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The antagonism of 17β-oestradiol by stilboestrols methylated in the phenyl rings

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Clark & O'Donnell (1965) found that the presence of four methyl substituents situated *ortho* to the phenolic hydroxyl groups in ψ-diethylstilboestrol produced an anti-oestrogen which was almost devoid of oestrogenic activity. Among related compounds lacking methyl groups in the nucleus, Emmens, Cox & Martin (1958, 1959) reported optimal anti-oestrogenic potency in dimethylstilboestrol and butoestrol. The effects of chain length in nuclear methylated derivatives of stilboestrol have been investigated by using 3,3′,5,5′-tetramethyl-α,β-diethylstilboestrol (I), 3,3′,5,5′-tetramethyl-α,β-dimethylstilboestrol (II) and 3,3′,5,5′-tetramethylstilboestrol (III).

In the uterine weight test in immature mice, only compound I was oestrogenic, being 2.4×10^{-4} times as potent as 17β-oestradiol [fiducial limits ($P=0.95$) 1.4×10^{-4}–3.2×10^{-4}]. Subcutaneous administration of mixtures of compound I (0.02 mg) or compound II (1 mg) with 17β-oestradiol (0.03–0.06 μg) in arachis oil failed to suppress the response of the uterus to oestradiol, but intra-vaginal administration to ovariectomized mice of mixtures of test compound I or II (5 μg) with 17β-oestradiol (1.5×10^{-4} μg to 13.5×10^{-4} μg) in 2% aqueous Tween 80 (0.01 ml.) demonstrated a highly significant inhibition of the vaginal cornification produced by oestradiol. Compound III was inactive in this latter test.

In order to elucidate further the mechanism of this oestrogen antagonism, the effect of compounds I and II on the uptake of tritiated oestradiol was investigated. The test compound (2.5 μg), was administered intravaginally together with 7.5×10^{-5} μg of [6,7-^{3}H]oestradiol-17β in 0.0025 ml. 2% aqueous Tween 80. Both I and II exhibited highly significant blockade of the uptake of the tritiated oestradiol by the vagina. Preliminary experiments on homogenized vaginal tissue followed by subcellular fractionation indicate that the main site of uptake of the tritiated oestradiol is the "nuclear-myofibrillar" fraction and that uptake by this fraction is inhibited by compound I.

Aqueous Tween 80 (2%) is believed to be a suitable vehicle because intravaginal administration of 0.01 ml. of a 10% w/v solution of Tween 80 containing 17β-oestradiol (0.4×10^{-4} and 0.8×10^{-4} μg) did not produce a significant difference in the mitotic index or epithelium thickness from that obtained with aqueous solutions of oestradiol. Furthermore intravaginal administration of 0.01 ml. of aqueous Tween 80 alone (concentration up to 40% w/v) did not alter the normal microscopic appearance of the vaginal epithelium.

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