CHEMISTRY LETTERS, pp. 95-98, 1982. 

# A NOVEL REACTION AND MECHANISM OF A DIHALOGENATED $\Delta^4$-3-KETOSTEROID: STEREOELECTRONIC CONTROL IN A COMPLICATED $S_N2'$ DISPLACEMENT

Toshitaka KOGA,* Namiko TOH, and Yasuyoshi NOGAMI
Daiichi College of Pharmaceutical Sciences
22-1, Tamagawa-cho, Minami-ku, Fukuoka 815

Stereochemistry of the acetolysis of 4,6β-dibromo-$\Delta^4$-3-ketosteroid was examined and a new route of simultaneous introduction of two O-functions at C-2 and C-6 on the steroid skeleton has been established. The reaction is interpreted to proceed by characteristic and successive $S_N2'$ reaction mechanisms, and stereoelectronic effects control the stereochemistry of the reaction. There is no occurrence of $S_N1$, $S_N2$, and any rearrangement courses.

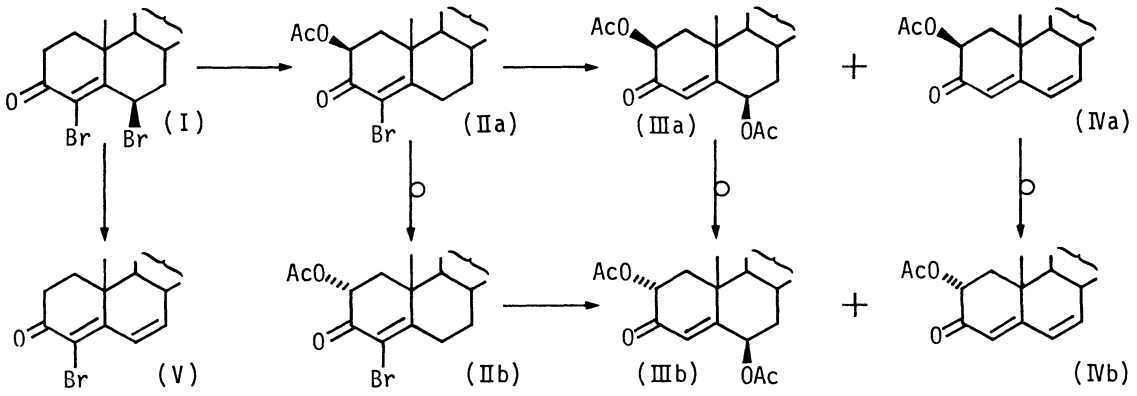
The acetolysis of monohalogenated $\Delta^4$-3-ketosteroids is well investigated,[1] and it has been revealed that the reactions of α- and γ-bromo-$\Delta^4$-3-ketone systems proceed not only *via* $S_N2'$ process but also *via* $S_N1$ or $S_N2$ process. For example, the acetolysis of 4-bromocholest-4-en-3-one afforded 2α-, 4-, and 6β-acetates.[1i] On the other hand, 6β-androstenedione gave 2α-, 2β-, and 6β-acetates.[1h]

As for the acetolysis of dihalogenated $\Delta^4$-3-ketosteroid, however, there is the only case of 2ξ,6β-dibromo-$\Delta^4$-3-ketone system reported;[2] an $S_N2'$ reaction of the 6-bromine once occurs to give 2-bromo-4-acetoxy intermediate which subsequently undergoes a 1,3-elimination rearrangement to produce 3-acetoxy-$\Delta^{2,5}$-4-ketosteroids. Consequently, on the acetolysis of the dihalogenated $\Delta^4$-3-ketone system, only an acetoxy group is introduced into the system.

We now report a new type of acetolytic displacement course and its mechanism on the $\Delta^4$-3-ketone system having two leaving groups at C-4 and C-6. In our case, characteristic $S_N2'$ displacements cross over the rings A and B successively under stereoelectronic control, and simultaneous introduction of two O-functions is smoothly completed.

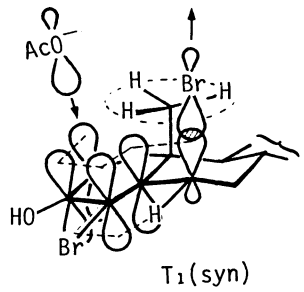
4,6β-Dibromocholest-4-en-3-one (I)[3] was treated with a 33 fold excess of potassium acetate in glacial acetic acid under reflux in a nitrogen atmosphere. The reaction was followed by TLC, and was complete in 30 min. Chromatography of the crude product afforded 2β-acetoxy-4-bromo-enone (IIa)

(11.2%) with a bromine atom remained and its isomeric 2α-acetate (IIb)(4.7%), 2β,6β-diacetate (IIIa) (6.9%) with thermodynamically less stable axial substituents and its 2α-isomer (IIIb) (14.2%), 2β-




acetoxy-dienone (IVa)(1.9%) and its 2α-isomer (IVb)(13.8%), and 4-bromo-dienone (V)(9.0%)(Scheme).

All of the compounds obtained are unknowns. Microanalyses, mass spectra, and other physical properties[4] of the compounds support their structures. Furthermore, the structures and configurations were confirmed by comparison of the CD spectra with those of related compounds in the literature.[1h]




$T_1$(syn)

Fig.1

The results of the reactions indicate that the introduction of two acetoxy functions into the $\Delta^4$-3-ketone system proceeds stepwise as follows. After enolization of the keto group toward C-2 under the acidic conditions, the successive nucleophilic substitution reactions might start with the $S_N2'$ displacement of the 6β-bromine by axial β-side attack of acetate ion on the enol at C-2; the reaction might proceed *via* a syn transition state ($T_1$)(Fig.1) under stereoelectronic control, forming the less stable 2β-acetoxy-4-bromo derivative (IIa). The first stage is a kind of syn-$S_N2'$ displacement.

The initial intermediate product (IIa), having a bromine as a leaving group for further $S_N2'$ displacement, might possibly isomerize to the β,γ-unsaturated form with the halogen atom at an allylic position under the acidic conditions. For the second displacement of the bromine in this form, two types of transition states are considerable. One is a syn transition state ($T_2$(syn)) with ring A in a more stable half-chair conformation with the C-4β bond axial, and another is an anti form ($T_2$(anti)) with a less stable twist-boat conformation of ring A in which the C-4α bond may become pseudoaxial (Fig.2). It is hard to say which transition state (syn or anti) might contribute greatly on the second stage since the bulky bromine atom, located in quasi-1,3-diaxial relationships with 10β-methyl group and also with the 2β-acetoxy group, may destabilize the conformation in the former and the maximum σ-π overlap around C-4, C-5, and C-6 may be more practicable

in the latter. In either case, however, attack of acetate ion under the normal stereoelectronic control might, favoring axial addition, form the 6β-substituted product IIIa.

When the isomerization of the acetoxy substituent would occur prior to the second displacement, 2α-acetoxy-4-bromo derivative (IIb) might be formed, and then acetate ion could attack C-6 from the axial β-side to give IIIb.

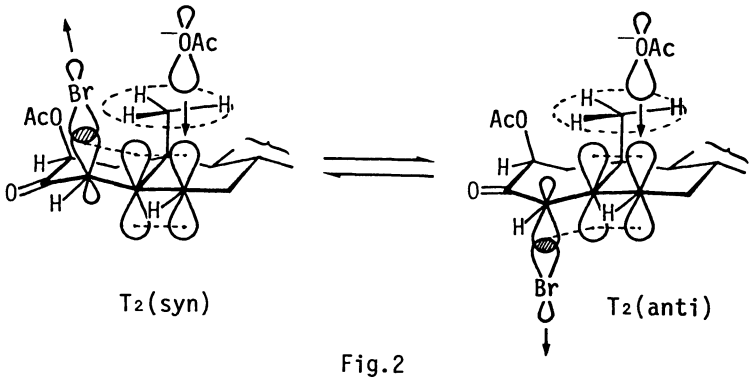



Fig.2

Our consideration of the mechanisms is supported by the following data. Actually, acetolysis of the 2β-acetoxy-4-bromo-enone (IIa) gave IIIa and IVa as the products with 2β-configuration retained, and also IIb, IIIb, and IVb as the products with 2α-acetoxy groups. On the other hand, under the same conditions, the 2α-isomer (IIb) gave only two products, IIIb and IVb.

Thus, the characteristic and successive $S_N2'$ reactions crossed over the rings A and B on the $\Delta^4$-3-ketosteroid were established. From the facts obtained, furthermore, it has become obvious that both the reactions proceed by the stereoelectronically controlled axial attack of the entering groups on the transition states at C-2 and C-6, forming β-substituted products, exclusively.

A careful examination of the products isolated revealed that no detectable amount of a compound with 4- or 6α-acetoxy[1j,5] function ($S_N2$ or $S_N1$) and any rearrangement product was formed under the reaction conditions; demonstrating a significant difference on the behavior between the 2,6-dibromo- and the 4,6-dibromo-enone systems in acetolytic conditions.

We are currently exploring the scope of the reaction including a wide variety of different nucleophiles and substrates for a much broader applicability of this reaction in organic synthesis, and the results will be reported in a subsequent publication.

References

1. a) F. Sondheimer, St. Kaufmann, J. Romo, H. Martinez, and G. Rosenkranz, J. Am. Chem. Soc., 75, 4712 (1953).
b) L. F. Fieser and M. A. Romo, ibid., 75, 4716 (1953).
c) J. Herran, G. Rosenkranz, and F. Sondheimer, ibid., 76, 5531 (1954).
d) G. Rosenkranz, O. Mancera, and F. Sondheimer, ibid., 77, 145 (1955).
e) R. L. Clarke, K. Dobriner, A. Mooradian, and C. M. Martini, ibid., 77, 661 (1955).
f) P. N. Rao and L. R. Axelrod, ibid., 82, 2830 (1960).
g) P. N. Rao, H. R. Gollberg, and L. R. Axelrod, J. Org. Chem., 28, 270 (1963).
h) R. D. Burnett and D. N. Kirk, J. Chem. Soc., Perkin I, 1830 (1973).
i) T. Koga and M. Tomoeda, ibid., 1848 (1973).
j) T. Koga and Y. Nogami, Tetrahedron Letters, 22, 3075 (1981).

2. P. L. Julian, L. Bauer, C. L. Bell, and R. E. Hewitson, J. Am. Chem. Soc., 91, 1960 (1969), and earlier literature cited therein: the reactions of 2,6-dibromo-$\Delta^4$-3-ketone system were erroneously reported as the reactions of 4,6-dibromo-$\Delta^4$-3-ketone system in early works.

3. D. J. Collins and J. J. Hobbs, Aust. J. Chem., 18, 1049 (1965).

4. IIa: colorless needles, mp 94.5-95.5°; IR(nujol) 1760, 1705, 1585cm$^{-1}$; UV 267nm(ε:12100); NMR ($CDCl_3$) δ5.45(1H, dd, J=11.8, 5.3Hz, 2α-H), 3.11(1H, br d, J=14.5Hz, 6α-H), 2.13(3H, s, OAc), 1.24(3H, s, 19-H). MS m/e: 520($M^+$), 478($M^+$-$CH_2CO$), 441($M^+$-Br), 381($M^+$-Br-$CH_3COOH$, base peak). *Anal.* Calcd. for $C_{29}H_{45}BrO_3$: C, 66.78; H, 8.70. Found: C, 66.59; H, 8.94. CD (MeOH)[θ](nm): -3300(300)(infl.), -31000(265)(negative max.), 0(239), +25700(205)(positive max.).

IIb: colorless needles, mp 57.5-58.5°; IR(nujol) 1760, 1715, 1585cm$^{-1}$; UV 262nm(ε:10400); NMR ($CDCl_3$) δ5.49(1H, dd, J=13.8, 6.0Hz, 2β-H), 3.23(1H, br d, J=14.5Hz, 6α-H), 2.15(3H, s, OAc), 1.35(3H, s, 19-H). MS m/e: 520($M^+$), 478($M^+$-$CH_2CO$), 441($M^+$-Br), 381($M^+$-Br-$CH_3COOH$, base peak). High MS Calcd. for $C_{29}H_{45}BrO_3$: 520.2554. Found; 520.2572. CD(MeOH)[θ](nm): +440(298)(infl.), +6330(265)(positive max.), 0(252), -9880(232)(negative max.), 0(209).

IIIa: colorless needles, mp 110.5-111°; IR(nujol) 1750, 1710, 1615cm$^{-1}$; UV 242nm(ε:13400); NMR ($CDCl_3$) δ5.98(1H, s, 4-H), 5.38(1H, s, 6α-H), 5.23(1H, dd, J=11.9, 5.4Hz, 2α-H), 2.13 (3H, s, 2β-OAc), 2.05(3H, s, 6β-OAc), 1.27(3H, s, 19-H). MS m/e: 500($M^+$), 458($M^+$-$CH_2CO$), 398($M^+$-$CH_2CO$-$CH_3COOH$). High MS Calcd. for $C_{31}H_{48}O_5$: 500.3523. Found: 500.3536. CD(MeOH) [θ](nm): +2960(325)(positive max.), 0(298), -2960(280)(infl.), -70500(241)(negative max.), 0(222), +40900(208)(positive max.).

IIIb: colorless needles, mp 120-121°; IR(nujol) 1745, 1705, 1620cm$^{-1}$; UV 236nm(ε:11800); NMR ($CDCl_3$) δ5.92(1H, s, 4-H), 5.46(1H, dd, J=13.5, 5.8Hz, 2β-H), 5.38(1H, s, 6α-H), 2.13 (3H, s, 2α-OAc), 2.03(3H, s, 6β-OAc), 1.40(3H, s, 19-H). MS m/e: 500($M^+$), 458($M^+$-$CH_2CO$), 398($M^+$-$CH_2CO$-$CH_3COOH$, base peak). *Anal.* Calcd. for $C_{31}H_{48}O_5$: C, 74.36; H, 9.66. Found C, 74.12; H, 9.94. CD(MeOH)[θ](nm): -6260(325)(negative max.), -850(275)(infl.), -2280 (248)(negative max.), 0(237), +30700(208)(positive max.).

IVa: colorless oil; IR(film) 1750, 1690, 1608cm$^{-1}$; UV 289nm(ε:17300). For further confirmation of the structure, the compound was converted to isomeric IVb under the acetolytic conditions.

IVb: colorless needles, mp 88-89.5°; IR(nujol) 1750, 1670, 1615, 1590cm$^{-1}$; UV 285nm(ε:20200); NMR($CDCl_3$) δ6.08(2H, s, 6,7-H), 5.68(1H, s, 4-H), 5.58(1H, dd, J=13.8, 6.0Hz, 2β-H), 2.15(3H, s, OAc), 1.24(3H, s, 19-H). MS m/e: 440($M^+$), 380($M^+$-$CH_3COOH$, base peak). High MS Calcd. for $C_{29}H_{44}O_3$: 440.3290. Found: 440.3305. CD(MeOH)[θ](nm): +6700(335)(positive max.), 0(306), -4280(280)(infl.), -9590(246)(negative max.), 0(222), +1860(214)(positive max.), 0(208).

V: colorless prisms, mp 84-85.5°; IR(nujol) 1680, 1610, 1547cm$^{-1}$; UV 301nm(ε:23000); NMR ($CDCl_3$) δ6.72(1H, dd, J=9.0, 3.5Hz, 6 or 7-H), 6.27(1H, dd, J=9.0, 2.5Hz, 6 or 7-H), 1.11 (3H, s, 19-H). High MS Calcd. for $C_{27}H_{41}BrO$: 460.2330. Found: 460.2349. CD(MeOH)[θ](nm): +17100(340)(positive max.), +390(295)(infl.), +1290(282)(positive max.), 0(271), -8400 (240)(infl.), -22200(212)(negative max.).

5. Proceeding by an $S_N1$ mechanism in part, a small amount of 6α-substituted products might be formed.[1j]

(Received November 18, 1981)