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Steroids. VI.[1] Alumina-Induced Reaction of 3β,5α-Diacetoxy-6-nitriminocholestane

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The compounds obtained from alumina-induced reaction of 3β,5α-diacetoxy-6-nitriminocholestane (3) are revised as 3β-acetoxy-6-Nα-, 7α- (4) and 7β-O-(Nβ-oxido)diazoxy-cholest-5-ene (5) the basis of their spectral data. Formation pathways of the oxadiazoles (4) and (5) from the nitrimine (3) and conversion pathways of the oxadiazoles (4) and (5) into 3β-acetoxy-6-formyl-B-nor-cholest-5-ene (8) are briefly examined.

We previously reported that 3β-acetoxycholest-5-ene reacted with sodium nitrite in the presence of acetic acid and conc. sulfuric acid to give the O-nitrite (**1**),[3] the alumina-induced reaction of which afforded the N-nitrite (**2**) assigned tentatively by its spectral data and chemical reactions.[4] Quite recently, we have revised the structure of **1** as the nitrimine (**3**) by another synthetic route.[5] Accordingly, the structure of **2**, which was deduced on the basis of the incorrect structure for **1**, should be revised. In this paper we report structural revision of **2**.

As reported already, on remaining over an alumina column for 48 hr and elution with benzene-hexane **3** gave two isomeric oxadiazoles (**4**) and (**5**) along with two ketones (**6**) and (**7**).[4] From their molecular formulae, it is clear that **4** and **5** were resulted by the loss of

Table I. ^{13}CNMR Data of **4** and Related Compounds[a)]

C	4	A[b)]	B[c)]	C	4	A[b)]	B[c)]
1	36.3	35.6	37.6	16	39.1	40.1	40.4
2	27.4	27.5	28.5	17	55.2	56.4	56.9
3	71.3	73.9	74.0	18	12.0	12.1	12.3
4	31.5	34.1	38.7	19	16.9	12.1	19.6
5	136.8	44.8	140.2	20	36.3	35.9	36.4
6	140.4	28.7	122.9	21	18.7	18.7	19.2
7	77.1	32.1	32.5	22	36.3	36.3	37.0
8	37.2	35.6	32.5	23	23.8	23.9	24.6
9	49.3	54.4	50.7	24	39.6	39.6	40.1
10	35.8	36.8	37.0	25	28.1	28.1	28.5
11	21.3	21.5	21.6	26	22.9	22.6	23.0
12	28.3	28.3	32.8	27	22.9	22.9	23.2
13	43.8	42.7	42.8	Me	21.3	21.2	19.9
14	50.9	56.5	57.3	CO	170.5	171.1	d)
15	24.9	24.3	24.9				

a) δ_C, ppm from tetramethylsilane ($CDCl_3$); Off-resonance technique was employed for assignments of each carbon.
b) A: 3β-acetoxy-5α-cholestane
c) B: 3β-acetoxycholest-5-ene; Original data converted using $\delta_C^{CS_2}$ 192.8 (dioxane) (H.J. Reich, M. Jautelat, M.T. Messe, F.J. Weigert, and J.D. Roberts, *J. Am. Chem. Soc.*, **91**, 7445 (1969)).
d) Figure is not described.

1) Part V: M. Onda and K. Takeuchi, *Chem. Pharm. Bull.* (Tokyo), 23, 677 (1975).
2) Location: *Minato-ku, Tokyo 108, Japan.*
3) M. Onda and A. Azuma, *Chem. Pharm. Bull.* (Tokyo), 20, 1467 (1972).
4) M. Onda and K. Takeuchi, *Chem. Pharm. Bull.* (Tokyo), 21, 1287 (1973).
5) M. Onda, Y. Konda, and R. Yabuki, *Chem. Pharm. Bull.* (Tokyo), 23, 611 (1975).

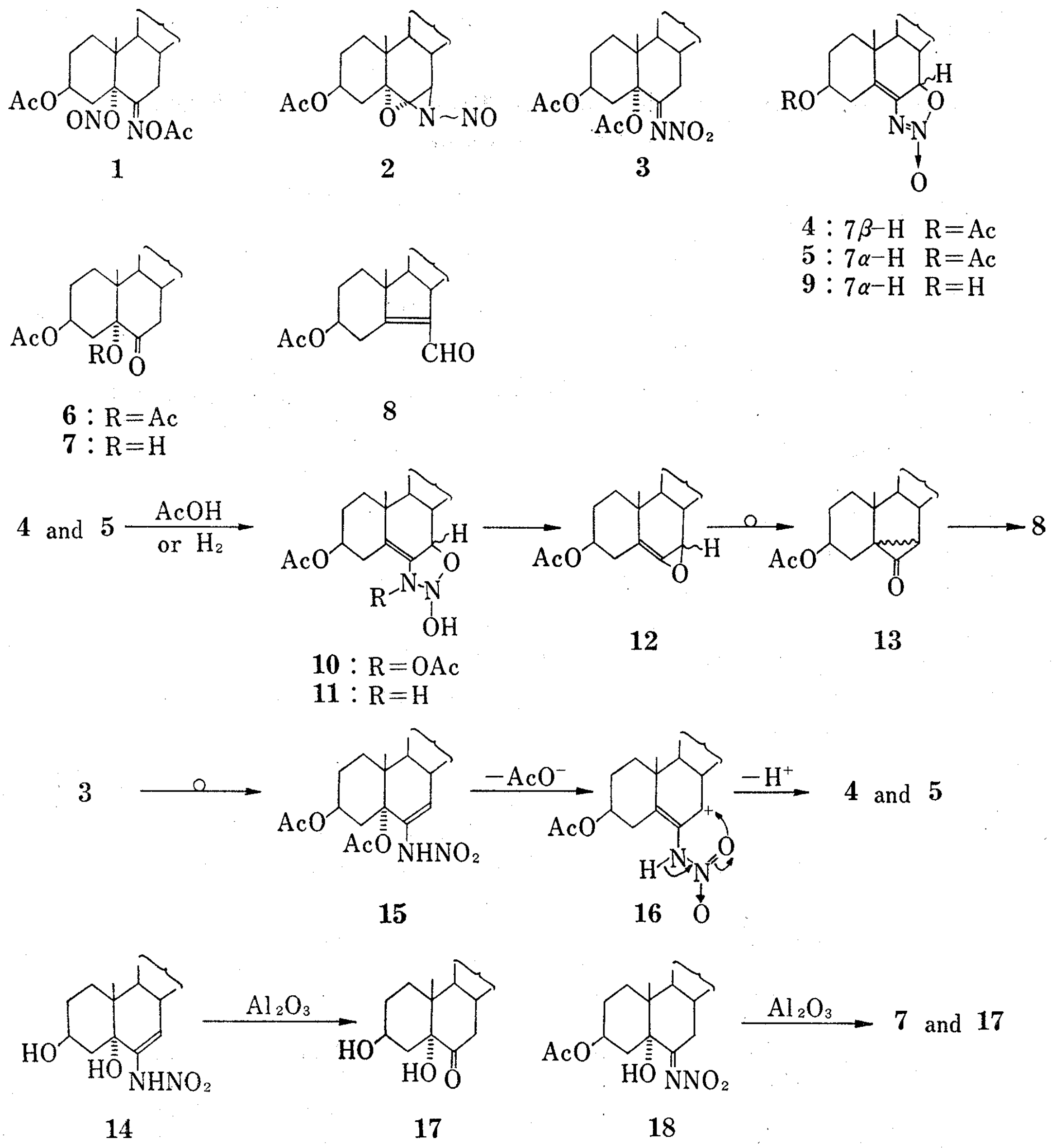

Chart 1

acetic acid from 3. That the acetic acid detached from 3 originates in the 5α-OAc group is confirmed by the nuclear magnetic resonance (NMR) spectra of 4 and 5 showing no signal for the 5α-OAc group. On treatment with acetic acid and hydrogenation over platinum oxide in benzene-methanol 4 and 5 afforded the aldehyde (8) by the loss of an N_2O unit.[4] Accordingly, 4 and 5 possess the substituent which liberates easily an N_2O unit to leave an oxygen function in the B ring. This is supported by the mass spectra of 4 and 5 which exhibit the same fragmentation pattern as that of 8 after the loss of an N_2O unit.[4]

On examination of the ^{13}CNMR data of 4 and the related compounds it can be seen that the carbons except the C-5, -6, and -7 are surely assignable (Table I). The carbons for the singlets at δ 136.8 and 140.4 correspond to those in a tetrasubstituted olefin and the one for the doublet at δ 77.1 corresponds to the tertiary with a hetero substituent. From these results, it is considered that 4 possesses the structure in which the double bond exists at the 5- and 6-positions and the 2-oxido-1,2,3-oxadiazole ring derived from the 6=NNO_2 group in 3 fuses at the 6- and 7-positions. Since the circular dichroism (CD) curves of 4 and 5 are closely of mirror image (Fig. 1), both compounds should be the stereoisomers at the 7-position. Examination of the Dreiding models displays that the 7α- and 7β-isomers have a twisted boat conformation and half chair one of the B ring, respectively. In the former the 7β-H is axial-like and close to the 10β-Me group, being expected to show a lower chemical shift and similar splitting pattern in the NMR spectrum compared to the 7α-H (axial) in the latter. The 10β-Me group in the 7β-isomer may be influenced by the *cis*-fused heterocycle to display a lower chemical shift than that of the 10β-Me group in the 7α-isomer. If these deductions are correct, from comparison of the NMR data of **4**, **5**, and the carbinol (**9**)[4] obtained from **5** (Table II), **4** and **5** can be assigned as 3β-acetoxy-6-Nα-,7α- and 7β-O-(Nβ-oxido)-diazoxychlest-5-ene, respectively.[6]

Formation of **8** from **4** and **5** by acetic acid and catalytic reduction may be explained as follows. The first steps would be addition of acetic acid and hydrogenation to give the hydroxylhydrazines (**10**) and (**11**), respectively, which collapse to **8** *via* the unstable intermediates (**12**) and (**13**).

The nitrimine (**3**) is known to rearrange to the nitramine (**14**).[7] The first step in formation of **4** and **5** would be rearrangement of **3** to the nitramine (**15**). The nitramine

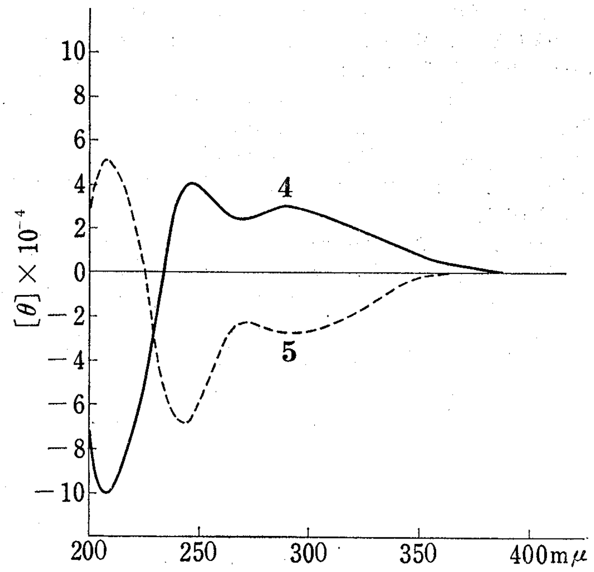

Fig. 1. CD Curves of **4** and **5**

Table II. NMR Data of **4**, **5**, and **9**[a)]

	3α-H	4α-H	7-H[d)]	3β-OAc	10β-Me
4[b)]	4.57, bs W_H 24	3.23, q J 16 and 4	β: 4.83, q J 8 and 4	2.00, s	1.00, s
5[b)]	4.53, bs	3.09, q J 16 and 4	α: *e*)	2.00, s	1.17, s
9[c)]	3.60, bs W_H 24	3.00, q J 16 and 4	α: 4.63, q J 8 and 4		1.20, s

a) δ, ppm from tetramethylsilane; J and W_H in Hz.
b) solvent; CCl_4
c) solvent; $CDCl_3$
d) Quartet splitting may be due to long range coupling with some proton.
e) This signal overlaps on that for the 3α-H.

(**15**) would eliminate acetate ion to give the carbonium ion (**16**) which affords nonstereoselectively **4** and **5**. As is clear from the Dreiding models, **4** is more sterically compressed and unstable than **5**. However, the product ratio of **4** and **5** was *ca.* 4:1.[4] In order to explain the predominant formation of **4**, it might be reasonable to consider that concerted allylic rearrangement of **15** to **4** occurrs concurrently. By the same procedure as employed for **3**, **14** gave the ketone (**17**) and no compound corresponding to **4** and **5**.[4] The difference in the chemical behaviors of **14** and **15** can be understood by the difference in abilities of the hydroxyl and acetoxy groups as leaving group. That formations of **6** and **7** from **3** are due to simple hydrolyses is confirmed by that the nitrimine (**18**) gave the ketones (**7**) and (**17**) in good yields by the same procedure employed for **3**.

6) The structure of **4** was confirmed by the X-ray analysis. This datum will be presented elsewhere.
7) The nitramine (**14**) was incorrectly assigned in lit.[3,4] and revised correctly in lit.[5]

Experimental

Melting points were determined on a micro hot-stage and are uncorrected. Ultraviolet (UV) spectra were measured with a Hitachi EPS-2U. Infrared (IR) spectra were taken on a JASCO IR-G. NMR spectra were measured on a Varian T-60. ^{13}CNMR spectra were taken on a JEOL JNM PS-100/PFT-100 at 25.1 MHz. CD curves were taken on a JASCO J-20.

The Oxadiazoles (4), (5), and (9)——**4**: Colorless needles of mp 177—179° (from methanol). UV λ_{max}^{EtOH} mμ (ε): 225 (6350), 292 (6770). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735 (OAc), 1690 (C=C), 1600 (N=N). CD (c=0.002, dioxane) $[\theta]^{26}$ (mμ): +288 (30538) (positive maximum), +266 (24812 (negative maximum), +245 (39126) (positive maximum), −208 (104019) (negative maximum). **5**: Colorless needles of mp 140—142° (from methanol). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1740 (OAc), 1705 (C=C), 1610 (N=N). CD (c=0.002, dioxane) $[\theta]^{26}$ (mμ): −292 (28629) negative maximum), −269 (22903) (positive maximum), −244 (68710) (negative maximum), +208 (50578) (positive maximum). **9**: Colorless needles of mp 186—190° (from methanol). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3400 (OH), 1705 (C=C), 1610 (N=N).

Reaction of 3β-Acetoxy-6-nitriminocholestan-5α-ol (18) on Alumina——A solution of **18** (330 mg) in benzene–hexane (1: 1) (1 ml) was remained on a column of neutral alumina (grade III) (15 g) for 48 hr. The eluate of benzene-chloroform (9: 1) gave 3β-acetoxy-5α-hydroxycholestan-6-one (7) (135 mg) which was recrystallized from benzene-hexane to give colorless needles of mp 229—232° and was identified with an authentic sample[3] by mixed mp, IR and NMR spectra. The eluate of chloroform–methanol (97: 3) afforded 3β,5α-dihydroxycholestan-6-one (**17**) (122 mg) as colorless needles of 230—234° which was identified with an authentic sample[3] by mixed mp, IR and NMR spectra.