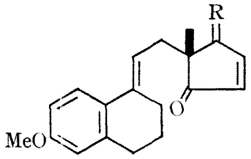
Total Synthesis of Oestrone *via* Oestriol Dimethyl Ether

By KENTARO HIRAGA, TSUNEHIKO ASAKO, and TAKUICHI MIKI*

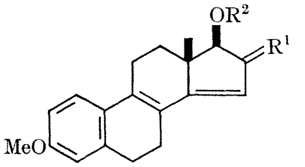
(*Chemical Research Laboratories, Research and Development Division, Takeda Chemical Industries, Ltd., Juso-Nishino-cho, Higashiyodogawa-ku, Osaka, Japan*)

Summary Cyclization of seco-oestrapentaene (IV) gave an oestriol derivative (V), which was further transformed to oestrone.

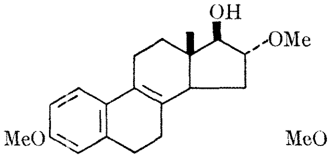
RECENTLY, two research groups[1,2] including ours reported the preparation of 3-methoxy-8,14-seco-oestra-1,3,5(10),9,15-pentaene-14,17-dione (I) by condensation of 6-methoxy-1-vinyl-1-tetralol and 4-hydroxy-2-methylcyclopentane-1,3-dione or its ester in the presence of a basic catalyst.



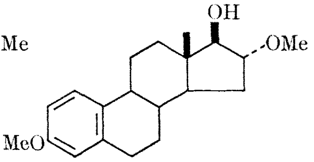
(I) R=O
(II) R=α-OH, β-H
(III)R=α-H, β-OH
(IV) R=α-H,β-OCOPh



(V) R^1=α-OMe, β-H; R^2=COPh
(VI)R^1=α-H, β-OMe; R^2=COPh
(VII) R^1=α-OMe, β-H; R^2=H



(VIII)



(IX)

We report here a synthesis of oestriol ethers, and their transformation to oestrone, starting from the seco-pentaenedione (I).

Meerwein–Ponndorf reduction of the dione (I) gave a mixture of 17α- and 17β-hydroxy-8,14-seco-oestra-1,3,5(10),9,-15-pentaen-14-ones, (II) m.p. 115°, and (III) oily substance; benzoate (IV) m.p. 112°.

The benzoate (IV) was subjected to the cyclization reaction with methanolic hydrogen chloride. Purification of the product by chromatography gave two oestrapentaenetriols (V) m.p. 142°, τ 8·96 p.p.m. (s, 13-CH_3), *J* 1·0 Hz. (16βH–15H); and (VI) oily substance, minor product τ 8·72 p.p.m. (s, 13-CH_3), *J* 2·5 Hz. (16α-H–15-H). The n.m.r. chemical shifts of the 13-methyl group indicate[3] that the former (V) may have a methoxy-group at 16α and the latter (VI) at 16β.

The hydrolysed compound (VII) was hydrogenated over Raney nickel to afford oestratetraenetriol (VIII) in good yield. Further reduction of (VIII) with potassium in liquid ammonia gave the 3,16-dimethyl ether of (±)-oestriol (IX). Compound (IX) was converted into (±)-oestrone by fusion[4] with pyridinium chloride. The total yield of (±)-oestrone from the benzoate of oestrapentaenetriol (V) was 55%.

We thank Dr. S. Tatsuoka and Dr. Y. Abe for encouragement.

(*Received, July 14th, 1969; Com. 1034.*)

---

[1] R. D. Hoffsommer, D. Taub, and N. L. Wendler, *J. Org. Chem.*, 1967, **32**, 3074.
[2] K. Hiraga, T. Asako, and T. Miki, Japan P. Appl., Feb. 9, 1967.
[3] *cf.* A. D. Cross and P. Crabbé, *J. Amer. Chem. Soc.*, 1964, **86**, 1221.
[4] J. C. Sheehan, W. F. Erman, and P. A. Cruickshank, *J. Amer. Chem. Soc.*, 1957, **79**, 147.