

## Studies on the Total Synthesis of Steroids: the Structure of 9,14-Epoxy-Steroids

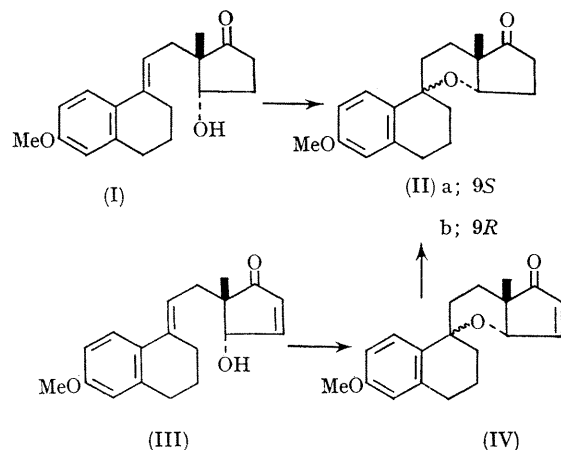
By TSUNEHICO ASAKO, KENTARO HIRAGA, and TAKUICHI MIKI\*

(Chemical Research Laboratories, Research and Development Division, Takeda Chemical Industries, Ltd., Juso-Nishino-cho Higashiyodogawa-ku, Osaka, Japan)

**Summary** The 9*S* configuration is assigned to the more stable 9,14 $\alpha$ -epoxy-3-methoxy-8,14-seco-oestra-1,3,5(10)-trien-17-one.

RECENTLY, 14 $\alpha$ -hydroxy-3-methoxy-8,14-seco-oestra-1,3,5(10),9-tetraen-17-one (I) was cyclized in the presence of a mild acid to give 9,14 $\alpha$ -epoxy-3-methoxy-8,14-seco-oestra-1,3,5(10)-trien-17-one (IIa).<sup>1</sup> This communication deals with the configuration at C-9, which has remained unclarified.

Meerwein-Ponndorf reduction of 3-methoxy-8,14-seco-oestra-1,3,5(10),9,15-pentaene-14,17-dione<sup>2</sup> gave the corresponding 14 $\alpha$ -hydroxy-compound (III), which was cyclized in benzene-toluene-*p*-sulphonic acid to an oily mixture of  $\Delta^{15}$ -9,14-epoxyoestratetraenes (IV). The mixture was hydrogenated in the presence of palladium on charcoal. Chromatographic separation of the reaction products on



silica gel gave two substances in a ratio of 3 : 2. One (m.p. 80—81°, rac.) was identified as (IIa), and the other [m.p. 100—101°, rac. (IIb)] showed spectra similar to those of (IIa). Since they were converted into the same 3-methoxy-13 $\alpha$ -oestra-1,3,5(10),8,14-pentaen-17 $\beta$ -ol with MeOH-HCl, and since (IIb) was isomerized into (IIa) with a weak acid, they must be isomeric at C-9. Thermodynamically, (IIa) may be more stable than its isomer (IIb).

The stability of 9 $\alpha$ , 14 $\alpha$ - and 9 $\beta$ ,14 $\alpha$ -epoxy-compounds was examined with Dreiding models. The equatorial hydrogen at C-8 of the 9 $\beta$ ,14 $\alpha$ -epoxy-compound approaches

one of the hydrogens at C-15 to within a distance of *ca.* 1.1 Å, which may cause strong van der Waals repulsion. Therefore, the 9 $\beta$ ,14 $\alpha$ -epoxy-compound (9*R*-configuration) is the less stable isomer, and the 9 $\alpha$ ,14 $\alpha$ -epoxy-compound (9*S*-configuration) the more stable isomer.

On the other hand, the interaction between hydrogens at C-8 and at C-15 in the  $\Delta^{15}$ -9 $\beta$ ,14 $\alpha$ -epoxy-compound is negligible. This may explain the fact that two isomers (IV) exist in the cyclization product of (III).

(Received, July 14th, 1969; Com. 1035.)

<sup>1</sup> T. Miki, K. Hiraga, and T. Asako, Japan P. Appl., March 11, 1966; N.P., 67-14023; H. Gibian, K. Kieslich, H. J. Koch, H. Kosmol, C. Rufer, E. Schröder, and R. Vössing, *Tetrahedron Letters*, 1966, 2321.

<sup>2</sup> K. Hiraga, T. Asako, and T. Miki, Japan P. Appl., Feb. 9, 1967; R. D. Hoffsommer, D. Taub, and N. L. Wendler, *J. Org. Chem.*, 1967, 32, 3074.