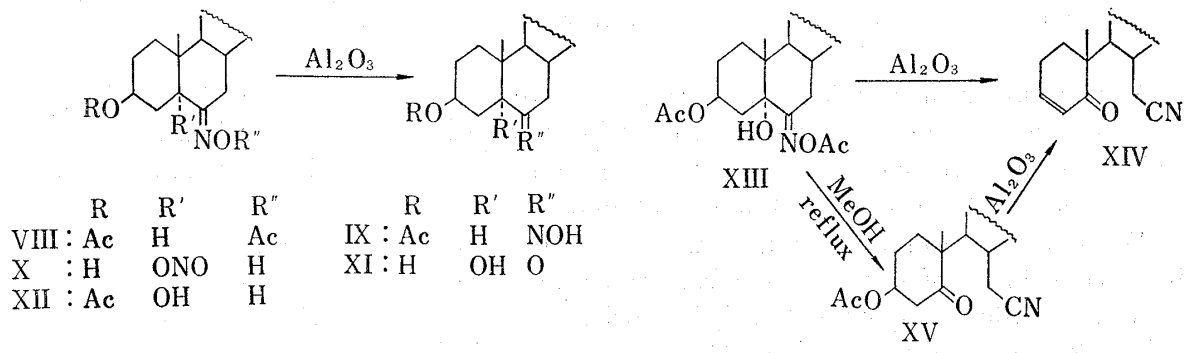

Chart 2

TABLE I. Partial Mass Spectra of II, III and VII[a]

m/e	Transition	Relative intensity II	III	VII[b]
426	M-$C_2H_4O_2$	100	100	
382	M-($C_2H_4O_2$+N_2O)	50	45	78
367	M-($C_2H_4O_2$+N_2O+Me)	21	12	20
353	M-($C_2H_4O_2$+N_2O+CHO)	59	40	88
269	M-($C_2H_4O_2$+N_2O+C_8H_{17})	20	9	19

a) These compounds did not show the peaks due to the molecular ions.
b) The base peak corresponded to *m/e* 18.

III is an isomer of II from the IR, NMR and mass spectra. Treatment of III with acetic acid, also, afforded VII. On the basis of the chemical shift of 10β-Me (III: δ 1.17), NO groups in II and III will be assigned *anti* and *syn*, respectively, to 10β-Me. IV was obtained during chromatographic purification of III. Its IR and NMR spectra show that IV is 3β-OH derivative of III resulted from hydrolysis of 3β-OAc groups.

In order to consider the formation pathways of II and III, chromatography of the relative compounds was examined under the same condition. 6-Acetoximino-3β-acetoxy-5α-cholestane (VIII) and 6-hydroximinocholestane-3β,5α-diol 5-nitrite (X) afforded an oxime (IX) and a diolone (XI), respectively. These reactions are the simple hydrolyses of acetoximino, hydroximino, and nitrite groups. 6-Hydroximino-3β-acetoxycholestan-5α-ol (XII) did not react on alumina. 6-Acetoximino-3β-acetoxycholestan-5α-ol (XIII) afforded a syrupy compound (XIV), $C_{27}H_{43}ON$, in a good yield. Its IR spectrum shows the absorptions at 2240 (CN) and 1676 cm^{-1} (CO), and NMR spectrum ($CDCl_3$) shows the signals for two vinyl

protons at δ 6.00 d (J=8) and 6.80 bd (J=8). These spectral data suggest that XIV is 6-cyano-5,6-secocholest-3-en-5-one. On the other hand, refluxing a solution of XIII in methanol quantitatively gave a cyanoketone (XV), $C_{29}H_{47}O_3N$, whose IR spectrum exhibited the absorptions at 2240 (CN), 1745 (OAc), and 1710 cm^{-1} (CO), and NMR spectrum (100 MHz, $CDCl_3$) had the signals at δ 5.42 bs (W_H=8, 3α-H) and 2.00 s (3β-OAc). These data are consistent with 3β-acetoxy-6-cyano-5,6-secocholestan-5-one[6] for XV. XV was also converted quantitatively into XIV by treatment with alumina.[7] It can be seen that an abnormal Beckmann rearrangement of XIII on alumina or in methanol is exclusively driven by 5α-OH group.

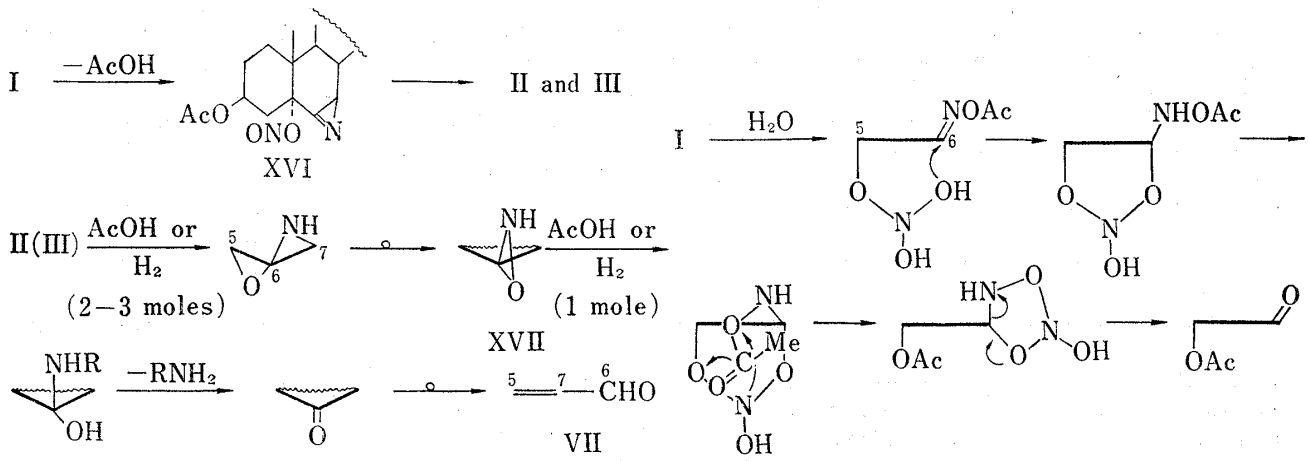

Chart 3

Chart 4

From above results, VIII, X, XII, and XIII-type compounds can be excluded from intermediates in the formation of II and III. As shown in Chart 3, I eliminates acetic acid to give an azirine (XVI) *via* the first step of the Neber rearrangement,[8] in which 5α-ONO group adds to the double bond of the azirine group to afford II and III. The formation pathways of VII by acetic acid and catalytic reduction are depicted in Chart 3. The first step would be acetolysis or hydrogenolysis of the nitrite group to afford an aziridine which rearranges to a spiro-oxaziridine (XVII). After acetolysis or hydrogenolysis XVII would be converted into a cyclopropanone which rearranges to VII.

It seems that the acetyl groups in 5α-OAc in V and VI migrate from 6=NOAc group and VIII, X, XII, and XIII-type compounds are, also, not intermediates in the formation of V and VI. Since 5α-ONO group was easily hydrolyzed (X→XI), the first step would be hydration at the double bond of 5α-ONO group and the successive steps are considered to be similar to that of the compounds containing 5α-OAc group from I by catalytic reduction[1] (Chart 4).

Experimental

Melting points were determined on a micro hot-stage and were uncorrected. Ultraviolet (UV) spectra were measured with a Hitachi EPS-2U. IR spectra were measured with a JASCO IR-G in carbon tetrachloride. NMR spectra were taken on a Varian HA-100 and T-60. Mass spectra were taken on a JEOL's

6) E. Zbrial, G. Nestler, and K. Kischa, *Tetrahedron*, **26**, 1427 (1970).
7) The chemical shift and half-height width of 3α-H in XV represent the characteristics of an equatorial proton attached to acetoxy-substituted carbon in cyclohexane systems. Since a study of the solvent-induced shift in the 100 MHz NMR spectrum of XV leads to "axial" methyl group ($\delta_{CDCl_3}-\delta_{C_6D_6}$=0.18 ppm) at C-10, it is considered that the A ring in XV does not exist in the chair form but in a flexible or twisted boat-like conformation. The facile elimination of acetic acid from the A ring in XV on alumina may be attributed to the location of the carbonyl group at β-position to acetoxyl group and the axial-like orientation of 3β-OAc group.
8) L.G. Donaruma and W.Z. Heldt, *Organic Reactions*, **11**, 45 (1960).

JMS-01SG. Exact mass measurements were performed by using the appropriate perfluorokrrosene peaks as refence masses. All spectra were determined at the lowest possible source temperature (100 to 160°) using the direct inlet system with an electron energy of 75 eV.

Reaction of 6-Acetoximino-3β-acetoxycholestan-5α-ol Nitrite (I) on Alumina——A solution of I (3.0 g) in *n*-hexane–benzene (1: 1) (10 ml) was remained on a column of neutral alumina (grade III) (150 g) for 48 hr. Elution with *n*-hexane–benzene (1: 1) afforded 3β-acetoxy-5α,6α-epoxy-6β,7β-isonitrosoiminocholestane (II) (384 mg) as colorless needles of mp 177—179° from methanol. UV: λ_{max}^{EtOH} 225 (ε 6350) and 292 mμ (ε 6770). *Anal.* Calcd. for $C_{29}H_{46}O_4N_2$: C, 71.57; H, 9.53; N, 5.76. Found: C, 71.23; H, 9.59; N, 5.64. The next fraction gave crude III (110 mg), whose re-chromatography gave III (56 mg) as colorless needles of mp 140—142° from methanol and IV (37 mg) as colorless needles of mp 185—191°. III, IR: 1740 (OAc), 1705 and 1610 cm^{-1} (>N-NO). NMR (CCl_4): δ 4.53 m (3α-H and 7α-H), 3.07 q (J=16 and 4, 4α-H), 2.00 s (3β-OAc), and 1.17 s (10β-Me). *Anal.* Calcd. for $C_{29}H_{46}O_4N_2$: C, 71.57; H, 9.53; N, 5.76. Found: C, 70.98; H, 9.53; N, 5.80. IV, IR: 3400 (OH), 1705 and 1610 cm^{-1} (>N-NO). NMR ($CDCl_3$): δ 4.63 q (J=8 and 3, 7α-H), 3.60 m (W_H=24, 3α-H), 3.00 q (J=16 and 4, 4α-H), and 1.20 s (10β-Me). *Anal.* Calcd. for $C_{27}H_{44}O_3N_2$: C, 72.93; H, 9.97; N, 6.30. Found: C, 73.04; H, 10.08; N, 6.25. Mass Spectrum: Calcd. for $C_{27}H_{44}O_3N_2$: mol. wt., 444.335. Found: M^+, 444.332. The following fraction, further, gave 3β,5α-diacetoxycholestan-6-one (V) (158 mg) as colorless needles of mp 175—178° from methanol, which was identified with an authentic sample[1] by mixed melting point, and IR and NMR spectral comparison. The final fraction eluted with chloroform gave 5α-acetoxycholestan-3β-ol-6-one (VI) (812 mg) as colorless needles of mp 181—183° from methanol, which was identified with an authentic sample[1] by mixed melting point, and IR and NMR spectral comparison.

Reaction of 6-Acetoximino-3β-acetoxy-5α-cholestane (VIII) on Alumina——A solution of VIII (130 mg) in chloroform (7 ml) was treated with neutral alumina (Grade III) (7 g) as described above. Elution with benzene–chloroform (1: 1) gave 6-hydroximino-3β-acetoxycholestane (IX) (92 mg) as colorless needles of mp 198—200° from methanol, which was identified with an authentic sample[9] by mixed melting point, and IR and NMR spectral comparison.

Reaction of 6-Hydroximinocholestane-3β,5α-diol 5-nitrite (X) on Alumina——A solution of X (100 mg) in chloroform–methanol (9: 1) (10 ml) was treated with neutral alumina (Grade III) (6 g) as described above. Elution with chloroform–methanol gave 3β,5α-dihydroxycholestan-6-one (XI) (41 mg) as colorless needles of mp 228—232° from chloroform, which was identified with an authentic sample[10] by mixed melting point, and IR and NMR spectral comparison.

6-Cyano-5,6-secocholest-3-en-5-one (XIV)——(1) A solution of 6-acetoxyimino-3β-acetoxycholestan-5α-ol (XIII) (860 mg) in *n*-hexane–benzene (1: 1) (2 ml) was treated with neutral alumina (Grade III) (45 g) as described above. Elution with *n*-hexane–benzene (1: 1) gave XIV (554 mg) as a syrup. Mass Spectrum Calcd. for $C_{27}H_{43}ON$: mol. wt., 397.334. Found: M^+, 397.331.

(2) A solution of 3β-acetoxy-6-cyano-5,6-secocholestan-5-one (XV) (143 mg) in *n*-hexane–benzene (1:1) (0.7 ml) was treated with neutral alumina (7 g) as described above. Elution with *n*-hexane–benzene (1:1) gave a syrupy compound (125 mg), which was identified as XIV by IR and NMR spectral comparison.

3β-Acetoxy-6-cyano-5,6-secocholestan-5-one (XV)——A solution of XIII (213 mg) in methanol (6 ml) was refluxed for 4 hr. After evaporation *in vacuo*, the residue was recrystallized from *n*-hexane to afford colorless needles (184 mg) of mp 95—97°. *Anal.* Calcd. for $C_{29}H_{47}O_3N$: C, 76.10; H, 10.35; N, 3.06. Found: C, 75.87; H, 10.25; N, 2.92.

3β-Acetoxy-6-formyl-B-norcholest-5-ene (VII)——(1) A solution of II (98 mg) in acetic acid (16 ml) was allowed to stand for 24 hr at room temperature. The reaction mixture was poured into ice-water and extracted with benzene. The benzene layer was washed with aq. Na_2CO_3 and water. The benzene residue afforded colorless needles (87 mg) of mp 128—129° from methanol. UV: λ_{max}^{EtOH} 253.5 mμ (ε 10400). *Anal.* Calcd. for $C_{29}H_{46}O_3$: C, 78.68; H, 10.47. Found: C, 78.48; H, 10.28. Mass Spectrum Calcd. for $C_{27}H_{42}O$: mol. wt., 382.323. Found: M^+-$C_2H_4O_2$, 382.325. 2,4-Dinitrophenylhydrazone: mp 208—209°. UV: λ_{max}^{EtOH} 384 mμ (ε 25,550). *Anal.* Calcd. for $C_{35}H_{50}O_6N_4$: C, 67.50; H, 8.09; N, 9.00. Found: C, 67.23; H, 8.13; N, 8.92. It was identified with an authentic sample[4] by mixed melting point and UV spectral comparison.

(2) A solution of III (38 mg) in acetic acid (6 ml) was allowed to stand for 3 days at room temperature. Work-up afforded VII (17 mg), mp 128—129°, and 6-formyl-B-norcholesta-3,5-diene (12 mg), whose 2,4-dinitrophenylhydrazone, mp 260—262°, was identified with an authentic sample[4] by mixed melting point and UV spectral comparison.

(3) A solution of II (500 mg) in benzene (20 ml) and methanol (30 ml) was hydrogenated over platinum black obtained from PtO_2 (100 mg) at room temperature and H_2 (100 ml) was absorbed during 2 hr. After filtration, the filtrate was evaporated *in vacuo*. The residue was recrystallized from methanol to give colorless needles of mp 128—129°.

9) J. Barnett, B.E. Dyman, and F. Smith, *J. Chem. Soc.*, **1946**, 528.
10) L.F. Fieser and S. Rajagopa, *J. Am. Chem. Soc.*, **71**, 3938 (1949).