THE BIOLOGICAL ACTIVITY OF ESTRA-1,3,5,(10),6,8-PENTAEN-3,16β,17β-TRIOL

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Received October 5, 1961

In our standard general screening assay, it was noted that the estrogen, estra-1,3,5(10),6,8-pentaen-3,16β,17β-triol (abbr. as triol I), is especially potent in reducing the size of the testes and ventral prostate of the rat. This is in keeping with the anti-prostatic effect of 16β,17β-dihydroxy estrogens in general (Katzman et al, 1960). Indeed, after having screened many estrogens, we have never observed so powerful a reduction in the ventral prostate of the 21-day old Holtzman rat with so little effect on body weight. These data are summarized in Table I.

This finding prompted us to compare the anti-prostatic activity of estra-1,3,5(10),6,8-pentaen-3,16β,17β-triol with similar activities of diethylstilbestrol and estradiol-17β, using the aged male Holtzman rat. It will be observed in Table II that triol I is fully as active as diethylstilbestrol or estradiol-17β in this test, with much milder effects on final body weight, spleen, and thymus. Significantly, the weight of the spleen is not reduced when this steroid is administered.

The estrus-producing activity of triol I, as measured in the adult castrate mouse by the Mather modification (Mather, 1942) of the Marrian-Parkes assay procedure (Marrian and Parkes, 1929), is very low, requiring 13.5 micrograms to produce estrus in 50% of the animals. This is

Table I

General Screening Assay Using 21-day Old Male Rats

	Initial Body Wt. g.	Final Body Wt. g.	Ventral Prostate mg.	Testes mg.	Levator Ani mg.	Adren. mg.	Left Kidney mg.	Liver g.	Spleen mg.	Thymus mg.
Controls	52	124	60.3	1019	40.1	34.2	643	8.0	446	436
Triol I[d]	53	115	17.1	340	30.4	42.1	633	7.7	496	287
Variation from control (%)		-7.3	-72	-67	-24	+23	-1.6	-3.8	+11	-34

All weights are arithmetic means of the group.
d) 10 animals in each group. Dosage schedule as in Table III.

Table II

Anti-prostatic Action of Three Estrogens Using Aged Male Rats

	Initial Body Wt. g.	Final Body Wt. g.	Testes g.	Ventral Prostate mg.	Spleen mg.	Thymus mg.
Control	428	433	3.40	601	876	281
Diethylstilbestrol[d]	428	319	2.54	224	649	56.5
Variation from control (%)		-26	-25	-63	-26	-80
Estradiol USP[d]	428	337	2.46	210	699	67.4
Variation from control (%)		-22	-28	-65	-20	-76
Triol I[d]	428	378	2.65	201	870	193
Variation from control (%)		-13	-22	-67	< 1	-31

[d]Dose 1 mg. per kg. subcutaneously in CMC every other day for 7 injections; autopsy on the 15th day; 20 animals in each group, including Control group; controls similarly injected with CMC diluent.

Table III

General Screening Assay Using 30-day Old Female Rats

	Initial Body Wt. g.	Final Body Wt. g.	Uterus mg.	Ovaries mg.	Corpora Lutea no.	Adren. mg.	Left Kidney mg.	Liver g.	Spleen mg.	Thymus mg.
Controls	82	157	201.7	45.9	9.6	45.7	795	10.2	730	455
Triol I[d]	82	139	203.7	33.0	1.8	47.4	691	7.8	526	352
Variation from controls (%)		-11	+1.0	-28	-81	+3.7	-13	-24	-28	-23

[d] Dose 50 micrograms per day subcutaneously in CMC for 14 days; autopsy on the 15th day; 10 animals in each group, including Control group; controls similarly injected with CMC diluent.

All weights are arithmetic means of the group.

approximately 1/800 the activity of estradiol-17β. Preliminary studies in the intact immature female rat using the Curtis-Doisy assay method (Curtis and Doisy, 1931) also show this triol to be among the weakest estrogenic substances which we have studied.

Because of the very mild estrus-producing activity of triol I, we were led to try its effect also in the intact 30-day old female Holtzman rat, the results of this study being summarized in Table III. In this test animal, as well as in the male, triol I in the amounts used appears to exert a suppressive effect on pituitary gonadotrophin. Since the uterine weights are not reduced, however, we assume that the slight estrus-producing activity of the steroid compensates for the reduction of endogenous estrogen due to lack of ovarian stimulation by pituitary gonadotrophin. Curiously, triol I appears to suppress the spleen of the female rat.

Estra-1,3,5(10),6,8-pentaen-3,16β,17β-triol has a melting point of 300-302° unc. in the open air with brilliant red coloration.

The Endocrine Laboratories of Madison, Wisconsin (Dr. Elva G. Shipley, Director), performed the bioassays summarized in Tables I, II, and III.

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