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Baeyer-Villiger Reaction of 2-Oxo-A-norsteroids

Our previous communication[1] described the Baeyer-Villiger reaction of 3-oxo-steroids with perbenzoic acid, in which we proved that the product can be resolved into isomeric lactones. As an extension of this study, is described here the analogous reaction of 2-oxo-A-norsteroids, and the selective introduction of oxygen atom in position 2 on the steroid nucleus is elaborated. 2-Oxa-steroids obtained by this reaction are of biological interest. Namely, 5α series of lactone, IIe demonstrates an intense anabolic action,[2] and 5β series of 2-oxa compounds have the same partial structure appeared in salamander alkaloids which have a strychnine-like action, *i.e.*, samandarine, samandarone.[3]

2-Oxo-A-nor-5α-steroids, served as the starting materials, Ia (R=C_8H_{17}, R'=H),[4] Ib (R=H, R'=H),[5] Id (R=OAc, R'=H)[6] were prepared by pyrolysis at 210 to 220° in vacuum from the corresponding 2,3-seco-diacid anhydrides. 17α-Methyl-17β-hydroxy-A-nor-5α-androstan-2-one (Ie), (m.p. 171~172°, IR ν_{max}^{Nujol} cm^{-1} : 3450, 1745; reported m.p. 168~170°[6]) was synthesized from Ic (R=OH, R'=H)[6~8] through four step process, that is, ketalization, oxidation, alkylation by methylmagnesium iodide and hydrolysis with 70% acetic acid at 70° for 2 hours.

Ia, Ib, Id, and Ie were treated with an excess of perbenzoic acid in chloroform at 30° for 3 to 7 days, to give the lactones (IIa) (m.p. 134~136°, IR : ν_{max} 1740 cm^{-1}, NMR : 5.72, 5.91, 6.07, 6.25 τ, J=11 c.p.s. in $CDCl_3$), (IIb) (m.p. 135~137°, IR: ν_{max} 1745 cm^{-1}, NMR : 5.61, 5.79, 5.90, 6.16 τ, J=11 c.p.s. in $CDCl_3$), (IId) (m.p. 150~153°, IR ν_{max} cm^{-1} : 1730, 1250), (IIe) (m.p. 236~239°, IR ν_{max} cm^{-1} : 3570, 1730, NMR : 5.63, 5.81, 6.00, 6.17 τ, J=11 c.p.s. in $CDCl_3$) in a yield of 70 to 90%. IId was converted to IIc (m.p. 201~203°, IR ν_{max} cm^{-1} : 3400, 1720) by alkaline hydrolysis and recyclization by heating with acetic acid in the presence of *p*-toluenesulfonic acid.

Proof of structures for IIa~e is as follows : The nuclear magnetic resonance spectra of these compounds show that the signal of two protons centered at ca. 6 τ were split into AB type quartet and that no further splitting was observed; therefore, the 3-oxa structures (III) were denided*1. Moreover, IIc, IIe were identified as 17β-hydroxy-2-oxa-5α-androstan-3-one and its 17α-methyl derivative, which had been synthesized from 1-en-3-one compounds (IVc), (IVe) *via* ozonization followed by reduction and cyclization.[3] From IVa was newly obtained a lactone by a similar method[2,9]. The lactone was also identical with IIa.

The same reactions were carried out in 5β series. 2-Oxo-A-nor-5β-steroids, Va (R=C_8H_{17}, R'=H, m.p. 108~109°, IR : ν_{max} 1740 cm^{-1}), Vb (R=H, R'=H, m.p. 114~116°, IR : ν_{max} 1740 cm^{-1}), Vd (R=OAc, R'=H, m.p. 150~152°, IR ν_{max} cm^{-1} : 1740, 1250) were prepared

*1 If the structures were III, the corresponding signal would split into more than quartet due to the spin-coupling with 5α-proton.

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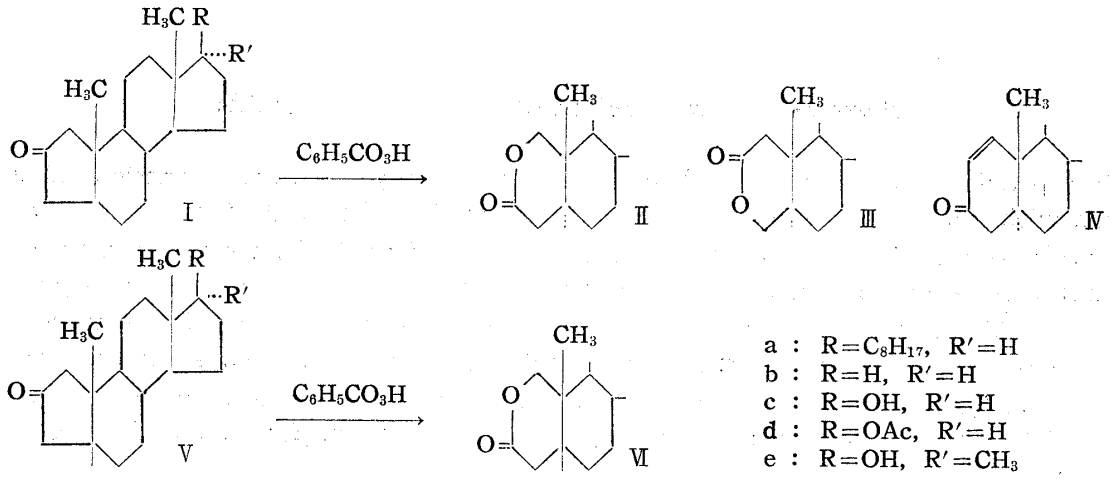

by the same method as described above from the corresponding 2,3-seco-diacids obtained in the previous paper[1] *via* anhydrides.

These ketones were similarly treated with peracid to give the lactones (Ⅵa) (m.p. 125~128°, IR : ν_{max} 1730 cm^{-1}, NMR : 5.64, 5.84, 6.15, 6.36 τ, J=12 c.p.s. in $CDCl_3$), (Ⅵb) (m.p. 119~122°, IR : ν_{max} 1745 cm^{-1}, NMR : 5.57, 5.77, 6.09, 6.28 τ, J=12 c.p.s. in $CDCl_3$), (Ⅵd) (m.p. 182~185°, IR ν_{max} cm^{-1} : 1735, 1245) in a high yield. Ⅵd was deacetylated to Ⅵc (m.p. 213~216°, IR ν_{max} cm^{-1} : 3460, 1730). The products are proved to be 2-oxa compounds on the basis of nuclear magnetic resonance pattern of the methylene protons adjacent to the ring oxygen which is similar to the pattern in case of 5α series.

The present study shows that in the Baeyer-Villiger reaction of 2-oxo-A-norsteroids, an oxygen atom is introduced selectively at position 2 in the steroid nucleus in contrast to the lack of the selectivity in the case of 3-oxo-steroids.

Recently, the steric effect has been stressed in the Baeyer-Villiger reaction on the basis of some results obtained in the oxidation of camphor derivatives.[10] According to these findings, 2,3-fission of 5α and 5β 2-oxo-A-norsteroids should occur through a stable transition state, chair form. This mechanism, however, does not apply to 1,2-fission of the present series of compounds. Not like camphor derivatives, the steroid compounds are non-rigid and likely to subject to ring inversion at the transition equilibrium.[10] These arguments may offer an explanation for the selectivity in the Baeyer-Villiger reaction described in this paper.

Satisfactory analyses have been obtained for all new compounds reported. Melting points are uncorrected.

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Women's Department, Tokyo College of Pharmacy
Ueno-Sakuragi-cho, Daito-ku, Tokyo, Japan

Shoji Hara (原 昭二)

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