[Chem. Pharm. Bull.
19(10)2116—2125(1971)]

UDC 547.92.04 : 546.284.04 : 546.621.04

Linear Steroid Analogues. IV.[1] Cyclization Reaction of 8,9-Seco-5α-androstane-8,9,11-trione Derivatives with Al_2O_3 and SiO_2

SADAO AOYAMA, KAZUO KAMATA, and TAICHIRO KOMENO

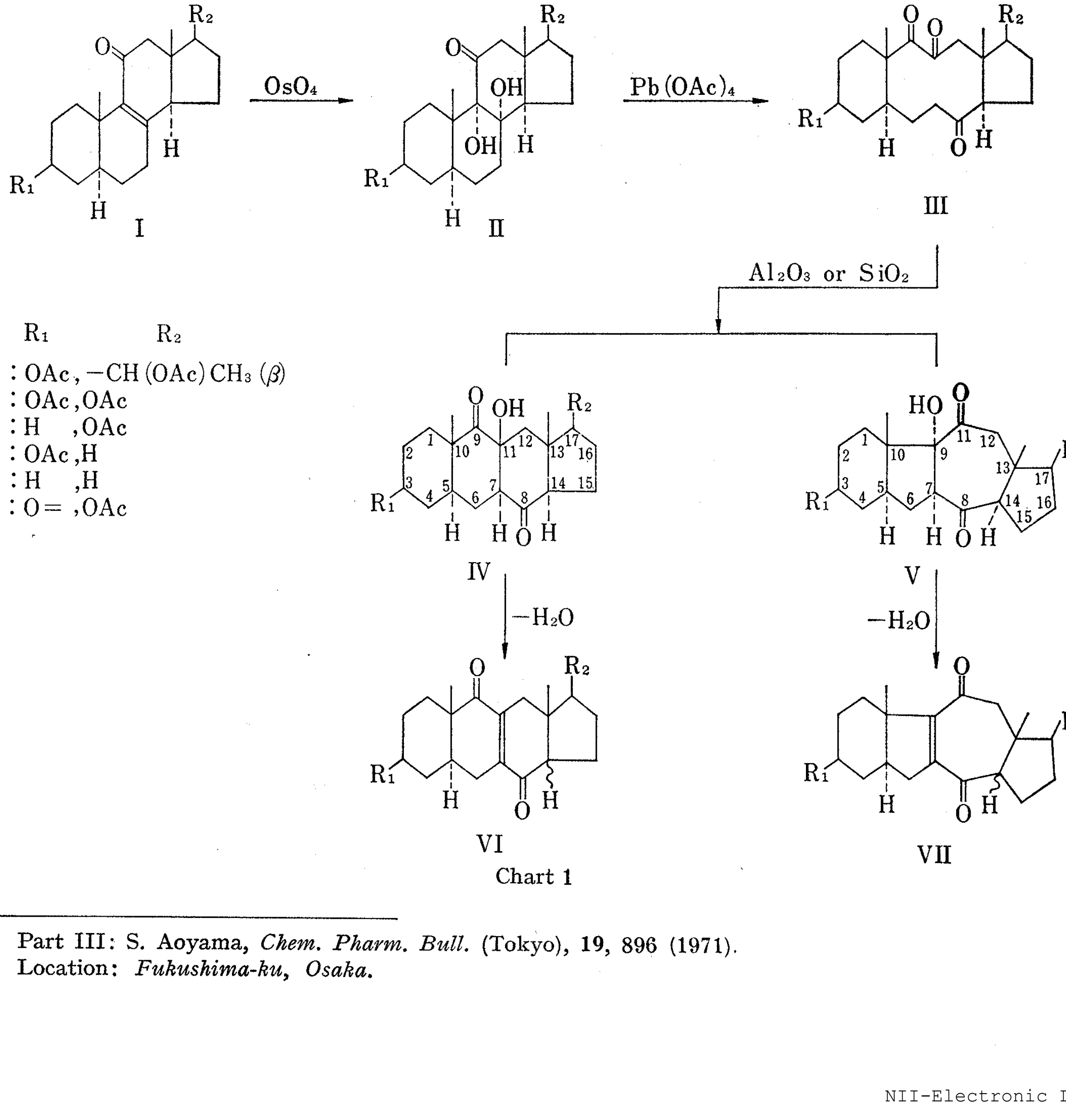
Shionogi Research Laboratory, Shionogi & Co., Ltd.[2]

(Received April 10, 1971)

8,9-Seco-5α-androstane-8,9,11-trione derivatives (III) were cyclized with Al_2O_3 or SiO_2 in CH_2Cl_2 or CH_3CN affording the diketo-ols (IV and V) and their dehydrated products, ene-diones (VI and VII). Introduction of substituents into the 3- and 17- positions of the triketone (III) caused systematic changes in the ratios of the cyclization products.

Al_2O_3 and SiO_2 showed a significantly different effects on the cyclizations, and solvent change also affected the cyclizations. These results are reported and interpreted in terms of a specific adsorption of substrate on the surface of the catalyst from a speculative view. The configuration of the BC ring junction of the diketo-ols (V), hitherto the only unresolved aspect of their structure, was assigned *α-cis* from the associated evidence of their circular dichroism, nuclear magnetic resonance and infrared spectra.

We have recently reported the cyclization[1] of 3β,20β-diacetoxy-8,9-seco-5α-pregnane-8,9,11-trione (IIIa) in benzene with Al_2O_3, affording predominantly the diabeosteroid (diketo-



	R_1	R_2
a	OAc	$-CH(OAc)CH_3$ (β)
b	OAc	OAc
c	H	OAc
d	OAc	H
e	H	H
f	O=	OAc

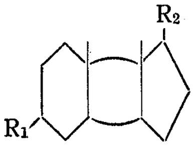
Chart 1

---

[1] Part III: S. Aoyama, *Chem. Pharm. Bull.* (Tokyo), 19, 896 (1971).

[2] Location: *Fukushima-ku, Osaka.*

TABLE I



Compds	Substituents		mp, °C	$[\alpha]_D$	Formula	Analyses			
						Calcd.		Found	
	R_1	R_2				C	H	C	H
IIIb	OAc	OAc	179—181	+34.4	$C_{23}H_{32}O_7$	65.69	7.67	65.48	7.73
IIIc	H	OAc	141—143	+58.7	$C_{21}H_{30}O_5$	69.58	8.34	69.47	8.15
IIId	OAc	H	117—118	+64.1	$C_{21}H_{30}O_5$	69.58	8.34	69.66	8.32
IIIe	H	H	150—155	+104.4	$C_{19}H_{28}O_3$	74.96	9.27	74.91	9.43
IIIf	O=	OAc	149—154	+66.1	$C_{21}H_{28}O_6$	67.00	7.50	67.12	7.56
IVb	OAc	OAc	264—268	−27.0	$C_{23}H_{32}O_7$	65.69	7.67	65.81	7.90
IVc	H	OAc	270—273	−29.6	$C_{21}H_{30}O_5$	69.58	8.34	69.73	8.31
IVd	OAc	H	230—233	−29.7	$C_{21}H_{30}O_5$	69.58	8.34	69.78	8.30
IVe	H	H	278—280	−45.5	$C_{19}H_{28}O_3$	74.96	9.27	75.02	9.18
IVf	O=	OAc	244—246	+ 8.7	$C_{21}H_{28}O_6$	67.00	7.50	67.18	7.64
Vb	OAc	OAc	199—200	+14.2	$C_{23}H_{32}O_7$	65.69	7.67	65.90	7.91
Vc	H	OAc	189—191	+26.6	$C_{21}H_{30}O_5$	69.58	8.34	69.77	8.50
Vd	OAc	H	196—202	+27.1	$C_{21}H_{30}O_5$	69.58	8.34	69.86	8.42
Ve	H	H	185—188	+34.9	$C_{19}H_{28}O_3$	74.96	9.27	75.00	9.35
Vf	O=	OAc	186—188	+75.4	$C_{21}H_{28}O_6$	67.00	7.50	65.49[a)]	7.77
VIb-14α	OAc	OAc	170—173	−98.7	$C_{23}H_{30}O_6$	68.63	7.51	69.01	7.58
VIb-14β	OAc	OAc	199—202	−67.7	$C_{23}H_{30}O_6$	68.63	7.51	68.84	7.80
VIIb-14α	OAc	OAc	174—176	−17.1	$C_{23}H_{30}O_6$	68.63	7.51	68.90	7.81
VIIb-14β	OAc	OAc	139—143	+ 6.6	$C_{23}H_{30}O_6$	68.63	7.51	68.38	7.71

a) recalcd. for $C_{21}H_{28}O_6\cdot\frac{1}{2}H_2O$: C, 65.41; H, 7.59. This is proved by inspection of the IR spectrum ($CHCl_3$), showing clearly bands due to H_2O at 3676 cm^{-1} and 1603 cm^{-1}.

ol IVa), and with SiO_2, affording a mixture of IVa (60%) and the abeosteroid (diketo-ol Va) (40%). In the course of efforts to improve yields of the desired products and to vary the ratio of cyclization products, the catalytic actions of Al_2O_3 and SiO_2 have been studied. In the present work, the effects on the cyclization of functionalities at the 3- and 17-positions of the triketone (III) in the 5α-androstane series, and the influence of factors on the ratio of the cyclization products are discussed. Arguments for the stereochemistry of the products are also presented.

The triketones (IIIb—IIIf) were prepared1) by Criegee oxidation of the keto-diols (IIb—IIf), available from the corresponding enones (Ib—If) by osmium tetroxide oxidation. Cyclization of these triketones was effected by treating them with 10 times their weight of Al_2O_3 (Woelm neutral Grade II) or SiO_2 (Merck HR) in CH_2Cl_2 or CH_3CN, termination of the reaction being indicated by disappearance of the yellow color of the starting triketones. Prolongation of the reaction time caused dehydration of the primary products, diketo-ols (IV and V), yielding the ene-diones (VI and VII). The ratios of the products (IV and V) were obtained directly by thin-layer chromatography (TLC) separation but the ene-dione fractions were subjected to gas liquid chromatography (GLC) analysis because of their poor separation on TLC.

Structural Studies on the Cyclization Products

The structures of these cyclization products were determined from their physical constants and spectral data listed in Tables I and II, corresponding data for the compounds possessing a pregnane side chain being used for comparison.

TABLE II

Compds	IR $\nu_{\max}^{CCl_4}$ cm^{-1}	UV $\lambda_{\max}^{EtOH}$ (ε)	NMR (τ) $CDCl_3$				
			18-H	19-H	OAc	12-H_2(J)	3,17-H (J, Hz)
IIIb	1740, 1712, 1685, 1238 1028, 906	222 287 434 (1914) (57) (33)	8.93	8.77	7.98 7.93	7.68(12) 6.72	5.50—4.92, m (2H)
IIIc	1745, 1711, 1683, 1238 1030, 904	219 290 434 (1862) (76) (32)	8.95	8.83	7.95	7.62(13) 6.79	4.99, t (8) (1H)
IIId	1741, 1709, 1690 (infl) 1684, 1240, 1028, 906	219 290 434 (1840) (84) (38)	8.93	8.78	7.97	7.67(12) 6.69	5.50—5.08, m (1H)
IIIe	1710, 1683, 1390, 1140 907, 595	219 285 436 (1886) (70) (37)	8.95	8.83	—	7.60(13) 6.73	—
IIIf	1745, 1725, 1714, 1687 1239, 1030	222 290 434 (1666) (100) (36)	8.90	8.57	7.93	7.73(12) 6.63	5.17, t (8) (1H)
IVb	[a]3581, 3406, 1730, 1030	[a]307 329(sh) (66) (33)	9.00	8.68	7.98 7.97		5.83—5.00, m (2H)
IVc	[a]3580, 3385, 1729, 1709 1032	[a]308 (64)	9.00	8.73	7.97		5.13, t (8) (1H)
IVd	[a]3586, 3425, 1723, 1708(infl), 1033	[a]310 (45)	9.08	8.68	7.98		5.67—5.15, m (1H)
IVe	[a]3567, 1724, 1705	[a]310 (69)	9.08	8.72	—		—
IVf	[a]3580, 3430, 1730, 1714 1033	[a]300 (82)	8.98	8.52	7.93		5.10, t (8) (1H)
Vb	3574, 3455, 1735, 1713 1240, 1027	301 (52)	9.33	9.25	7.97 7.95	7.55(12) 6.75	5.83—4.93, m (2H)
Vc	[a]3566, 1739(infl.), 1735 1713, 1705, 1064, 1026 960	300 (52)	9.32	9.30	7.93	7.53(12) 6.75	5.13, t, (8) (1H)
Vd	3564, 1726, 1711, 1028	300 (44)	9.33	9.25	7.97	7.48(11) 6.73	5.50—5.17, m (1H)
Ve	3576, 3480, 1714, 1705 1388, 1211, 961	300 (44)	9.33	9.30	—	7.52(12) 6.88	—
Vf	[a]3556, 3430, 1731, 1712 1125, 1025	300 (55)	9.32	9.07	7.93	7.53(12) 6.72	5.08, t, (8) (1H)
VIb-14α	1740, 1696, 1690(infl.) 1684, 1238, 1028	261 320 376 (10054) (74) (41)	9.20	8.98	7.98 7.95		5.50—4.83, m (2H)
VIb-14β	1746, 1682, 1240,1028,	264 330 388 (10435) (68) (36)	8.96	8.96	7.97 7.95		5.50—4.83, m (2H)
VIIb-14α	3015(infl.), 1742, 1669 1574, 1236, 1028	263 338 (9087) (182)	9.12	8.92	7.97 7.94	7.20, 2H, s	5.47—4.95, m (2H)
VIIb-14β	1738, 1671, 1592, 1240 1026	265 334 (6906) (186)	8.88	8.92	7.98 7.95	7.53(13) 7.30	5.83—5.00, m (2H)

[a] Measured in $CHCl_3$.

Although crucial evidence is lacking, one of the likely conformations for the triketones (IIIb—IIIf) can be depicted in Chart 2 on the basis of the physical data at hand. The ultraviolet (UV) spectra in Table II, exhibiting dual n—π^* bands at 285—290 and 434—436 mμ, indicate that the α-diketone groupings adopt *trans*-coplanar forms.[3] This is consistent with the observed dipole moment (μ=2.6 D[4]) which corresponds to one carbonyl. It would appear that the triketones (IIIb—IIIf) assume the same conformation even on change of the substituents at the 3- and 17-positions, because of resemblance of their spectral properties as are observed in Table II and Fig. 1. As seen in Table II, the most distinct differences between the diketo-ols (IVb—IVf) and (Vb—Vf) are in their nuclear magnetic resonance (NMR) spectra; the 10- and 13-angular methyl signals of the former compounds appear at a

---

[3] S.F. Mason, *Quart. Rev.* (London), **15**, 287 (1961).
[4] This is observed for the diketo-ol (Ve).

lower field than those of the latter and only in the latter compounds do the 12-methylene proton signals appear as an AB type quartet at τ 7.7—6.6.

The stereochemistry of the BC ring junction of the diketo-ols (V), hitherto the only point of ambiguity in their structures, has been assigned *α-cis* from the following arugument. Among the four possible configurations for the BC ring junction; 9β-7β, 9β-7α, 9α-7β and 9α-7α, the first two can be excluded because the circular dichroism (CD) spectra[5] of the diketo-ols (V) show an apparent[6] positive Cotton effect ($[\theta]_{312-315\ m\mu}$ +9000) and because the infrared (IR) spectrum (ν 3576 cm^{-1}, a weekly H-bonded hydroxyl band) indicates that the hydroxyl is axial with respect to the 11-carbonyl group. This is also supported by the NMR substituent effect[7] of the hydroxyl group on the angular methyl groups, shown by conversion of the diketo-ol (Vb) to the enedione (VIIb-14α) (*cf.* Chart 2). While in the conversion of IVb to VIb-14α in the 6,6 ring system, the 10- and 13-angular methyl chemical shifts exhibit clear proximity effects of the C_{11}-hydroxyl group on these methyl groups, supporting the β-configuration, in the corresponding conversion of Vb to VIIb-14α, no such effect of the hydroxyl group in question is observed. Of the remaining two possibilities, 9α-7β and 9α-7α, inspection of the NMR spectrum of the keto-diol (VIII), obtained by the partial reduction of Vb with $NaBH_4$, favors the latter form. The proton on the carbon bearing the newly formed hydroxyl group resonates at τ 6.08 as a doublet[8] (J=3.0 Hz). The coupling constant of 3 Hz is in accord with the 7α- and 8α-H configuration.[9] The newly formed hydroxyl group exerts a profound proximity effect both on the 10- and 13-angular methyl chemical shifts supporting its β-configuration. This agrees with the finding that the hydroxyl group resisted acetylation. Observation of an AB type quartet lines due to C_{12}-methylene protons in the keto-diol (VIII) proves that the carbonyl group reduced is at the 8-position and the

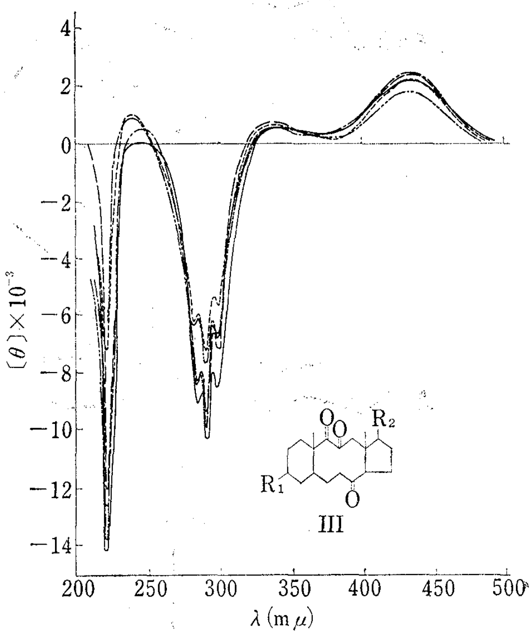


Fig. 1. CD Curves (Dioxane Solution) of the Triketones (IIIb—f)

IIIb: ——— IIIe: ·········
IIIc: —··— IIIf: —·—
IIId: - - - -

---

[5] See Experimental.

[6] As there are two carbonyl groups in the molecules, the observed values for [θ] are only apparent ones.

[7] N.S. Bhacca and D.H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, London, Amsterdam, 1964.

[8] This coupling pattern was initially disturbed by further coupling with the hydroxyl hydrogen, however, addition of D_2O revealed it as a doublet.

[9] For all the possible configurations at the C_7 and the C_8, the dihedral angles between H_7 and H_8, and H_8 and H_{14} are:

Configuration at		$\phi_{H_7-H_8}$ (°)	$\phi_{H_8-H_{14}}$ (°)
C_7–H	C_8–H		
α	α	65— 55	80—100
α	β	180—160	120—140
β	α	180—140	70— 0
β	β	10— 70	180—135

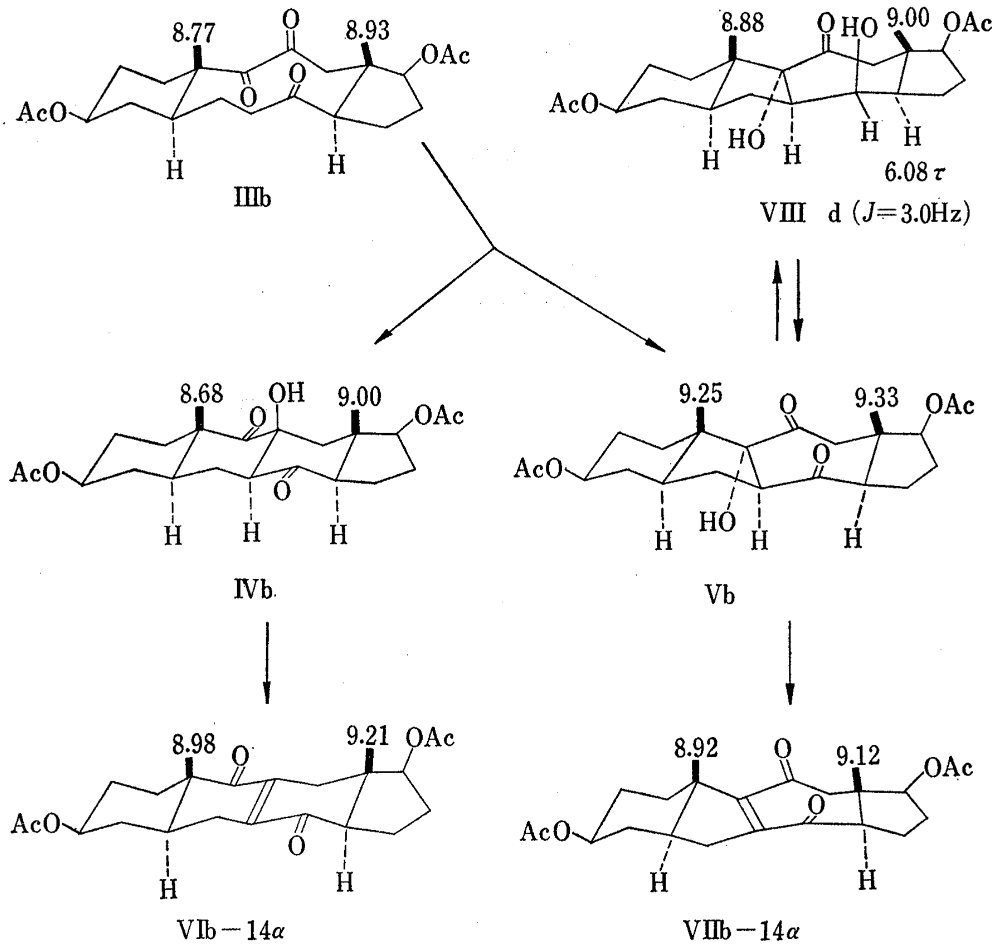


Chart 2

The figures on the angular methyl groups show the chemical shifts (τ).

Table III. Effect of the Substituents on the Ratio of the Cyclization Products

Triketone III	R_1	R_2	[Al_2O_3-grade II]					
			CH_2Cl_2			CH_3CN[a]		
			Reaction time	IV (6,6)	V (5,7)	Reaction time	IV (6,6)	V (5,7)
e	H	H	80 (min)	96 (%)	4 (%)	30 (min)	95 (%)	5 (%)
c	H	OAc	30	88	12	10	94	6
d	OAc	H	10	70	30			
f	O=	OAc	10	70	30			
b	OAc	OAc	45	60	40	10	91	9
			[SiO_2]					
e	H	H	26 (hr)	60	40			
c	H	OAc	1.5	50	50			
d	OAc	H	3	37	63			
f	O=	OAc	0.5	30	70			
b	OAc	OAc	1.5	21	79	30 (min)	66	34

[a] Cyclizations of triketones with catalysts in CH_3CN were carried out in a manner similar to those described for CH_2Cl_2.

retained configurations at the neighboring junctions are confirmed by the recovery of the original diketo-ol (Vb) on careful oxidation.

Effects Influencing the Cyclization Products

As is seen in Table III, change of the substituents at the 3- and 17-positions of the triketone (III) caused a marked difference in formation of the diketo-ols (IV and V).

In the reactions with Al_2O_3 and SiO_2 in CH_2Cl_2, introduction of an acetoxyl group into the 17-position resulted in an 8—16% increase in the product (V), while an acetoxyl group of the 3-position caused a 23—29% increase in this product. Compared with the cyclization with Al_2O_3, that with SiO_2 generally gave greater amounts of the product (V), behavior which is similar to that seen in the cyclization of IIIa.[1] When the medium is replaced by CH_3CN, a solvent possessing a much higher dielectric constant ($\varepsilon=34$), the reaction with Al_2O_3 gave over 90% of IV, and even with SiO_2, the product (IV) was predominant. Although the reason is not clear it is seen that for the reaction in CH_2Cl_2, the more substituents that are introduced into the substrate, the more the formation of V is favored.

TABLE IV. Effect of Activity of Al_2O_3 on Cyclizations

Al_2O_3 grade (H_2O %)	Reaction time (hr)	6,6 Ring system			5,7 Ring system		
		Total (%)	IVb (%)	VIb (%)[a]	Total (%)	Vb (%)	VIIb (%)[a]
I (0)	0.6	74	64	10	26	20	6
II (3)	1	60	56	4	40	27	13
V (10)	12	52	50	2	48	33	15
SiO_2	1.5	21	21	—	79	79	—

substrate: IIIb

a) The ratios were obtained by GLC analysis, see Experimental.

In order to study the difference between the properties of Al_2O_3 and SiO_2 which influence the ratios of the cyclization products, reactions were carried out with Al_2O_3 of varing activities using the triketone (IIIb) since this substrate was found to give a markedly differing results with Al_2O_3 and SiO_2. From the results listed in Table IV, it can be seen that as the activity of Al_2O_3 decreases, formation of the product possessing a 5,7 ring system increases. This seems to imply that the mode of cyclization is subject to the activity of the catalyst, and/or that there may be an interconversion of the products between the 6,6 and the 5,7 ring systems. It can also be seen from Table IV that, while the dehydration product (VIb) decreases as the activity of Al_2O_3 decreases, the dehydration product (VIIb) does not decrease on reduction of Al_2O_3 activity. This indicates that the diketo-ol (Vb) is dehydrated more easily than the diketo-ol (IVb) in this reaction.

The markedly differing properties of Al_2O_3 and SiO_2 in this reaction can be compared from the view-point of the solid acidity strength[10,11] and adsorption potency. The acidity of the catalysts on an H_0 scale was measured using Hammett's reagent as bases in absolute benzene. In determining the adsorption potency, it would have been desirable to use the triketone (IIIb) itself but its lability to catalyst made it impossible, therefore, androsta-4, 9(11)-diene-3,17-dione was used instead. The flow distances in a uniform column were compared and the results are shown in Table V. Unfortunately, comparison of neither the order of solid acidity strength nor that of adsorption potency of Al_2O_3 and SiO_2 reflected the catalyst order obtained from the product ratio although activity change of Al_2O_3 alone correlates well with both acidity strength and adsorption potency.

---

10) C. Walling, *J. Am. Chem. Soc.*, **72**, 1164 (1950).
11) K. Tanabe and T. Takeshita, "Acid-Base Catalysis," Sangyo Tosho Pub. Co., Ltd., 1966.

Table V. Properties of Al_2O_3 and SiO_2

Catalyst	H_0 (pK_a) in benzene	Adsorption potency[a] Flow distance (cm)
Al_2O_3 (I)	$+4.8-+6.8$	2
Al_2O_3 (II)	$\approx +6.8$	7
Al_2O_3 (V)	$>+7.0$	9.5
SiO_2	$+4.0-+4.8$	6

a) Androsta-4,9(11)-diene-3,17-dione was taken as substrate.
A catalyst containing 0.5% fluorescence was packed in a nylon column (0.8 × 15 cm), and a sample (5 mg) in $CHCl_3$ containing 3% MeOH (1 ml) was adsorbed in the column and developed with 10 ml of the same solvent. The flow distance was measured under UV light.

Table VI. Treatment of the Diketo-ols (IVb and Vb) with the Catalysts

Starting diketo-ol	Catalyst	Reaction time (hr)	Product (%)			
			IVb	VIb $\left\{\begin{matrix}14\alpha\\14\beta\end{matrix}\right\}$[a]	Vb	VIIb $\left\{\begin{matrix}14\alpha\\14\beta\end{matrix}\right\}$[a]
IVb	Al_2O_3 II	1	81	19		
IVb	Al_2O_3 II	3	67	33		
IVb	Al_2O_3 II	20	40	60		
IVb	SiO_2	20	>95	trace		
Vb	Al_2O_3 I	0.5	4	12	68	16
Vb	Al_2O_3 I	3	trace	58	—	40
Vb	Al_2O_3 II	1	3	11	76	10
Vb	Al_2O_3 II	20	6	12	trace	81
Vb	SiO_2	20	—	—	60	40 (14α)
IVb+Vb	Al_2O_3 II	1	50	2	30	18

a) The ratios were obtained by GLC analysis. See Experimental.

The possibility of an interconversion of the products between the 6,6 and the 5,7 ring systems was examined in detail using the diketo-ols (IVb and Vb), and the results are shown in Table VI. On treatment with Al_2O_3, the compound (IVb) underwent only dehydration, giving the ene-diones (VIb). The compound (IVb) on treatment with SiO_2, even for longer time, did not give any dehydration products. On the other hand, Al_2O_3 treatment of Vb clearly afforded IVb and VIb as well as VIIb. Further, the conversion rate from the 5,7 to the 6,6 ring system seems to increase as the activity of Al_2O_3 increases and on prolongation of the reaction time. However, under the conditions[12] employed for cyclization of IIIb hitherto, the conversion rate was at most 15%. Even on longer treatment of Vb with SiO_2, any conversions to IVb or VIb were not recognized, only the ene-dione (VIIb-14α) being obtained. When a 1:1 mixture of IVb and Vb was treated with Al_2O_3, the diketo-ol (Vb) was dehydrated preferentially. The observation led us to propose a reaction path as follows;

$$\begin{tikzcd}
 & \mathrm{IVb} \arrow[r] & \mathrm{VIb\text{-}14\alpha} \arrow[r, shift left] & \mathrm{VIb\text{-}14\beta} \arrow[l, shift left] \\
\mathrm{IIIb} \arrow[ur] \arrow[dr] & & & \\
 & \mathrm{Vb} \arrow[uu] \arrow[uur] \arrow[r] & \mathrm{VIIb\text{-}14\alpha} \arrow[r, shift left] & \mathrm{VIIb\text{-}14\beta} \arrow[l, shift left]
\end{tikzcd}$$

We have previously proposed a similar path[1] for the cyclization of the triketone (IIIa) possessing a pregnane side chain. In that case, a route from Va to IVa was not detected, however, the actual isolation of IVb in the treatment of Vb in the present case, substantiated the route. Thus, for the formation of VIb from Vb, the two reaction paths Vb→IVb→VIb and

---

[12] Al_2O_3-II, ~1 hr.

Vb→VIb should exist, the latter being the major one because, as is seen from Table VI, the treatment of Vb with Al_2O_3 always afforded a larger amount of VIb than IVb in spite of the dehydration process from IVb to VIb being rather slow, as has been demonstrated in the treatment of IVb with Al_2O_3.

The data accumulated in this study does not conclusively explain the cyclization features showed, but one speculative explanation would be that the difference observed in the reaction with Al_2O_3 and SiO_2 is ascribable to the different surface structures of these catalysts leading to different modes of adsorption of the substrate triketones by them. Upon introduction of the polar acetoxyl or ketone group into the 3- and 17-positions, the substrate is able to be adsorbed on the surface of the catalyst in a specific manner favoring the formation of the product possessing the 5,7 ring system. A long-range inductive effect may contribute to a certain extent, however, the observed data is conflicting. In the cyclization of IIIb with Al_2O_3 of varing activities, as the activity of the catalyst diminishes, longer reaction time required and the products possessing the 5,7 ring system begin to increase. This is partly because the rearrangement of the product (Vb) into the product possessing the 6,6 ring system decreases and partly because the reaction under milder conditions would show a higher selectivity. An increase in solvent polarity will weaken the interaction between the substrate and the catalyst, under which conditions the molecule of the triketone should gain higher mobility and the formation of the product (Vb) becomes unfavorable.

Experimental

General Methods——All melting points were determined on Yanagimoto Micromelting apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$ containing 1% EtOH on a Perkin Elmer Polarimeter type 141 (c= 1.0—0.3, l=1 cm). Unless otherwise stated, UV spectra were recorded in 95% EtOH on a Hitachi EPE-2 spectrophotometer and IR spectra in CCl_4 on a Hitachi grating IR spectrophotometer Model EPI-G3. CD spectra were taken on a Jasco Model ORD/UV-6. NMR spectra were measured in $CDCl_3$ on a Varian A-60 spectrometer. Chemical shifts are reported in τ value. For preparative and analytical TLC, Silica gel G or GF (E. Merck Co.) was used and for cyclization of the triketone (III), alumina (Woelm neutral 60/200 mesh) and silica gel (E. Merck, HR) were used. GLC analyses were carried out on a Shimazu GC-4A Gas Chromatograph (column 3 m) packed with Gaschrom 80/100 mesh support coated with 1% QF 1 stationary phase.

Procedure for Osmium Tetroxide Oxidation of 5α-Androst-8(9)-en-11-one Derivatives Ib—If——Osmium tetroxide (mol. wt., 254.2, 1.1 mmol) in abs. ether (0.1 mol) was added to a solution of an enone I (1 mmol) in abs. ether (0.2—0.3 mol, if necessary, dry CH_2Cl_2 (dried through alumina column) is used as co-solvent) under stirring and the solution was kept at room temp. in the dark for 3 days. Dark brown crystals deposited were collected, washed with ether and dissolved in a mixture of $CHCl_3$ and benzene. Into the cooled solution was bubbled H_2S gas for 30 min. Sludgy osmium sulfides appeared were filtered and washed several times with $CHCl_3$ and the combined filtrate was washed in succession with 5% HCl, 5% Na_2CO_3 and water, dried and evaporated to dryness. The residue was crystallized from solvents to the keto-diol (II).

3β,17β-Diacetoxy-8α,9α-dihydroxy-5α-androstan-11-one (IIb)——The enone (Ib) (10 g) was treated in the manner described and the product was crystallized from CH_2Cl_2–ether to give IIb (8.2 g) mp 185—193°, $[\alpha]_D^{21}$ −76.9°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 1726, 1705 (sh), 1025. *Anal.* Calcd. for $C_{23}H_{34}O_7$: C, 65.38; H, 8.11. Found: C, 65.19; H, 8.09.

17β-Acetoxy-8α,9α-dihydroxy-5α-androstan-11-one (IIc)——The enone (Ic) (3 g) was treated as described and the product was crystallized from CH_2Cl_2–ether to give IIc (2.2 g), mp 165—169°. $[\alpha]_D^{21}$ −70.6°. IR ν_{max} cm^{-1}: 3480, 1742, 1726, 1699, 1236, 1050, 1021. *Anal.* Calcd. for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.42; H, 8 .77.

3β-Acetoxy-8α,9α-dihydroxy-5α-androstan-11-one (IId)——The enone (Id) (2 g) was treated similarly and the product was crystallized from MeOH to give IId (1.5 g), mp 166—169°, $[\alpha]_D^{23}$ −79.3°. IR $\nu_{max}$$cm^{-1}$: 3455, 1736, 1720, 1244, 1030. *Anal.* Calcd. for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.04; H, 8.96.

8α,9α-Dihydroxy-5α-androstan-11-one (IIe)——The enone (Ie) (5 g) was treated similarly and the product was crystallized from MeOH to give IIe (3.2 g), mp 157—160°, $[\alpha]_D^{21}$ −103.9°. IR ν_{max} cm^{-1}: 3445, 1705 (sh), 1692. *Anal.* Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.70; H, 9.87.

17β-Acetoxy-8α,9α-dihydroxy-5α-androstane-3,11-dione (IIf) The enone (If) (2.5 g) was treated similarly and the product was crystallized from CH_2Cl_2–ether to give IIf (1.9 g), mp 199—204°, $[\alpha]_D^{22}$ −48.0°. IR $\nu_{max}^{CHCl_3}$$cm^{-1}$: 3450, 1714, 1050, 1013.

Procedure for the Preparation of 8,9-Seco-5α-androstane-8,9-11-trione Derivatives IIIb—IIIf——Pb(OAc)$_4$ (mol. wt., 443.4, 1.1 mmol) in dry CHCl$_3$ (0.5 mol, dried through Al$_2$O$_3$ column) was added into a stirred solution of a keto-diol (II) (1 mmol) in dry CHCl$_3$ (0.5 mol) at room temp. and the mixture was stirred for 30—60 min, then filtered. The filtrate was washed in succession with 1% NaHSO$_3$, 5% HCl, 5% NaHCO$_3$ and water, dried and evaporated under reduced pressure. The yellow crystalline solids were crystallized from solvents to give III.

3β,17β-Diacetoxy-8,9-seco-5α-androstane-8,9,11-trione (IIIb)——The keto-diol (IIb) (8g) was treated in the manner described. Work-up gave the product, crystallized from CH$_2$Cl$_2$–ether to give IIIb (7.6 g). The physical data are listed in Table I and II.

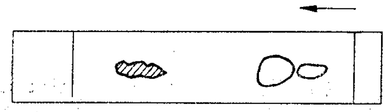
17β-Acetoxy-8,9-seco-5α-androstane-8,9,11-trione (IIIc)——The keto-diol (IIc) (2 g) was treated in the manner described and the product was crystallized from ether-petr. ether to give IIIc (1.85 g).

3β-Acetoxy-8,9-seco-5α-androstane-8,9,11-trione (IIId)——The keto-diol (IId) (1.2 g) was treated similarly and the product was crystallized from MeOH to give IIId (1.1 g).

8,9-Seco-5α-androstane-8,9,11-trione (IIIe)——The keto-diol (IIe) (3.0 g) was treated similarly and the product was crystallized from MeOH to give IIIe (2.7 g).

Cyclization of Triketones (IIIb—IIIf)

Diketo-ols (IVb and Vb) and Ene-diones (VIb-14α, VIb-14β, VIIb-14α and VIIb-14β)——a) With Al$_2$O$_3$: A mixture of IIIb (200 mg) and Al$_2$O$_3$ (2.0 g) in dry CH$_2$Cl$_2$ (5 ml, dried throguh Al$_2$O$_3$ column) was stirred at room temp. until the yellow of the triketone (IIIb) disappeared (1 hr). The catalyst was filtered and washed 5 times with CHCl$_3$ containing 3% MeOH. The combined filtrate was evaporated to dryness *in vacuo*. The product (202 mg), whose TLC was shown, was separated by preparative TLC (CH$_2$Cl$_2$–AcOEt, 5:1). The most polar fraction (55 mg, 27%) was crystallized from ether–petr. ether to give the diketo-ol (Vb). The next polar fraction (110 mg, 56%), on crystallization from CH$_2$Cl$_2$–ether, gave the diketo-ol (IVb). The less polar fraction (dehydrated products) (35 mg, 17%) was still a mixture. After the fraction was accumulated from several runs it was separated twice by TLC (CH$_2$Cl$_2$–AcOEt, 10:1, twice development and ether–petr. ether 1:2 twice development) affording the four components (VIb–14α, VIb–14β, VIIb–14α and VIIb–14β). Authentic samples of these compounds, however, will be prepared later by different ways.



b) With SiO$_2$: A mixture of IIIb (200 mg) and SiO$_2$ (2.0 g) in dry CH$_2$Cl$_2$ (6 ml) was stirred for 1.5 hr at room temp. Work-up in the manner described above gave the product mixture which was separated by TLC to give IVb (41 mg, 21%) and Vb (156 mg, 79%). The fraction corresponding to the ene-diones was only a trace amount (4 mg).

Ene-diones (VIb-14α and VIb-14β)——SOCl$_2$ (0.2 ml) was added dropwise to a stirred solution of IVb (200 mg) in pyridine (4 ml) under cooling and the solution was stirred for 10 min, then poured into ice–water. Usual work-up gave the product, crystallized from ether–petr. ether to pure VIb-14α (170 mg). A portion of VIb-14α (120 mg) obtained above and KOH (100 mg) in MeOH (7 ml) was refluxed for 30 min, then poured into water. After the product was extracted, it was acetylated with Ac$_2$O–pyridine at 60° for 2 hr and worked up. The product (116 mg), upon separation by TLC (CH$_2$Cl$_2$–AcOEt, 10: 1 twice development), gave VIb-14α (22 mg) and VIb-14β (90 mg). Crystallization of VIb-14β from MeOH gave a sample.

Ene-diones (VIIb-14α and VIIb-14β)——A mixture of Vb (200 mg) and SiO$_2$ (2.0 g) in dry CH$_2$Cl$_2$ was stirred at room temp. for 30 hr. After usual work-up, the product was separated by TLC (CH$_2$Cl$_2$–AcOEt, 10: 3). A major fraction corresponding to an ene-dione gave pure VII-14α (130 mg), crystallized from ether–*n*-pentane to a sample. A minor fraction (54 mg) was found to be the starting diketo-ol Vb.

A portion of VIIb-14α (100 mg) obtained above was treated with KOH (100 mg) in MeOH (10 ml) for 50 min under reflux, then poured into water. The product, after extraction, was acetylated with Ac$_2$O–pyridine. Usual work-up gave the product (99 mg), separated by TLC (ether–petr. ether, 1: 2, 3 times development) to VIIb-14α (57 mg) and VIIb-14β (39 mg). Crystallization of VIIb-14β from ether–*n*-pentane gave its sample.

GLC Analyses of the Mixtures of Ene-diones——After the fractions corresponding to the ene-diones were separated from the cyclization products, they were subjected to GLC analyses at the column temp. 240°. The diketo-ols were found to decompose in the column. Fortunately, VIb-14α and VIb-14β, and VIIb-14α and VIIb-14β appeared as single peaks respectively. Thus ,the ratios of the ene-diones between the 6,6 and 5,7 ring systems were obtained by direct comparison of the peak areas.

NaBH$_4$ Reduction of Vb——A solution of Vb (100 mg) in abs. MeOH (5 ml) was added to a cooled solution of NaBH$_4$ (50 mg) in abs. MeOH (5 ml) under stirring and the mixture was stirred for 10 min at 4°, then poured into ice–water. The product was extracted with CHCl$_3$. After the solvent evaporated, the residue, showing two spots on TLC, was separated by preparative TLC (CHCl$_3$: MeOH, 10: 1). The less polar fraction (70 mg) was crystallized from CH$_2$Cl$_2$–ether–petr. ether giving VIII (40 mg), mp 246—249°, $[\alpha]_D^{20}$ +32.0°. IR $\nu_{max}^{CHCl_3}$cm^{-1}: 3625, 3565, 1730, 1705, 1022. H-bonding $\nu_{max}^{CCl_4}$ (c=1.9×10^{-3} mol): 3634 (free secondary), 3582 (H-bonding). CD (c=0.119, MeOH) $[\theta]$ (mμ): 0 (346), +9560 (305), 0 (252).NMR τ: 9.00 (3H, s, 18-H), 8.88 (3H, s, 19-H), 7.98 (OAc), 7.95 (OAc), 7.74, 6.89 (12-H$_2$, d of d, J=11 Hz), 6.08 (H, ill-defined q, Wh/2=

10, after addition of D_2O, it appeared as a doublet, $J=3.0$ Hz). *Anal.* Calcd. for $C_{23}H_{34}O_7$: C, 65.38; H, 8.11. Found: C, 65.40; H, 8.02. The polar fraction (27 mg) has very poor solubility in usual organic solvents and was not examined in detail but the IR spectrum ($\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3338, 3275, 1737, 1242, 1232) indicates it to be a triol.

An attempted acetylation of the keto-diol (VIII) (10 mg) with Ac_2O–pyridine at 90° for 2 hr failed and the starting VIII was recovered.

Oxidation of VIII with Jones Reagent——Jones reagent (0.1 ml) was added dropwise into a stirred solution of VIII (20 mg) in acetone (1 ml) under cooling and the mixture was stirred for 25 min at 3°. Usual work-up gave the product which was separated by TLC affording Vb (10 mg) and a small amount of the starting VIII (5 mg). The identification was done by the mixed melting point and comparison of the IR spectra.

Diketo-ols IVc and Vc——a) With Al_2O_3: A mixture of IIIc (100 mg) and Al_2O_3 (1.0 g) in dry CH_2Cl_2 (3 ml) was stirred at room temp. for 30 min. Usual work-up gave a crude product (101 mg). TLC separation (CH_2Cl_2–AcOEt, 30: 1, twice development) of the product gave IVc (85 mg), Vc (12 mg) and a mixture of dehydration products (3 mg). The product (IVc) was crystallized from CH_2Cl_2–ether–petr. ether to give a sample.

b) With SiO_2: IIIc (170 mg) was treated with SiO_2 (1.7 g) in dry CH_2Cl_2 (5 ml) for 1.5 hr. The product mixture (171.5 mg), on TLC separation with the same solvent systems as above, gave IVc (84 mg) and Vc (85 mg). The product (Vc) was crystallized from ether–petr. ether giving a sample.

Diketo-ols IVd and Vd——a) With Al_2O_3: IIId (200 mg) was treated with Al_2O_3 (2.0 g) in dry CH_2Cl_2 (4 ml) for 10 min. The product (198 mg) was separated by TLC (CH_2Cl_2–AcOEt, 20:1 twice development) affording IVd (136 mg), Vd (58 mg) and a trace amount of the dehydration products. Crystallization of the product (IVd) from CH_2Cl_2–ether afforded a sample. The product (Vd), on crystallization from ether–petr. ether, gave a sample.

b) With SiO_2: IIId (100 mg) was treated with SiO_2 (1.0 g) in dry CH_2Cl_2 (4 ml) for 3 hr. A mixture of the products (101 mg) was separated by TLC to afford IVd (36 mg) and Vd (62 mg).

Diketo-ols IVe and Ve——a) With Al_2O_3: IIIe (150 mg) was treated with Al_2O_3 (1.5 g) in dry CH_2Cl_2 (3 ml) for 80 min. The product mixture was separated by TLC (CH_2Cl_2–AcOEt, 30: 1) giving IVe (146 mg), Ve (6 mg) and the starting IIIe (5 mg). The product (IVe) was crystallized from CH_2Cl_2–ether to a sample.

b) With SiO_2: IIIe (200 mg) was cyclized with SiO_2 (2.0 g) in dry CH_2Cl_2 (6 ml) for 26 hr. TLC separation of the product gave IVe (114 mg), Ve (76 mg) and the starting (IIIe) (9 mg). Crystallization of Ve from ether–petr. ether gave a sample. Dipole moment of Ve: $\mu=2.62$ D in dioxane at 25°.

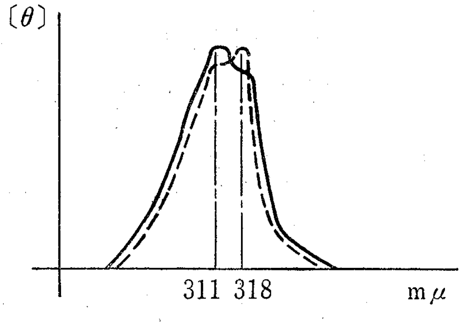
Diketo-ols IVf and Vf——a) With Al_2O_3: IIIf (150 mg) was treated with Al_2O_3 (1.5 g) in dry CH_2Cl_2 (3 ml) for 10 min. The product mixture was separated by TLC (benzene: MeOH, 20: 3 twice development) to afford IVf (102 mg) and Vf (43 mg). Crystallization of IVf from CH_2Cl_2–ether and of Vf from ether–petr. ether gave their samples.

b) With SiO_2: A similar treatment of IIIf (150 mg) with SiO_2 (1.5 g) in dry CH_2Cl_2 (6 ml) afforded, after separation by TLC, IVf (45 mg) and Vf (103 mg).

CD Spectra of V. [θ] (mμ) in MeOH

Vb	($c=0.142$)	0 (351)	+8966 (312)	0 (250)
Vc	($c=0.163$)	0 (354)	+8816 (315)	+29 (252)
Vd	($c=0.164$)	0 (353)	+9460 (313.5)	0 (250)
Ve	($c=0.155$)	0 (355)	+9078 (315)	0 (267)
Vf	($c=0.138$)	0 (352)	+8600 (305)	0 (240)

Variable-Temperature CD of Ve in EPA (ethanol–isopentane–ether) ($c=0.0638$) *cf.* Fig.



R.T.	−68°	−190°
+8169 (311)	+9907 (311)	+9269 (310)
	+9687 (318)	+9671 (318)

Acknowledgement We are greatly indebted to Dr. K. Takeda, the director of this laboratory and to Dr. K. Sasaki of Kuise factory of our company for their encouragements throughout this work. Thanks also due to the staffs of the physical chemistry section, this laboratory, for the spectral measurements, and the analysis room of our laboratory for the ultramicroanalyses.