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OESTROGENIC, ANTI-OESTROGENIC AND FERTILITY EFFECTS OF SOME TRIPHENYLETHANES AND TRIPHENYLETHYLENES RELATED TO ETHAMOXYTRIPHETOL (MER 25)

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1 Five triphenylethylenes, a triphenylethane and a triphenylethanol, carrying methyl substituents ortho to one or both of the ring oxygen functions, have been examined for oestrogenic, and anti-oestrogenic activity in mice, and three of the compounds, α-[4-(β-diethylaminoethoxy)-3, 5-xylyl]-α-phenyl-β-4-methoxyphenyl-ethanol (IV), α'-[4-(β-diethylaminoethoxy)-3, 5-xylyl]-4-methoxy-bibenzyl (V) and α'-[4-(β-diethylaminoethoxy)-3, 5-xylyl]-4-methoxy-stilbene (VI), were tested for their effects on fertility in mice.

2 Orthomethylation reduces oestrogenic and/or anti-oestrogenic activity compared with the reported activities of non-methylated analogues.

3 The anti-oestrogenic ethamoxytriphetol (MER 25) reduced fertility in mice whereas its inactive dimethylated analogue (IV) was ineffective. The weakly active anti-oestrogens, V and VI, did not affect fertility in mice.

Introduction

Since the report of ethamoxytriphetol (MER 25) (Lerner, Holthaus & Thompson, 1958) several triphenylethylene or triphenylethane derivatives have been investigated for anti-oestrogenic and possible anti-fertility activity e.g. MRL 41 (Holtkamp, Davis & Rhodes, 1961), MRL 37 (Barnes & Meyer, 1962), ICI 46,474 (Harper & Walpole, 1966) and CN-55,945 (Callantine, Humphrey, Lee, Windsor, Schottin & O'Brien, 1966), but unlike MER 25 all possess some form of oestrogenic activity (Terenius, 1971).

The introduction of methyl groups *ortho* to the phenolic hydroxyls in ψ-diethylstilboestrol and diethylstilboestrol reduces oestrogenic activity and produces compounds with local anti-oestrogenic activity but no systemic anti-oestrogenic activity (Clark & O'Donnell, 1965; Clark & McCracken, 1971).

In the search for non-oestrogenic, systemic anti-oestrogens the effect of ring methylation *ortho* to ring oxygen in several triphenylethylene and triphenylethane derivatives has been studied.

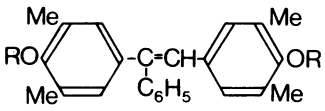
A preliminary account of some of this work was presented to the British Pharmacological Society Meeting (Clark, Evans & Jordan, 1973).

Methods

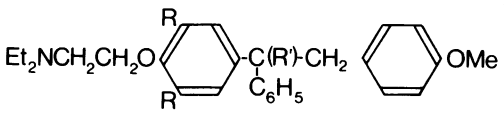
The synthesis and identification of the test compounds (I–VII) shown in Figure 1 will be reported elsewhere (microanalyses and spectral data for the test compounds are in accord with the given structures). MER 25 was supplied by Wm. S. Merrell Co. Cincinnati, Ohio, U.S.A. Mice were of the Tuck No. 1 strain.

Oestrogenic and anti-oestrogenic properties

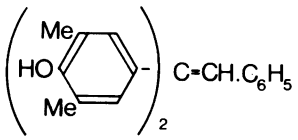
The preparation of solutions and experimental procedures for the immature mouse uterine weight test and the Allen-Doisy test have been described previously (Clark & McCracken, 1971). In the immature mouse uterine weight test, mice were injected (s.c.) with 17β-oestradiol and/or test compounds on three consecutive days and on the morning of the fourth day, animals were killed and uteri were dissected out and weighed wet. The levels of significance between groups were determined by Student's *t* test. For oestrogenic activity test groups were compared with arachis oil controls and for anti-oestrogenic activity with the related 17β-oestradiol treated group. In the Allen-Doisy test 17β-oestradiol



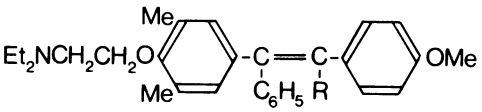
R = Me I
R = H II



R = Me, R' = OH IV
R = Me, R' = H V
R = H, R' = OH MER 25
R = R', = H MRL 37



III



R = H VI
R = Br VII

Figure 1 The chemical structures of compounds described in the text.

and/or test compounds were administered (s.c. in oestrogen tests and intravaginally in anti-oestrogen tests) to ovariectomized mice on two consecutive days. Vaginal smears were taken twice on day 3 in intravaginal assays or on days 3 and 4 in systemic assays.

Antifertility properties

Mature female mice were randomly distributed into groups of ten. Five mature male mice were admitted to each cage for four days. Throughout this period and for one further day female mice were treated daily (s.c.

Table 1 Non-basic compounds. Mean uterine weights (mg) for groups of immature female mice treated with 0, 0.03 or 0.06 μg 17β-oestradiol, increasing doses of compounds I, II, III or 17β-oestradiol (0.03 or 0.06 μg) in combination with increasing doses of compounds I, II or III.

Compound	*Total dose of compound (mg) per mouse*	*Total dose of 17β-oestradiol (μg) per mouse* 0	0.03	0.06
I	0	12.42 ± 0.84	32.68 ± 1.89	47.19 ± 3.15
	1.0	14.49 ± 1.54	32.51 ± 2.63	46.43 ± 5.6
	2.0	17.28 ± 2.05	30.35 ± 2.1	49.32 ± 4.74
II	0	17.98 ± 1.35	27.95 ± 1.77	45.55 ± 3.96
	1.0	20.14 ± 2.02	30.47 ± 2.56	45.07 ± 2.98
	2.0	21.40 ± 0.82*	31.58 ± 2.79	47.70 ± 5.02
	4.0	24.49 ± 1.06**	30.40 ± 1.98	42.52 ± 3.16
III	0	14.63 ± 1.00	31.89 ± 2.03	46.36 ± 2.24
	0.5	–	28.93 ± 2.17	44.14 ± 2.54
	1.0	–	30.45 ± 2.14	36.04 ± 2.17**
	2.0	–	29.23 ± 2.11	42.05 ± 2.73
	0	14.27 ± 0.91	30.88 ± 1.11	56.90 ± 2.02
	0.5	14.61 ± 1.22	–	–
	1.0	14.67 ± 1.30	–	–
	2.0	14.65 ± 0.60	–	–
	4.0	17.12 ± 1.15	–	–

Uterine weights (mg) are given ± s.e. mean. The total dose per animal was administered subcutaneously in three daily subdoses. Each subdose was dissolved in 0.05 ml arachis oil (10 mice per group).
Levels of significance (Student's *t* test) when compared with related control: *$P < 0.05$; **$P < 0.01$.

administration) with the test compounds dissolved in 0.05 ml arachis oil or arachis oil (0.05 ml) alone. Doses of compounds IV and V and MER 25 were 1.0 mg daily and compound VI 0.5 and 1.0 mg daily. After ten days each female was caged individually and at birth litter numbers were recorded.

Results

The test compounds (Figure 1) were examined for oestrogenic and anti-oestrogenic properties by the immature mouse uterine weight test (Tables 1, 2, 3) and compounds I, II, IV, V, VI and VII were also examined in the Allen-Doisy test (Table 4).

Doses up to 2.0 mg of compound I neither increased the uterine weight of immature mice when administered alone nor decreased it when administered simultaneously with 17β-oestradiol (Table 1). Although 2.0 and 4.0 mg of the related diphenolic compound (II) produced significant ($P<0.05$ and $P<0.01$ respectively) increases in uterine weight when compared with controls, neither these nor a 1 mg dose suppressed the increase in uterine weight produced by 17β-oestradiol (Table 1). Compound III, a structural isomer of II, neither produced increases in uterine weight at doses up to 4.0 mg nor antagonized in a dose-dependent manner, the effects of 17β-oestradiol, although 1.0 mg of compound III produced a significant reduction ($P<0.01$) in the increase in uterine weight produced by 0.06 µg 17β-oestradiol (Table 1).

Amongst the aminoethoxy derivatives (Table 2) compounds IV and V were non-oestrogenic at doses up to 8.0 mg whereas VI and VII produced increases in the immature mouse uterine weight, compound VII being approximately four times more active than its non-brominated analogue (VI). Both compounds VI and VII are partial agonists since the maximum response produced by VII was approximately 85%,

Table 2 Oestrogenic activity of amino-ethoxy derivatives. Mean uterine weights (mg) for groups of immature female mice treated with increasing doses of 17β-oestradiol or increasing doses of Compounds IV, V, VI and VII.

Compound	*Total dose of compound (mg) per mouse*	*Total dose of 17β-oestradiol (µg) per mouse*	*Mean uterine weight (mg)*
IV	0	0	13.82 ± 1.13
	0.5	0	12.26 ± 0.70
	2.0	0	13.47 ± 0.69
	8.0	0	12.82 ± 0.90
	0	0.03	32.19 ± 1.23
	0	0.06	49.56 ± 2.54
V	0	0	12.64 ± 1.11
	1.0	0	12.02 ± 0.59
	2.0	0	11.77 ± 0.88
	4.0	0	11.99 ± 0.80
	8.0	0	13.16 ± 0.61
	0	0.03	32.49 ± 1.11
	0	0.06	46.68 ± 1.58
VI	0	0	17.65 ± 1.15
	2.0	0	21.91 ± 1.11*
	4.0	0	31.44 ± 1.17**
	8.0	0	37.79 ± 1.46**
	0	0.02	24.33 ± 0.96
	0	0.04	38.76 ± 1.56
	0	0.08	57.89 ± 1.27
VII	0	0	14.16 ± 0.78
	0.5	0	25.11 ± 1.35**
	1.0	0	37.91 ± 1.71**
	2.0	0	44.55 ± 1.75**
	0	0.02	25.57 ± 0.75
	0	0.04	41.30 ± 1.39
	0	0.08	57.47 ± 1.08

Uterine weights (mg) are given ± s.e. mean. The total dose per animal was administered subcutaneously in three daily subdoses. Each subdose was dissolved in 0.05 ml arachis oil (10 mice per group).
Levels of significance (Student's t test) of test compounds when compared with related arachis oil controls: *$P<0.01$; **$P<0.001$.

and that by VI approximately 60% of that which could be obtained with 17β-oestradiol (Figure 2).

In the immature mouse uterine weight test (Table 3) the anti-oestrogenic properties of MER 25 were confirmed but none of the novel aminoethoxy compounds (IV, V, VI, and VII) was more effective than MER 25. Compound IV, the most closely related to MER 25, was inactive as an anti-oestrogen at doses up to 4.0 mg whereas doses of 2.0 mg of compounds V or VI produced highly significant ($P<0.001$) decreases in the uterine response to 0.06 μg 17β-oestradiol. Compound VI is approximately twice as anti-oestrogenic as V (Figure 3). Compound VII at sub-oestrogenic doses increased ($P<0.05$) rather than decreased the uterine weight response to low doses (0.03 μg) of oestradiol (Table 3).

In the Allen-Doisy tests, compounds I, II, IV, V, VI and VII were neither oestrogenic nor anti-oestrogenic at the doses tested (Table 4) whether administered intravaginally or subcutaneously.

The effects of anti-oestrogenic doses of compounds V and VI on reproduction in female mice were compared with those produced by MER 25 (Table 5). Compound IV was similarly tested to determine whether a lack of anti-oestrogenic activity in a compound closely related to MER 25 would affect anti-fertility activity.

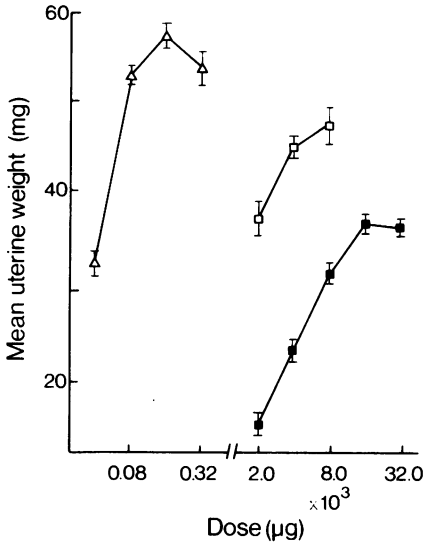


Figure 2 Mean uterine weights (mg) for groups of immature female mice treated with increasing doses of 17β-oestradiol (△), compound VI (■) or compound VII (□). Vertical lines show s.e. mean. The total dose per animal was administered subcutaneously in three daily subdoses, and each subdose was dissolved in arachis oil (0.05 ml).

Table 3 Anti-oestrogenic activity of amino-ethoxy derivatives. Mean uterine weights (mg) for groups of immature female mice treated with 0, 0.03 or 0.06 μg 17β-oestradiol alone or in combination with increasing doses of MER 25, IV, V, VI or VII.

Compound	*Total dose of compound (mg) per mouse*	*Total dose 17β-oestradiol (μg) per mouse* 0	0.03	0.06
MER 25	0	12.12 ± 0.82	29.09 ± 0.91	46.18 ± 1.25
	0.5	–	23.27 ± 1.04**	25.67 ± 0.92**
	1.0	–	17.91 ± 0.81**	22.01 ± 0.88**
	2.0	–	14.59 ± 0.43**	17.26 ± 0.77**
IV	0	9.64 ± 0.43	31.75 ± 1.90	41.89 ± 2.01
	1.0	–	26.93 ± 2.07	38.66 ± 2.53
	2.0	–	29.42 ± 1.44	38.39 ± 2.48
	4.0	–	27.56 ± 1.74	40.09 ± 1.71
V	0	13.80 ± 1.02	34.73 ± 1.60	45.70 ± 1.36
	0.5	–	31.65 ± 1.48	40.83 ± 1.45
	1.0	–	30.14 ± 1.78	39.25 ± 1.67
	2.0	–	28.65 ± 1.13*	36.19 ± 1.65**
VI	0	15.14 ± 1.73	36.85 ± 1.14	53.08 ± 1.86
	0.5	–	32.27 ± 0.62*	44.89 ± 2.80
	1.0	–	29.33 ± 1.70*	42.57 ± 1.77**
	2.0	–	27.60 ± 0.90*	34.99 ± 0.99**
VII	0	13.6 ± 0.93	29.25 ± 1.16	55.37 ± 1.64
	0.05	–	31.30 ± 1.51	52.51 ± 2.37
	0.1	–	33.92 ± 1.61	60.15 ± 2.63
	0.2	–	39.99 ± 1.26**	54.28 ± 1.85

Uterine weights (mg) are given ± s.e. mean. The total dose per animal was administered subcutaneously in three daily sub-doses. Each sub-dose was dissolved in 0.05 ml arachis oil (10 mice per group).
Levels of significance (Student's t test) when compared with related 17β-oestradiol-treated controls: *$P<0.01$; **$P<0.001$.

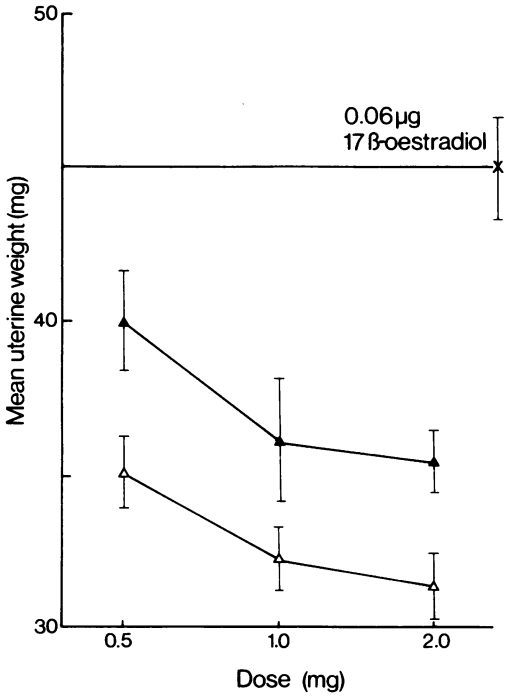


Figure 3 Mean uterine weights (mg) for groups of immature female mice treated with 0.06 µg 17β-oestradiol alone or in combination with increasing doses of compound V (▲) or VI (△). The total dose per animal was administered subcutaneously in three daily subdoses and each subdose was dissolved in arachis oil (0.05 ml).

Five of the females receiving compound V became pregnant. Three produced normal healthy litters, one produced a single underweight offspring which died 3 h after birth and the fifth ate the young at birth (the number and size of the progeny are unknown as the births occurred at night). In no test group was the number of pregnancies significantly different from control and only in the group treated with MER 25 was the mean size of the litters significantly smaller ($P < 0.05$). Compound VI, with both oestrogenic and anti-oestrogenic properties produced no consistent decrease in fertility.

Discussion

Clark & McCracken (1971) reported that ring-tetra methylation *ortho* to ring oxygen in diethylstilboestrol reduced the oestrogenic activity and endowed the molecule with anti-oestrogenic activity when administered intravaginally with 17β-oestradiol. Unfortunately the compound $\alpha\alpha'$-diethyl-3,3', 5,5'-tetramethylstilboestrol was oestrogenic in the immature mouse uterine weight test although large doses were autoinhibitory.

It was hoped that the introduction of methyl groups *ortho* to ring oxygen in hydroxylated triphenylethylenes might similarly decrease oestrogenic activity but without an associated decrease in the affinity for the oestrogen receptor (Jensen & Jacobsen, 1962) thus producing a systemic anti-oestrogen. The parent triphenylethylenes chosen to test the effects of ring methylation, viz. α-phenyl-stilboestrol and α-phenyl-β,β-di(*p*-hydroxyphenyl)ethylene are both oestrogenic, subcutaneous MED_{50} for vaginal cornification in mice being respectively 15 and 9 µg (Emmens, 1940/41). Tetramethylation to produce compounds II and III dramatically reduced oestrogenic potencies and only compound II was weakly oestrogenic at doses above 2 mg in the immature mouse uterine weight test. Interpretation of these results was complicated by the ease of oxidation of the compounds. The chemically stable dimethyl ether of II, compound I, was non-oestrogenic at 2.0 mg. The loss of oestrogenic activity was also accompanied by a lack of ability to antagonize the systemic effects of 17β-oestradiol on

Table 4 The maximum total doses of compounds administered to ovariectomized mice either subcutaneously in arachis oil (two daily sub-doses each in 0.05 ml) or intravaginally in 2% aqueous Tween 80 (two daily sub-doses each in 0.01 ml) to test for oestrogenic or anti-oestrogenic activity by the Allen-Doisy technique.

	Subcutaneous administration total dose (mg)		*Intravaginal administration total dose (µg)*	
Compound	*Oestrogenic*	*Anti-oestrogenic*	*Oestrogenic*	*Anti-oestrogenic*
I	–	8.0	–	4.0
II	–	–	4.0	–
IV	–	–	8.0	9.0
V	2.0	2.0	–	32.0
VI	2.0	2.0	8.0	8.0
VII	2.0	–	4.0	–

In anti-oestrogenic tests the total dose of 17β-oestradiol was either 0.08 µg subcutaneous or 8×10^{-4} µg intravaginally. No compound exhibited significant activity in any test.

Table 5 Number of litters per group and the numbers of young per litter following the daily subcutaneous administration for five days of various doses of test compounds (IV, V, VI, MER 25) in arachis oil (0.05 ml) or arachis oil alone (0.05 ml) to mature female mice (10 mice per group).

Experiment	*Daily treatment*	*Number of pregnancies*	*Number per litter*
1	Arachis oil	6	12, 13, 8, 10, 14, 12
	1.0 mg V	5	16, 11, 10, 1*, 0**
2	Arachis oil	6	13, 11, 10, 12, 11, 13
	1.0 mg MER 25	4	7, 9, 8, 2†
	1.0 mg IV	10	13, 16, 10, 12, 11, 11, 12, 11, 12, 11
3	Arachis oil	5	7, 10, 8, 12, 11
	0.5 mg VI	4	11, 8, 11, 11
	1.0 mg VI	8	10, 10, 12, 10, 10, 7, 11, 4
	1.0 mg IV	9	11, 9, 8, 12, 8, 8, 11, 13, 13

Mature male mice (5 mice per group) were introduced on day one and removed on day five of treatment. * Died 3 h after birth; ** eaten by mother (see text).
† Comparison of mean litter size with control, $P < 0.05$ (t test).

the uterus or vagina. In contrast, the aminoethoxy compounds (IV, V, VI and VII), provided an interesting variety of biological properties. The anti-oestrogenic and the antifertility activity shown by MER 25 confirmed the findings of other workers (Lerner, *et al.* 1958; Martin, Emmens & Cox, 1960) and provided a reference with which to compare the activities of these compounds.

The established non-steroidal systemic anti-oestrogens MER 25, MRL 37, MRL 41, ICI 46,474, CN-55,945 and U 11,100A all possess an alkyl-aminoethoxy side-chain, and Lednicer, Lyster & Duncan (1967), after a consideration of structure-activity relationships amongst compounds related to U-11,100A, suggested that the presence of a basic group at a given position in space is required to obtain a molecule that will antagonize the effects of concurrent oestrogen administration. Emmens, Collins, Hobbs, Miller & Owen (1969) have further suggested that the essential feature of the side-chain is its polarity rather than its basicity and that its importance lies in modifying the physical properties of the molecule.

In the present investigation, the introduction of two methyl groups *ortho* to the *N,N*-diethylaminoethoxy side-chain will alter, by steric hindrance, the conformational possibilities of the molecule and the side-chain will no longer be able to lie in the plain of the aromatic ring, but will take up a position approximately at right angles to it (Clark & Williams, 1967; Coggan, McPhail & Roe, 1969). This conformational change, as well as the electron donating effects of the methyl groups, will lead to an increase in the electron density of the ether oxygen and, via an inductive mechanism, a change in the electron density of the tertiary amine group.

This type of substitution in MER 25 is clearly disadvantageous since the resultant compound, (IV), is neither oestrogenic nor anti-oestrogenic, and lacks the anti-fertility activity of the anti-oestrogenic MER 25.

The related triphenylethylene (VI) was both oestrogenic and anti-oestrogenic in the uterine weight test; thus the inability of compound IV to provide effective receptor combination can be overcome by alterations elsewhere in the molecule. Although the lack of antifertility activity of anti-oestrogenic doses of compound VI was unexpected, Collins, Hobbs & Emmens (1971) have described a similar effect with a closely related triphenylethylene.

The introduction of a bromine atom at the double bond of VI to produce VII increased the oestrogenic potency. This is consistent with previous reports of this type of chemical modification (Emmens, 1947).

Compound V, which bears the same structural relationship to MRL 37 as IV does to MER 25, retained some anti-oestrogenic activity without a resultant increase in oestrogenic properties although its performance in the antifertility test did not produce a consistent inhibitory result and it is probably less active than MRL 37 (Emmens, Humphrey, Martin & Owen, 1967). The successful litters from both control and compound V-treated mothers continued to grow normally during the two weeks following birth with the growth rates depending more upon litter size (small litters, faster growth) than the treatment received during conception.

None of the compounds tested was either oestrogenic or anti-oestrogenic whether administered intravaginally or subcutaneously in the Allen-Doisy test. This inactivity may have been a reflection of the doses used, although Emmens, Cox & Martin (1960) reported a similar type of insensitivity by the mouse vagina to the subcutaneous or intravaginal administration of MER 25. Indeed, the simultaneous administra-

tion of compound VI to ovariectomized and immature female mice produced parallel increases in uterine weights whilst vaginal smears of the ovariectomized mice remained negative.

In summary, therefore, it is clear that the introduction of ring methyl groups into triphenylethylenes and triphenylethanes *ortho* to phenolic hydroxyls or alkyl amino ethoxy side-chains is a disadvantageous procedure which provided no compounds with any apparent advantages over the established triphenyl ethylene-triphenyl ethane types of anti-oestrogen.

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