Anti-fertility agents 45. Synthesis and activity of 1,2-cis-1-(p-(β-pyrrolidinoethoxy)phenyl)-2-phenyl-5-methoxyindane

ARTICLE *in* EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY · MARCH 1989

Impact Factor: 3.45 · DOI: 10.1016/0223-5234(89)90115-3

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Eur. J. Med. Chem. 24 (1989) 193–197

Anti-fertility agents 45. Synthesis and activity of 1,2-*cis*-1-(*p*-(β-pyrrolidinoethoxy)phenyl)-2-phenyl-5-methoxyindane*

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(Received January 5, 1988, accepted September 5, 1988)

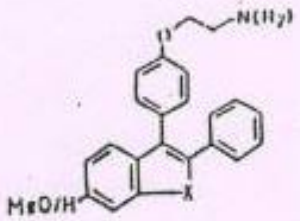
1,2-cis-diarylindane / anti-fertility agents

Introduction

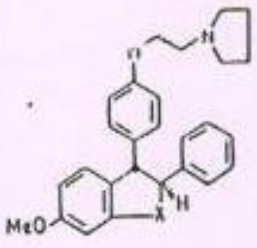
Cyclic triarylethylenes of general structures Ia–e and their reduced versions, *trans*-isomers IIa–e and *cis*-isomers III–V possess anti-fertility, estrogenic and anti-estrogenic activities [1–11]. Whereas both *trans*- and *cis*-dihydronafoxidines IIb and III [6, 7] show anti-fertility activity at 10 μg / day / rat, the *trans*-chromans IId–e are much more potent [11] as anti fertility agents than *cis*-chromans IV and V. Such comparative anti-fertility / estrogenic / anti-estrogenic data for *cis* / *trans*-1,2-diarylindanes, which are of special interest due to stereochemical aspects of the fused indeno ring, have not been documented so far. We reported earlier the anti-implantation, estrogenic and anti-estrogenic profile of *trans*-1,2-diarylindane IIa / *IG* [4, 5]. Herein, we report the synthesis, anti-implantation, estrogenic and anti estrogenic activities of 1,2-*cis*-1-(*p*-(β-pyrrolidinoethoxy)phenyl)-2-phenyl-5-methoxyindane VI / 12 and also a comparative evaluation of *cis* / *trans* isomers 12 and 16.

Chemistry

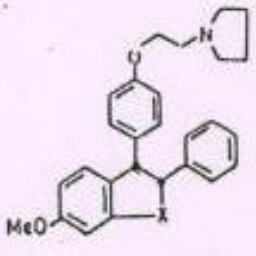
The method of synthesis is outlined in Scheme 1. Condensation of methoxydesoxybenzoin, 1 with *m*-anisaldehyde 2 gave corresponding 1,2,3-triarylpropenone 3 as a mixture of *E*- and *Z*-isomers which, upon hydrogenation, gave the corresponding propanone 4 in which two protons on C-3 appeared separately in the NMR spectrum. Demethylation of 4 afforded a mixture of mono- and dihydroxypropanones 5 and 6 in 45 and 10% yields, respectively. 5 and 6 were characterized by converting them into acetates 7 and 8. Similar to 4, the protons on C-3 of 5–8 appeared separately. Cyclization of 5 whith *p*-TsOH yielded 1-(*p*-hydroxyphenyl)-6-methoxy-2-phenylindene 9, which, upon hydrogenation afforded 1,2-*cis*-1-(*p*-hydroxyphenyl)-6-methoxy-2-phenylindane 10 showing the proton on C-1 as a doublet at δ 4.41, J = 8 Hz and $C_2C_3H_2$ protons 0.16 ppm upfield than the *trans* isomer. Acetylation of 10 gave acetate 11 and alkylation of 10 with β-pyrrolidinoethyl chloride in the presence of K_2CO_3 furnished 1,2-



Ia-c X = $(CH_2)_n$, n = 1,2,3
Id X = OCH_2
Ie X = $OCMe_2$



IIa-c X = $(CH_2)_n$, n = 1,2,3
IId X = OCH_2
IIe X = $OCMe_2$



III X = CH_2CH_2
IV X = OCH_2
V X = $OCMe_2$
VI X = CH_2

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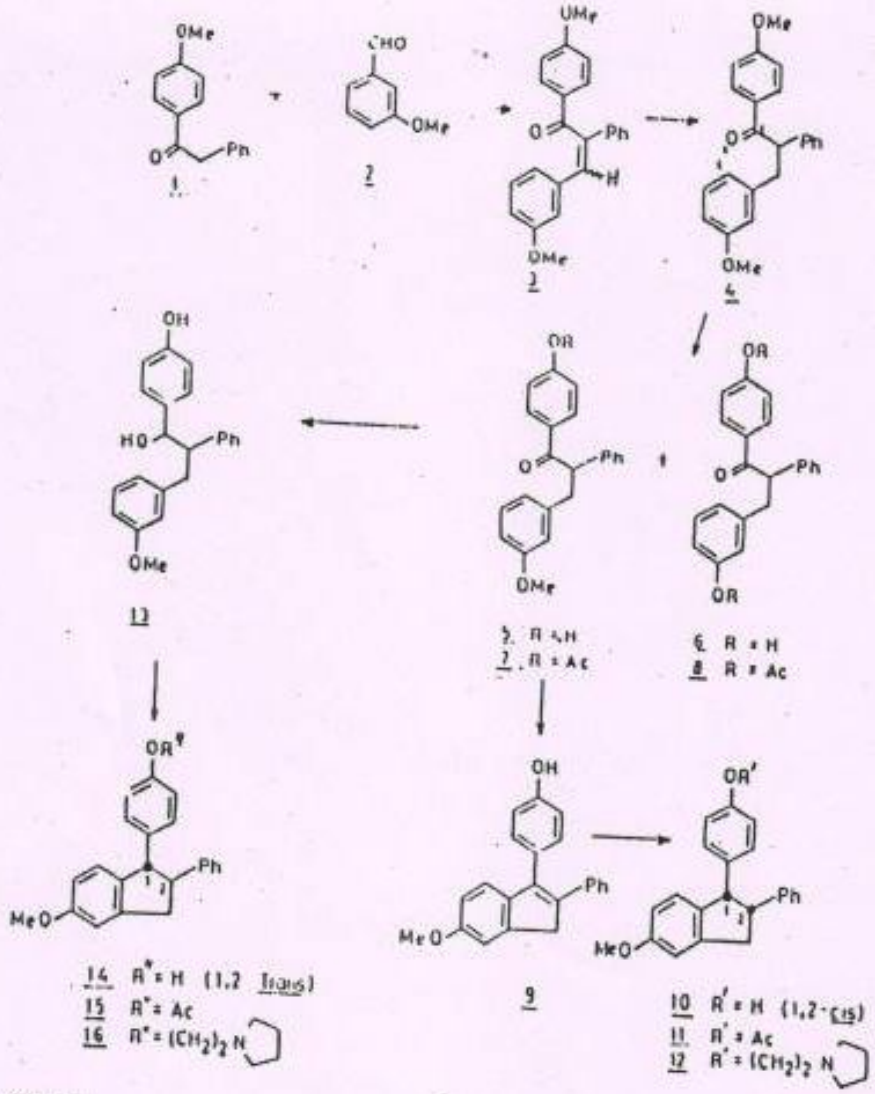

Scheme 1.

cis-1-(*p*-(β-pyrrolidinoethoxy)phenyl)-2-phenyl-5-methoxyindane **12**.

The intermediate, triarylpropanone **5** provided an alternative synthesis [4] for the corresponding 1,2-*trans*-analog **14**/**16** in yields better than those reported. Thus, $LiAlH_4$ reduction of **5** gave a mixture of diastereomeric 1-propanols **13** which, upon cyclization, yielded the required 1,2-*trans*-1-(*p*-hydroxyphenyl)-2-phenylindane **14** in 58% yield. It was acetylated and alkylated to obtain the corresponding 1,2-*trans*-indane derivatives **15** and **16**, respectively.

Both isomers **10** and **14** showed $J_{1,2} = 8$ Hz in ^{1}H NMR, so these were distinguished on the basis of the hydrogenation step of synthesis which obviously yields **10** as a *cis*-isomer. The assignments were supported by ^{13}C NMR in which both isomers **10** and **14** showed characteristic patterns and carbon chemical-shift values within ±3 ppm of the calculated values. The C_1, C_2 and C_3 carbons of isomers **14**, appeared at 2.61, 4.67 and 2.84 ppm downfield from the respective carbons of **10**. Thus, in the light of our reported [12] results on 1,2-disubstituted indane derivatives, isomers **10** and **14** have *cis*- and *trans*-stereochemistry, respectively, which corresponds to the presumed assignments.

Biological results

The anti-fertility, estrogenic and anti-estrogenic activities of compound **12** are described in Table 1. Compound **12** prevented pregnancy in adult female rats at a daily oral dose of 0.5 mg/kg administered on days 1–5 *postcoitum*, while the normal number of implantation sites were observed at 0.25 mg/kg dose.

In an estrogenic (Es) assay, **12** induced a significant increase in uterine wet weight at contraceptive dose, but had little effect on the vagina, as none of the treated animals exhibited premature opening of the vagina and only 10–20% of the cell in the vaginal smears were cornified. A significant uterotrophic effect was also observed at half the contraceptive dose (0.25 mg/kg), but at lower doses (0.01–0.05 mg/kg) no Es responses were discerned. Taking 100% increase in uterine weight as the parameter, compound **12** (dose level 0.182 mg/kg) was found to be 152 times less Es than ethinyl estradiol (EE) (dose level 0.0012 mg/kg).

In anti-estrogenic (AEs) testing, EE (0.02 mg/kg) induced a significant increase in uterine weight and there was a premature opening of the vagina in all the animals and almost all cells in the vaginal smears were cornified. Simultaneous administration of EE (0.02 mg/kg) and compound **12** (0.025–2.5 mg/kg) also caused a significant increase in uterine weight but extent of the uterotrophic response was always significantly less than that produced by EE alone. The compound, however, failed to inhibit the EE-induced premature opening of the vagina or cornification of the vaginal epithelium.

In a competition assay, both the compounds **12** and **16** exhibited similar relative binding affinities (RBA) for immature rat uterine cytosol estrogen receptors and was of the order of 0.42 and 0.45% of estradiol-17β, respectively.

Discussion

Results of the present study show that the *cis*-isomer **12**, like its *trans*-isomer **16**, possesses postcoital anti-fertility activity and, in ovariectomized immature female rats, it exhibits mild estrogenic as well as anti-estrogenic activities. On comparison, the two isomers appear to elicit similar estrogenic responses at their respective contraceptive doses, except that the *cis*-isomer **12**, in addition, induced a very mild cornification of the vaginal epithelium. In the anti-estrogenic assay also, the *cis*- and *trans*-isomers exhibited similar responses and the inhibition in the ethinyl

Table 1. Antifertility, estrogenic and anti-estrogenic activities of test compounds.

Treatment	Anti-fertility activity			Dose[a,b]	Estrogenic activity[c]			Anti-estrogenic activity[d]		
	dose[a]	implantations[e]			uterine weight[f]		vaginal opening/ cornification (%)	uterine weight[f]		vaginal opening/ cornification (%)
Control	–	9.7±0.8	(7/7)	–	17.1±0.8	(12)	0/0	17.1±0.8	(12)	0/0
Comp. **12**	0.25	8.5±0.6	(7/6)	0.01	17.9±0.9	(8)	0/0			
	0.5	nil	(11/0)	0.025	17.0±1.4	(7)	0/0	94.9±4.7	(7)	100/100
	1.0	nil	(8/0)	0.05	19.0±1.1	(8)	0/0	84.9±4.1[m]	(7)	100/100
				0.25	41.5±1.5[n,k]	(8)	0/rare	81.7±4.0[n]	(6)	100/100
				0.50	41.6±2.3	(7)	0/10–20	80.0±4.7[n]	(7)	100/100
				1.00	40.0±6.0	(8)	0/10–20	70.2±3.0[p]	(7)	100/100
				2.50	50.0±3.7	(8)	100/90–60	67.4±2.9[q]	(7)	100/100
Comp. **16**	0.25	nil	(8/0)	0.25	39.2±2.1[p]	(6)	0/0	75.0±3.3[n,o]	(6)	100/100
Ethinyl estradiol				0.001	32.0±3.7[p]	(8)	0/rare			
				0.002	42.5±3.6[p]	(8)	13/20–30			
				0.005	67.0±6.9[p]	(7)	57/60–70			
				0.01	84.0±4.0[p]	(7)	72/80–90			
				0.02	100.7±5.3	(7)	100/100			
				0.10	107.3±6.5	(8)	100/100			

[a] mg/kg.
[b] For anti-estrogenicity, + 0.02 mg/kg ethinyl estradiol.
[c] Mean±SE, total/pregnant rats between parentheses.
[d] Twice daily for 3 days.
[e] Uterine weight, mean±SE, total number of rats between parenthesis.
[f] $p<0.001$, statistical significance *vs* controls.
[g] $p<0.05$.
[h] $p<0.01$.
[i] $p<0.001$, statistical significance *vs* preceding value.
[m] $p<0.05$.
[n] $p<0.01$.
[o] $p<0.001$, statistical significance *vs* 0.02 mg/kg of ethinyl estradiol *per se* treated group.

estradiol-induced uterine weight gain was 20 and 25%, respectively.

It appears that cis-compound **12** exerts its contraceptive action by virtue of its Es and AEs properties. The comparable anti-fertility, Es / AEs activities and RBA results for the *cis*-isomer **12** and *trans*-isomer **16** and their similar modes of action indicate that the receptor site accommodates both isomers similarly.

Experimental protocols

Chemistry

Melting points were taken in a sulfuric acid bath and are uncorrected. Purity of the compounds was routinely checked on silica gel G thin layer chromatography (TLC) plates. IR spectra were recorded on Perkin Elmer 157 or 577 spectrophotometers and ^{1}H NMR spectra were recorded on Varian A 60D or Perkin - Elmer R-32 using tetramethylsilane as the internal reference. ^{13}C NMR spectra were determined on Varian CFT 20 and mass spectra were run on Jeol JMS D300 spectrometer. All compounds showed elemental analyses for C and H within ±0.4% of the calculated values. J_g and J_v refer to $J_{geminal}$ and $J_{vicinal}$, respectively. The cis- and trans-isomers denote the geometrical isomerism of cyclic structures.

1-(p-Methoxyphenyl)-3-(m-methoxyphenyl)-2-phenylprop-2-en-1-one **3**

NaOMe, prepared from 15 ml of MeOH and Na (0.23 g), was mixed with *p*-methoxydesoxybenzoin **1** (2.26 g, 10 mmol) (prepared by reacting anisole with phenylacetic acid in polyphosphoric acid (PPA) and refluxed for 0.5 h. To this cooled reaction mixture *m*-anisaldehyde (1.36 g, 10 mmol) was added and refluxed for 4 h. The solvent was distilled out, the residue was suspended in an excess of water and the oily suspension was extracted with EtOAc. The extract was washed with water, saturated NaCl solution, dried (Na_2SO_4) and concentrated to dryness to get a mixture which was purified by column chromatography on silica gel (eluant benzene) to give 1.2 g of **3** as an oil, yield 35%. IR (neat) cm^{-1} 1660 (CO). ^{1}H NMR ($CDCl_3$) δppm: 3.25 (s, 3H, OCH_3); 3.66 (s, 3H, OCH_3 of *p* to CO); 6.97 (s, 1H, C=C*H*); 6.35–7.5 (m, 11H, Ar*H*); 7.85 (dd, 2H, Ar*H* *o* to CO, *J* = 9 & 2 Hz). MS: *m/z* 344(M$^+$), 316, 313, 135. Anal. $C_{23}H_{20}O_3$ (C, H).

1-(p-Methoxyphenyl)-3-(m-methoxyphenyl)-2-phenylpropan-1-one **4**.
A suspension of **3** (1.72 g, 10 mmol) in EtOAc (30 ml) and 10% Pd-C (0.17 g) was stirred under hydrogen atmosphere until the absorption of gas ceased. The catalyst was filtered off, the filtrate was concentrated and the residue was crystallized from MeOH to get 1.65 g of **4**. mp: 94-95°C; yield 95%. IR (KBr) cm^{-1} 1675 (CO). ^{1}H NMR ($CDCl_3$) δ ppm 2.83 (dd, 1H, C_3H, J_v = 7 Hz, J_g = 14 Hz); 3.35 (dd, 1H, C_3H, J_g = 14 Hz, J_v = 7 Hz); 3.47 (s, 3H, OCH_3); 3.56 (s, 3H, OCH_3 of *p* to CO); 4.56 (t, 1H, C_2H, *J* = 7 Hz); 6.35 (bs, 1H, Ar*H* *o* to OMe); 6.4–6.95 (m, 5H, Ar*H* *o*, *m* & *p* to OMe); 7.0 (s, 5H, C_6H_5); 7.65 (dd, 2H, Ar*H* *o* to CO, *J* = 9 & 2 Hz). MS: *m/z* 346 (M$^+$), 226, 211, 135, 121, 77. Anal. $C_{23}H_{22}O_3$ (C, H).

1-(p-Hydroxyphenyl)-3-(m-hydroxy and m-methoxyphenyl)-2-phenyl)-2-phenyl-propan-1-ones **6** *and* **5**
A suspension of ketone **4** (1.04 g, 3 mmol), anhydrous $AlCl_3$ (1.2 g, 9 mmol) in benzene (40 ml) was refluxed under stirring for 3.5 h. The reaction mixture was cooled and decomposed by 15 ml of 6 N HCl and extracted with EtOAc. The extract was washed with water, saturated NaCl solution, dried (Na_2SO_4) and concentrated to dryness. The residue which consisted of a mixture of products was separated by chromatography on silica gel (eluant benzene and then $CHCl_3$). The initial fractions obtained from the column by elution with benzene gave 0.45 g of *p*-hydroxy product **5**, mp: 160–161°C (MeOH); yield 45%. IR (KBr) cm^{-1} 1650 (CO), 3300 (OH). ^{1}H NMR ($CDCl_3$) δ ppm: 1.85 (b, 1H, O*H*, D_2O exchangeable); 3.54 (s, 3H, OCH_3). MS: *m/z* 332 (M$^+$), 121. Anal. $C_{22}H_{20}O_3$ (C, H). The later fractions obtained from the column by elution with $CHCl_3$ gave 0.1 g of *p*, *m*-dihydroxy product **6**; mp: 178–180°C (MeOH); yield 10%. IR (KBr) cm^{-1} 1650 (CO), 3250 (OH). ^{1}H NMR ($CDCl_3$) δ ppm: 1.96 (b, 2H, 2×O*H*, D_2O exchangeable). MS: *m/z* 318 (M$^+$). Anal. $C_{21}H_{18}O_3$ (C, H).

1-(p-Acetoxyphenyl)-3-(m-methoxy- and m-acetoxyphenyl)-2-phenyl-propan-1-ones **7** *and* **8**
These were prepared by usual acetylation of **5** and **6** with Ac_2O-pyridine.
7: mp: 90–91°C; yield 84%. IR (KBr) cm^{-1} 1680 (CO), 1750 (OCOMe). ^{1}H NMR ($CDCl_3$) δ ppm: 2.12 (s, 3H, $COCH_3$); 3.53 (s, 3H, OCH_3); 4.62 (t, 1H, C_2H, *J* = 7 Hz). Anal. $C_{24}H_{22}O_4$ (C, H).
8: mp: 95–96°C (MeOH), yield 75%. IR (KBr) cm^{-1} 1680 (CO), 1750 (OCOMe). ^{1}H NMR ($CDCl_3$) δ ppm: 2.12 (s, 6H, 2×$OCOCH_3$). Anal. $C_{25}H_{22}O_5$ (C, H).

3-(p-Hydroxyphenyl)-6-methoxy-2-phenylind-2-ene **9**
A solution of **5** (0.33 g, 1 mmol) and *p*-TsOH (0.33 g) in benzene (30 ml) was refluxed under a Dean - Stark trap until the separation of water ceased (3 h). The reaction mixture was allowed to cool and the residue was crystallized from MeOH to give 0.3 g of **9**. mp: 155–57°C (MeOH); yield 96%. IR (KBr) cm^{-1} 3300 (OH). ^{1}H NMR ($CDCl_3$) δ ppm: 3.22 (s, 5H, C_1H_2 & OCH_3). MS: *m/z* 314 (M$^+$). Anal. $C_{22}H_{18}O_2$ (C, H).

1,2-cis-1-(p-Hydroxyphenyl)-5-methoxy-2-phenylindane **10**
A suspension of **9** (0.31 g, 1 mmol) in EtOAc (20 ml) and 10% Pd-C (0.3 g) was stirred in the atmosphere of hydrogen at room temperature and pressure and worked as described for **4** to get 0.3 g of **10**. mp: 138–39°C, yield 96%. IR (KBr) cm^{-1} 3400 (OH). ^{1}H NMR ($CDCl_3$) δ ppm: 3.15 (m, 2H, C_3H_2); 3.72 (s, 3H, OCH_3); 3.85 (m, 1H, C_2H); 4.41 (d, 1H, C_1H, *J* = 8 Hz); 6.29 (s, 5H, C_6H_5). MS: *m/z* 316 (M$^+$), 298, 285, 256, 241, 222, 208. ^{13}C NMR ($CDCl_3$) 55.7 (C_1), 52.5 (C_2), 37.3 (C_3), 113.0 (C_4), 159.2 (C_5), 110.1 (C_6), 126.2 (C_7), 141.6 (C_8), 138.3 (C_9) ppm. Anal. $C_{22}H_{20}O_2$ (C, H).

1,2-cis and trans-1-(p-Acetoxyphenyl)-5-methoxy-2-phenylindanes **11** *and* **15**
These were prepared by usual acetylation of **10** and **14** with Ac_2O-pyridine.
11: mp: 99–100°; yield 81%. ^{1}H NMR ($CDCl_3$) δ ppm: 2.07 (s, 3H, $OCOCH_3$); 3.12 (m, 2H, C_3H_2); 3.70 (s, 3H, OCH_3); 3.84 (m, 1H, C_2H); 4.31 (d, 1H, C_1H, *J* = 7.5 Hz). Anal. $C_{24}H_{22}O_3$ (C, H).
15: mp: 135–37°C (lit. [4] mp: 135°C); yield 90%. ^{1}H NMR ($CDCl_3$) δppm: 2.12 (s, 3H, $OCOCH_3$); 3.24 (m, 2H, C_3H_2); 3.36 (m, 1H, C_2H); 3.68 (s, 3H, OCH_3); 4.18 (d, 1H, C_1H, *J* = 8 Hz).

1,2-cis-1-(p-(β-Pyrrolidinoethoxy)phenyl)-5-methoxy-2-phenylindane **12**
A mixture of **10** (0.16 g, 0.5 mmol), β-pyrrolidinoethyl chloride hydrochloride (0.08 g, 0.5 mmol) and K_2CO_3 (0.14 g, 1 mmol) in dry acetone (10 ml) was refluxed under stirring for 12 h. The precipitated material was filtered, the filtrate was concentrated to dryness and the residue was crystallized from MeOH to get 0.17 g of **12**. mp: 86–87°C; yield 81%. ^{1}H NMR ($CDCl_3$) δ ppm: 1.70 (m, 4H, 2×CH_2); 2.50 (m, 4H, CH_2-N-CH_2); 2.73 (t, 2H, N-CH_2, *J* = 6 Hz); 3.17 (m, 2H, C_3H_2); 3.73 (s, 3H, OCH_3); 3.87 (t, 2H, OCH_2, *J* = 6 Hz); 3.90 (m, 1H, C_2H); 4.45 (d, 1H, C_1H, *J* = 8 Hz). MS: *m/z* 413 (M$^+$), 335, 281, 270, 246. Anal. $C_{28}H_{31}NO_2$ (C, H, N).

1-(p-Hydroxyphenyl)-3-(m-methoxyphenyl)-2-phenylpropan-1-ol **13**
A solution of **5** (0.33 g, 1 mmol) in dry tetrahydrofuran (THF) (20 ml) was added dropwise under stirring to a suspension of $LiAlH_4$ (0.04 g, 1 mmol) in dry THF (15 ml) at 10°C. The stirring was continued at room temperature for 2h. The cooled (0°C) reaction mixture was decomposed by 50% NH_4Cl solution. It was filtered, the filtrate was diluted with ether and the organic layer was washed with water and saturated NaCl solution, dried (Na_2SO_4) and concentrated to dryness. The crude product was crystallized from benzene to yield 0.3 g of **13**. mp: 142–43°C (benzene); yield 90%. IR (KBr) cm^{-1} 3500 (OH). MS: *m/z* 334 (M$^+$), 317, 316, 238, 225, 212. Anal. $C_{22}H_{22}O_3$ (C, H).

1,2-trans-1-(p-Hydroxyphenyl)-5-methoxy-2-phenylindane **14**
A suspension of **13** (0.33 g, 1 mmol) and *p*-TsOH (0.1 g) in benzene (30 ml) was refluxed under a Dean - Stark trap until the separation of water ceased (2 h). The reaction mixture was allowed to cool and was washed with water and a saturated NaCl solution, dried (Na_2SO_4) and concentrated to dryness. The residue thus obtained was crystallized from MeOH to give 0.18 g of **14**. mp: 122–23°C (lit. [4] mp: 122°C), yield 58%. ^{13}C NMR ($CDCl_3$) 56.3 (C_1), 57.2 (C_2), 40.2 (C_3), 112.8 (C_4), 159.1 (C_5), 109.8 (C_6), 126.1 (C_7), 143.5 (C_8), 138.6 (C_9) ppm

Biological methods

Colony bred immature (25–35 g) and adult (150–250 g) Sprague-Dawley rats maintained in air conditioned (24 ± 1°C) quarters under uniform husbandry conditions were used. Animals were kept in groups of 6 and were fed a pellet diet (Hindustan Levers Ltd., Bombay) and tap water *ad libitum*. Compound 12 and ethinyl estradiol were individually macerated with an equal amount of gum acacia, suspended in glass-distilled water and administered by the oral route.

For determining the anti-fertility effect, adult female rats mated to coeval males of proven fertility were treated with different doses (Table 1) of compound 12 or the vehicle alone on days 1–5 of pregnancy (day 1: day of spermatozoan presence in vaginal smear). Animals were laparotomized under ether anesthesia on day 10 of pregnancy and the number of implantation sites were recorded.

Estrogenic (ES) and anti-estrogenic (AES) activities were determined in immature female rats ovariectomized 7 days earlier. For ES activity, the compound was administered twice daily (1000 and 1500 h), for 3 consecutive days and, at autopsy on the 4 th day (1500 h), status of the vagina (open or closed), extent of vaginal cornification and uterine wet weight were noted. For those animals whose vagina was still closed, a smear was made by puncturing the membrane. For AES activity, each rat received 0.02 mg/kg of ethinyl estradiol (EE), in addition to the test compound at each time interval. Animals in the control groups received the vehicle alone in a similar manner. Relative binding affinity (RBA) of the two isomer compounds 12 and 16 for immature rat uterine cytosol estrogen receptors (ER) was determined using a competition assay employing dextran-coated charcoal (DCC) for separation of unbound steroids, as described earlier by this laboratory [13]. RBA was expressed as a percent of estradiol-17β. Student's *t* test was used for statistical evaluation of the differences in number of implantations and uterine weights.

Acknowledgments

Technical assistance for biological determinations was provided by Mrs. Rukmini Agarwal, Miss Mohini Chabbra and Miss T.S. Kunjumol.

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