[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF THE LAKESIDE LABORATORIES, INC.]

Synthetic Estrogenic Substances.[1] II. Hexesterol and Some of its Esters

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Since the discovery of the estrogenic activity of diethylstilbestrol by Dodds and co-workers,[2] many other relatively simple compounds have been tested for this property. Of the compounds studied, some derivatives of triphenylethylene,[3,4] diethylstilbestrol and hexestrol[5] appear to show promise of clinical usefulness. In view of the interest in the effectiveness and duration of action of the esters of estradiol, diethylstilbestrol and testosterone as well as the demonstrated estrogenic activity of hexestrol diacetate,[6] it seemed desirable to prepare and determine the estrogenic activity of some esters of hexestrol.

Although two very satisfactory syntheses of hexestrol[7,8] have been published recently, the procedure worked out in these laboratories is included as it appears to have certain advantages in regard to convenience.

Results obtained in our laboratory indicate that oil-soluble hexestryl esters are less potent estrogens than hexestrol, but that the estrogenic action is more prolonged. When tested on castrated female rats, a dose of 4 micrograms produced pro-estrus smears lasting for eight to ten days. The estrogenic activity of hexestryl disuccinate in aqueous solution approximates that of hexestrol. The results of the physiological and pharmacological studies on these compounds will be presented in detail elsewhere.

Experimental Part

Preparation of Hexestrol (3,4-Di-*p*-hydroxylphenylhexane).—A mixture of 20 g. of crude dianisylhexane,[7,8] 125 ml. of glacial acetic acid and 75 ml. of hydriodic acid (sp. gr. 1.7) was distilled slowly through a short column until no more methyl iodide distilled over and the temperature at the head of the column rose to 110°. The cooled residue in the distilling flask was diluted with 500 ml. of cold water and the aqueous solution extracted with three 100-ml. portions of isopropyl ether. After washing with water, sodium bicarbonate solution and again with water, the ethereal solution was dried over "Drierite."

The solvent was removed on the steam-bath and the residual phenol crystallized from 200 to 250 ml. of benzene. The yield of product melting at 183–185° was practically quantitative.

Preparation of Hexestryl Esters.—A solution of 1 g. of hexestrol and two to three times the theoretically required amount of acid anhydride in 10 ml. of pyridine was gently refluxed for two to three hours. After cooling, the pyridine solution was poured into 200 ml. of water and the solid ester collected by suction, washed with a little sodium bicarbonate solution and dried in a vacuum desiccator over concentrated sulfuric acid. The esters generally crystallized well from benzene or petroleum ether (b. p. 60–68°).

Because of its solubility in water, some modification of the general procedure is required for the preparation of hexestryl disuccinate. The ester is extracted from the aqueous pyridine solution with chloroform and crystallized from a mixture of chloroform and petroleum ether.

TABLE I

PROPERTIES OF HEXESTRYL ESTERS

				Analyses			
				Calcd.		Found[a]	
Ester	Cryst. from	M. p., °C.	Formula	C	H	C	H
Propionate	Pet. ether	127–128	$C_{24}H_{30}O_4$	75.4	7.1	75.7	8.0
Butyrate	Pet. ether	106–107	$C_{26}H_{34}O_4$	76.1	8.3	76.2	8.9
Benzoate	Benzene	236–237	$C_{32}H_{30}O_4$	80.3	6.3	80.2	6.5
Caproate	Pet. ether	96– 97	$C_{30}H_{44}O_4$	76.8	9.4	77.0	9.1
Succinate	Chloroform + pet. ether	150–153	$C_{26}H_{30}O_8$	66.4	6.4	66.6	6.8

[a] Microanalyses by Dr. Carl Tiedcke, New York, N. Y.

Acid chlorides may be substituted for the anhydrides in the preparation of hexestryl esters but the product is then contaminated with a tarry material and is purified with difficulty.

Summary

Satisfactory procedures have been described for the preparation of hexestrol and its esters.

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[1] For the first paper of this series see Mellish, Baer and Macias, *Endocrinology*, **26**, 273 (1940).

[2] Dodds, Robinson, *et al.*, (a) *Nature*, **141**, 247 (1938); (b) *Proc. Roy. Soc.* (London), **B127**, 140 (1939).

[3] Robson, Schonberg and Fahim, *Nature*, **142**, 292 (1938).

[4] Schönberg, Robson, Tadros and Fahim, *J. Chem. Soc.*, 1327 (1940).

[5] Campbell, Dodds and Lawson, *Proc. Roy. Soc.* (London), **B128**, 253 (1940).

[6] Kerschbaum, Kleedorfer, *et al.*, *Naturwissenschaften*, **27**, 131 (1939).

[7] Docken and Spielman, THIS JOURNAL, **62**, 2163 (1940).

[8] Bernstein and Wallis, *ibid.*, **62**, 2871 (1940).