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The Structure of 9,14-Epoxy-8,14-seco Steroids[1]

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The more stable compound, 9,14α-epoxy-3-methoxy-8,14-secoestra-1,3,5(10)-trien-17-one (IVa), given by cyclization of 14α-hydroxy-3-methoxy-8,14-secoestra-1,3,5(10),9-tetraen-17-one (II), has been assigned to a 9α,14α-epoxy compound (9*S* configuration).

Recently we found that reduction of 3-methoxy-8,14-secoestra-1,3,5(10),9-tetraene-14,17 dione (I) with sodium borohydride afforded *rac*-14α-hydroxy-3-methoxy-8,14-secoestra-1,3,-5(10),9-tetraen-17-one (II).[3] Treatment of II with boiling methanolic hydrochloric acid gave *rac*-3-methoxy-13α-estra-1,3,5(10),8,14-pentaen-17β-ol (III), whereas under milder acidic condition was obtained another compound. The structure of the compound was already clarified by us[4] and Schering group[5] to be 9,14α-epoxy-3-methoxy-8,14-secoestra-1,3,5(10)-trien-17-one (IVa).

The configuration at C-9 in IVa has remained unclarified, although the epoxydation of II appeared to proceed stereospecifically at C-9.

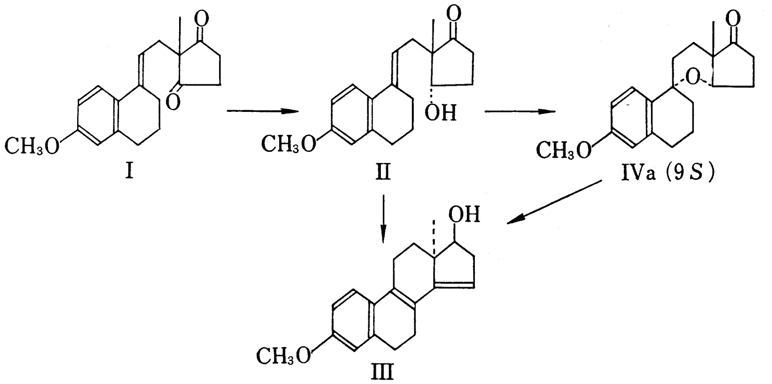

Chart 1

During the study on an alternative route to estrone, we obtained a new 9,14-epoxy compound (IVb).

Treatment of *rac*-14α-hydroxy-3-methoxy-8,14-secoestra-1,3,5(10),9,15-pentaen-17-one (V)[6] with *p*-toluenesulfonic acid in benzene gave an oily product, which was found to be a mixture consisting of two components from its nuclear magnetic resonance (NMR) spectrum (Fig. 1).

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[1] Preliminary communication, T. Asako, K. Hiraga, and T. Miki, *Chem. Commun.*, **1969**, 1011.

[2] Location: *Juso-Nishinocho, Higashiyodogawa-ku, Osaka.*

[3] T. Asako, K. Hiraga, and T. Miki, *Chem. Pharm. Bull.* (Tokyo), **21**, 107 (1973).

[4] T. Miki, K. Hiraga, and T. Asako, Japan. Patent Appl., March 11, 1966.

[5] H. Gibian, K. Kieslich, H.J. Koch, H. Kosmol, C. Rufer, E. Schroder, and R. Vossing, *Tetrahedron Letters*, **1966**, 2321.

[6] T. Asako, K. Hiraga, and T. Miki, *Chem. Pharm. Bull.* (Tokyo), **21**, 697 (1973).

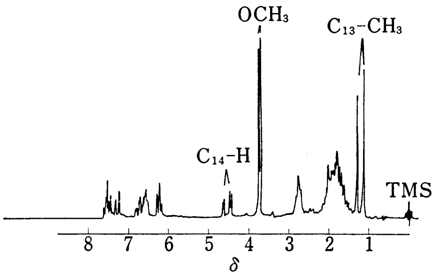


Fig. 1. NMR Spectrum of a Mixture of VIa and VIb in $CDCl_3$

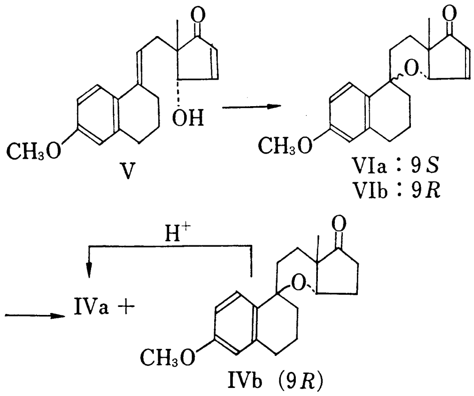
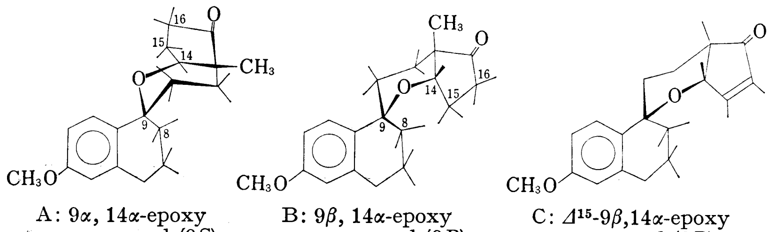


Chart 2

The oily mixture was hydrogenated over Raney Ni or palladium on charcoal, and the products were separated on silica gel into two compounds: one, mp 80—81°, was identified as *rac*-IVa; and the other, mp 100—101°, showed spectra similar to those of *rac*-IVa except NMR spectrum.

Since the latter (IVb) was easily isomerized in acidic solution into IVa and both of them were converted into 3-methoxy-13α-estra-1,3,5(10),8,14-pentaen-17β-ol (III), it was evident that they are stereoisomers due to the difference in the configuration at C-9. Furthermore, the fact that IVb is readily isomerized into IVa indicates that IVa is thermodynamically more stable than IVb. Considering the fact that the cyclization of II gave a single product IVa whereas two isomers (VIa and VIb) were obtained from V, it was presumed that the steric hindrance of the protons at C-15 and/or C-16 with other part of the molecule in IVb might be more significant than that in IVa.

An attempt was next made to determine the configuration at C-9 of IVa and IVb having natural configuration at C-13, where $18\text{-}CH_3$ takes β-position, by examining the stability of the molecule with Dreiding model. A and B in Fig. 2 showstructures of 9β,14α (9*R* configuration) and 9α,14α (9*S* configuration), in which the rings B and C (epoxy ring) take chair form and the ring A is placed in such a way that it takes equatorial orientation for the ring C, so as to minimize the conformational energy.[7]



A: 9α, 14α-epoxy compound (9*S*)
B: 9β, 14α-epoxy compound (9*R*)
C: Δ^{15}-9β,14α-epoxy compound (9*R*)

Fig. 2

The equatorial hydrogen at C-8 of the 9β,14α-epoxy compound (9*R*) approaches within *ca.* 1.1 Å to one of the hydrogens at C-15, which may cause strong Van der Waals repulsion[7] and destabilize the molecule.

On the other hand the interaction between hydrogens at C-8 and at C-15 in the Δ^{15}-9β,14α-epoxy compound (C in Fig. 2) is negligible. This may explain the fact that two isomers (VIa and VIb) exist in the cyclization product of V.

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[7] E.L. Eliel, "Conformational Analysis," John Wiley & Sons, Inc., New York, 1965.

Thus, the more stable isomer (IVa) may be assigned to 9α,14α-epoxy compound (9*S*) and the less stable one (IVb) to 9β,14α-epoxy compound (9*R*).

Spectral data also supports this assignment.

The chemical shifts of C_{14}-H (in CCl_4) are observed at 4.07 ppm in IVa and at 3.60 ppm in IVb (Fig. 3). Fig. 4 shows conformation of the ring D and relative position of C_{14}-H in IVa and IVb drawn according to the Dreiding model of the most stable strainless structures. The hydrogen at C-14 of IVa is located nearly in the same plane that C_{17} carbonyl group forms but in IVb this hydrogen stands above the plane with the angle of about 40°. Assuming the anisotropy of carbonyl group influences the chemical shift of C_{14}-H, it is understood that absorption of the C_{14}-H in IVa appears at lower field than IVb.[8]

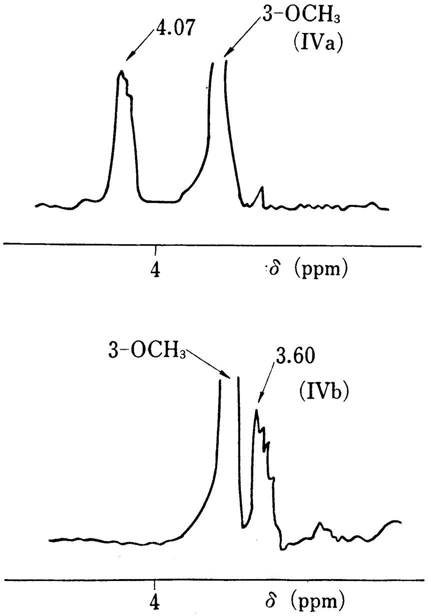

Fig. 3. Chemical Shift of C_{14}-H in the NMR Spectra of IVa and IVb in $CDCl_3$

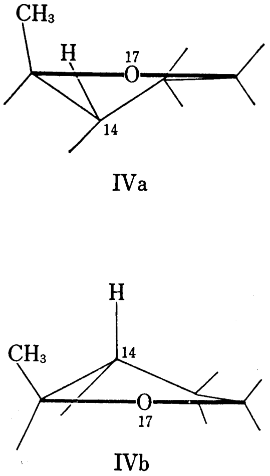

Fig. 4. Comformation of Ring D in 9,14α-Epoxy Compound

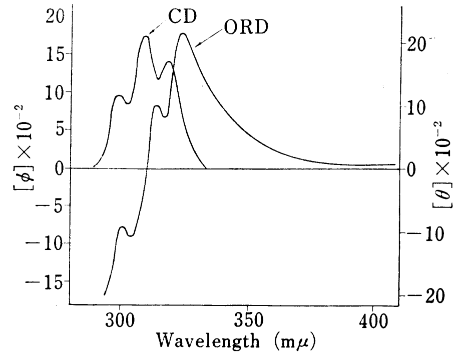

Fig. 5. ORD and CD Curves of Optically Active 9α,14α-Epoxy Compound (IVa) in Dioxane

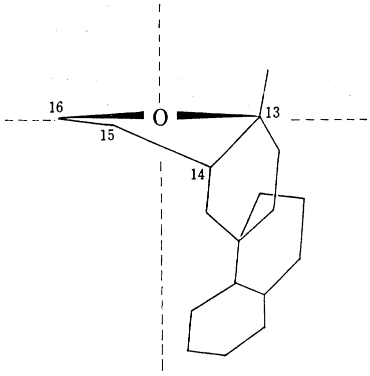

Fig. 6. Back Octant Diagram of IVa

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[8] N.S. Bhacca and D.H. Williams, "Applications of NMR spectroscopy in organic chemistry," Holden-Day, Inc., San Francisco, 1964.

Fig. 5 shows the optical rotatory dispersion (ORD) and circular dichroism (CD) curves of optically active IVa,[3] which has natural configuration at C-13. Positive Cotton effect[9] corresponds to the back Octant Diagram (Fig. 6) drawn for the above stereostructure of 9α,14α-epoxy compound (9*S* configuration).

Experimental

***rac*-3-Methoxy-9α,14α-epoxy-8,14-secoestra-1,3,5(10)-trien-17-one (IVa) from II**[2]——To a solution of 0.4 g of *rac*-II in 30 ml of MeOH was added 1 ml of 6N HCl and the resulting mixture was allowed to stand for 4 hr at room temperature. The reaction mixture was poured into water, extracted with ether and washed with water, a 5% aqueous $NaHCO_3$ solution and water. The organic layer was dried and concentrated to give a yellow oil of 0.4 g. When this oil was chromatographed on silica gel with the solvent (benzene: ether=9: 1), 0.3 g of *rac*-IVa was obtained as crystals. mp 81—83° (from MeOH). UV $\lambda_{\max}^{\text{EtOH}}$ mμ (ε): 276 (1545), 283 (1500). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1742, 1620, 1595, 1509, 836. NMR δ_{ppm} (CCl_4): 0.92 (3H, singlet, C_{13}–CH_3), 3.67 (3H, singlet, OCH_3), 4.07 (1H, multiplet, C_{14}–H), 6.37 (1H, doublet, C_4–H, J=2 Hz), 6.55 (1H, quartet, C_2–H, J=2 Hz & 8 Hz), 7.10 (1H, doublet, C_1–H, J=8 Hz). *Anal.* Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.95; H, 7.94.

***rac*-3-Methoxy-13α-estra-1,3,5(10),8,14-pentaen-17β-ol (III) from (IVa+IVb)**——0.15 g of *rac*-3-methoxy-9,14α-epoxy-8,14-secoestra-1,3,5(10)-trien-17-one (mixture of IVa and IVb) was dissolved in MeOH and 1.5 ml of conc. HCl was added. This solution was stirred at 70—80° for 20 min and then poured into water and extracted with ether. The organic layer was washed with a 5% $NaHCO_3$ solution and a sat. aqueous NaCl solution and dried over Na_2SO_4. Evaporation of ether gave 0.14 g of *rac*-III. mp 101° (from EtOH). UV $\lambda_{\max}^{\text{EtOH}}$ mμ (ε): 311 (2.0×10^4). IR $\nu_{\max}$ cm^{-1}: 3400, 1615, 1510.

***rac*-3-Methoxy-9,14α-epoxy-8,14-secoestra-1,3,5(10),15-tetraen-17-one (VI)**——To a solution of 0.2 g of 14α-hydroxy-3-methoxy-8,14-secoestra-1,3,5(10),9,15-pentaen-17-one (V)[6] in 10 ml of dry benzene was added 1 ml of sat. *p*-TsOH–benzene solution and the mixture was stirred at room temperature for an hour. The reaction mixture was poured into water and extracted with ether. The organic layer was washed with a 5% aqueous $NaHCO_3$ solution and water, and dried over Na_2SO_4. Crude product obtained by evaporation of ether was chromatographed on silica gel with benzene–AcOEt to give 0.18 g of VI as an oily material. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 1714, 1610, 1502.

***rac*-3-Methoxy-9β,14α-epoxy-8,14-secoestra-1,3,5(10)-trien-17-one (IVb) and IVa from VI**——A solution of 0.32 g of an oil VI (mixture of isomers) and 20 ml of EtOH was shaken under a stream of hydrogen in the presence of 0.08 g of Raney Ni. After about 20 ml of hydrogen was absorbed, catalyst was filtered off and the filtrate was concentrated to give 0.3 g of an oily mixture of IV. When this oil was chromatographed on silica gel with the solvent system of benzene–*n*-hexane (3: 1), 0.09 g of *rac*-IVb was obtained. mp 100—101°. UV $\lambda_{\max}^{\text{EtOH}}$ mμ (ε): 276 (1410), 282 (1320). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1740, 1613, 1590, 1502, 1252. NMR δ_{ppm} (CCl_4): 0.91 (3H, singlet, C_{13}–CH_3), 3.60 (1H, multiplet, C_{14}–H), 3.72 (3H, singlet, OCH_3), 6.58 (2H, multiplet, C_2 & C_4–H), 7.27 (1H, doublet, C_1–H, J=8 Hz). *Anal.* Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.32; H, 8.05.

Further elution with only benzene gave 0.14 g of *rac*-IVa. This is identified by comparison with the authentic sample mentioned above.

Isomerization of IVb into IVa occurred readily by the treatment with MeOH–HCl at room temperature.

Acknowledgement The authors wish to thank Drs. S. Tatsuoka and Y. Abe for their constant encouragement throughout this work.

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[9] W. Klyne, *Tetrahedron*, **13**, 29 (1961).