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1. Lindqvist, I. and Zackrisson, M. *Acta Chem. Scand.* **14** (1960) 453.
2. Kindler, K. *Ann.* **431** (1923) 209.
3. Zackrisson, M. and Lindqvist, I. *J. Inorg. Nuclear Chem.* **17** (1961) 69.

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### 6 $\alpha$ -Trifluoromethyl-17 $\alpha$ -acetoxyprogesterone and some Unsaturated Analogs

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It has recently been shown <sup>1,2</sup> that introduction of an  $\alpha$ -orientated fluorine, chlorine or bromine atom in the 6-position of 17 $\alpha$ -acetoxyprogesterone causes a remarkable increase of its oral progestational activity, and that this activity is further increased by  $\Delta^1$ ,  $\Delta^6$  or  $\Delta^{1,6}$  unsaturation of these compounds. It seemed therefore of interest to synthesize 6 $\alpha$ -trifluoromethyl-17 $\alpha$ -acetoxyprogesterone and some of its corresponding unsaturated analogs.

When a solution of 17 $\alpha$ -acetoxyprogesterone-3-ethyl enol ether (I)<sup>3</sup> in trifluoroiodomethane<sup>3</sup> containing pyridine was irradiated in a quartz vessel at room temperature with ultraviolet light from a high pressure mercury lamp, 6-trifluoromethyl-17 $\alpha$ -acetoxyprogesterone-3-ethyl enol ether (II) [m.p. 184–186°C,  $[\alpha]_D^{20}$  –181° (all rot. in CHCl<sub>3</sub>),  $\lambda_{\max}^{\text{EtOH}}$  256 m $\mu$ ,  $\epsilon$  21 400. Found: C 66.53; H 7.66. Calc. for C<sub>26</sub>H<sub>35</sub>F<sub>3</sub>O<sub>4</sub>: C 66.65; H 7.53] was obtained in 60 % yield. Acid catalyzed hydrolysis of II afforded smoothly 6 $\alpha$ -trifluoromethyl-17 $\alpha$ -acetoxyprogesterone (III) (m.p. 206–207°C,  $[\alpha]_D^{20}$  +30°,  $\lambda_{\max}^{\text{EtOH}}$  234 m $\mu$ ,  $\epsilon$  15 600. Found: C 65.37; H 6.98. Calc. for C<sub>24</sub>H<sub>31</sub>F<sub>3</sub>O<sub>4</sub>: C 65.45; H 7.10).

The  $\alpha$ -configuration of the trifluoromethyl group in III followed from stability toward treatment with hydrogen chloride in acetic acid<sup>4</sup>, and from the fact, that the rotatory dispersion curve was very similar to that of 17 $\alpha$ -acetoxyprogesterone<sup>5</sup>.

Selenium dioxide dehydrogenation of III yielded 6 $\alpha$ -trifluoromethyl- $\Delta^{1,4}$ -pregnadiene-17 $\alpha$ -ol-3,20-dione acetate (IV) (m.p. 213–215°C,  $[\alpha]_D^{20}$  –29°,  $\lambda_{\max}^{\text{EtOH}}$  242 m $\mu$ ,  $\epsilon$  17 350. Found: C 65.40; H 6.80. Calc. for C<sub>24</sub>H<sub>29</sub>F<sub>3</sub>O<sub>4</sub>: C 65.73; H 6.67).

6-Trifluoromethyl- $\Delta^{4,6}$ -pregnadiene-17 $\alpha$ -ol-3,20-dione acetate (V) (m.p. 233–234°C,  $[\alpha]_D^{20}$  0°,  $\lambda_{\max}^{\text{EtOH}}$  270 m $\mu$ ,  $\epsilon$  20 300. Found: C 65.44; H 6.89. Calc. for C<sub>24</sub>H<sub>29</sub>F<sub>3</sub>O<sub>4</sub>: C 65.73; H 6.67) was synthesized from the 3-cycloethylene ketal of III<sup>6</sup> (m.p. 178–182°C,  $[\alpha]_D^{20}$  +66°. Found: C 64.28; H 7.29. Calc. for C<sub>26</sub>H<sub>35</sub>F<sub>3</sub>O<sub>5</sub>: C 64.45; H 7.28) by bromination at C-7 with NBS followed by dehydrobromination in boiling collidine and hydrolysis of the ketal with methanol-sulfuric acid.

The oral progestational activities of II, III, IV, and V, determined by the Mc Phail modification of the Claiberg assay are given in Table 1.

Table 1. Oral progestational activity — Claiberg assay.

Compound	Relative activity
6 $\alpha$ -Methyl-17 $\alpha$ -acetoxyprogesterone	1
6 $\alpha$ -Trifluoromethyl-17 $\alpha$ -acetoxyprogesterone	1–2
6 $\alpha$ -Trifluoromethyl-17 $\alpha$ -acetoxyprogesterone-3-ethyl enol ether	0.5–1
6-Trifluoromethyl- $\Delta^{4,6}$ -pregnadiene-17 $\alpha$ -ol-3,20-dione acetate	0.5–1
6 $\alpha$ -Trifluoromethyl- $\Delta^{1,4}$ -pregnadiene-17 $\alpha$ -ol-3,20-dione acetate	0.5–1

1. Ringold, H. J., Batres, E., Bowers, A., Edwards, J. and Zderic, J. *J. Am. Chem. Soc.* **81** (1959) 3485.
2. Bowers, A., Ibáñez, L. C. and Ringold, H. J. *J. Am. Chem. Soc.* **81** (1959) 5991.
3. The addition of trifluoroiodomethane to unsaturated systems has been extensively investigated by Haszeldine. See, e.g., Walling, C. *Free Radicals in Solution*, John Wiley & Sons, New York 1957, pp. 247–272.
4. Bowers, A., Ibáñez, L. C. and Ringold, H. J. *Tetrahedron* **7** (1959) 138.
5. Djerassi, C., Osiecki, J., Riniker, R. and Rinker, B. *J. Am. Chem. Soc.* **80** (1958) 1216.
6. Prepared from III by the dioxolane method: Dauben, H. J., Löken, B. and Ringold, H. J. *J. Am. Chem. Soc.* **76** (1954) 1359.

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