

THE ANOMALOUS CHLORINATION OF ESTRADIOL 17 $\beta$ -ACETATE

WITH ISOCYANURIC CHLORIDE

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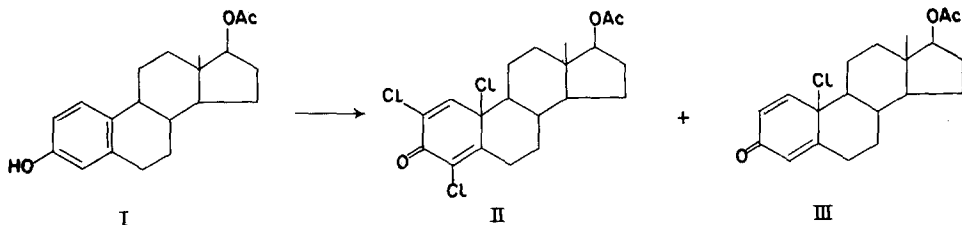
INTRODUCTION of halogen atoms at various positions of the steroid molecules has often given rise to interesting biological properties.

Now, the author wishes to report the synthesis of 2,4,10 $\beta$ -trichloro-17 $\beta$ -acetoxy-1,4-estradiene-3-one and 10 $\beta$ -chloro-17 $\beta$ -acetoxy-1,4-estradiene-3-one by a novel reaction. Chlorination of estradiol 17 $\beta$ -acetate (I) with isocyanuric chloride<sup>1</sup> in *t*-butyl alcohol-acetic acid gave a mixture which afforded by fractional crystallization 2,4,10 $\beta$ -trichloro-17 $\beta$ -acetoxy-1,4-estradiene-3-one (II), m.p. 205°,  $[\alpha]_D^{17} + 1.9$  (c 1.3, CHCl<sub>3</sub>), (Found: C, 57.67; H, 5.46; Cl, 24.13 Calc. for C<sub>20</sub>H<sub>23</sub>O<sub>3</sub>Cl<sub>3</sub>: C, 57.60; H, 5.56; Cl, 25.51) and 10 $\beta$ -chloro-17 $\beta$ -acetoxy-1,4-estradiene-3-one (III), m.p. 124°,  $[\alpha]_D^{18} + 10.7$  (c 1.0, CHCl<sub>3</sub>), (Found: C, 68.28; H, 7.22; Cl, 9.90. Calc. for C<sub>20</sub>H<sub>25</sub>O<sub>3</sub>Cl: C, 69.02; H, 7.24; Cl, 10.19). The structure of II was based on its infrared absorption at 6.20  $\mu$  (1,4-diene-3-one)<sup>2</sup> and ultraviolet absorption maximum at 258 m $\mu$  (E 15.400).

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<sup>1</sup> F. Mukawa, J. Chem. Soc. Japan **78**, 450 (1957).

<sup>2</sup> N. Jones and F. Herling, J. Org. Chem. **19**, 1252 (1954).



The orientation of 10 $\beta$ -chlorine atom was supported by the fact that the rotatory dispersion curve of II was nearly identical with 4-chlorotestosterone.<sup>3</sup> (Fig. 1).

The ultraviolet spectrum of II in ethanolic alkaline solution<sup>4</sup> showed a maximum at 300 m $\mu$ , which is typical for the 3-hydroxyestra-1,3,5(10)-triene system.<sup>5</sup> Reduction of II with zinc and acetic acid gave I, similarly, reduction with sodium borohydride in methanol gave 2(or 4)-chloro-estradiol 17 $\beta$ -acetate (IV), m.p. 235 $^{\circ}$  (dec.),  $\lambda_{\max}^{\text{dioxane}}$  282 m $\mu$  (E 2,300),<sup>6</sup> infrared:  $\lambda_{\max}$  2.9(s), 5.9(v.s), 7.7(m), 1.9(m),

<sup>3</sup> C. Djerassi, Private communication. (1958); C. Djerassi, R. Rimiker and B. Rimiker, J. Amer. Chem. Soc. **78** 6362, 6377 (1956).

<sup>4</sup> A. S. Meyer, J. Org. Chem. **20**, 1240 (1955).

<sup>5</sup> L. Dorfman, Chem. Rev. **53**, 47 (1953).

<sup>6</sup> 2,4-Dibromoestradiol [R. B. Woodward, J. Amer. Chem. Soc. **62**, 1625 (1940)] has a maximum at 293 m $\mu$  (E 3,300, dioxane) in the ultraviolet region.

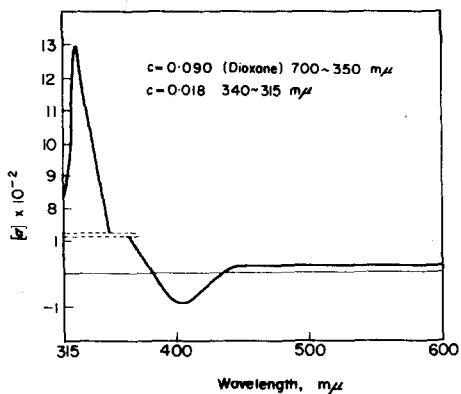


FIG. 1.

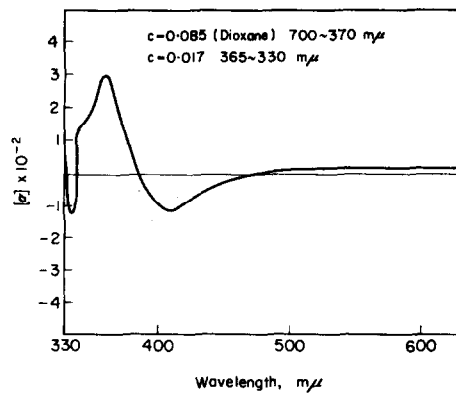


FIG. 2.

9.2(w), 9.6(w), 9.9(w), 11.6(w), 12.8(m) $\mu$ , (Found: C, 68.80; H, 7.51; Cl, 10.30. Calc. for C<sub>20</sub>H<sub>25</sub>O<sub>3</sub>Cl: C, 69.02; H, 7.24; Cl, 10.19). The monochloride (III) was readily transformed into I in alkaline solution. The reduction of III with sodium borohydride in methanol or the hydrogenation of II in the presence of palladium catalyst also gave I. The presence of the 1,4-diene-3-one system was revealed by its ultraviolet spectrum ( $\lambda_{\text{max}}^{\text{EtOH}}$  248 m $\mu$ , E 16,000) and infrared absorption spectra (band at 6.20  $\mu$ ). The  $\beta$ -orientation of chlorine atom was supported by the fact that the shape of the rotatory dispersion curve roughly coincided with that of cholest-1,4-diene-3-one type. (Fig. 2).<sup>3</sup> Thus the structure of III is elucidated as 10 $\beta$ -chloro-17 $\beta$ -acetoxy-1,4-estradiene-3-one. Bioassay: II showed estrogenic action when tested with adult ovariectomized mice (Allen - Doisy vaginal smear method), and a slight androgenic activity with castrate immature rats. III showed estrogenic action with duration.

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