We hope shortly to be in a position to decide whether or not the interesting antispermatogenic actions of hexamethylphosphoramide are a function of this molecule or arise from some contaminant material. In the latter event, the analytical data imply that it must either be isomeric or a highly potent impurity.

H. JACKSON
A. W. CRAIG

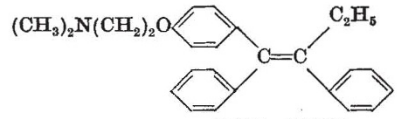
Department of Experimental Chemotherapy,
Paterson Laboratories,
Christie Hospital,
Manchester 20.

[1] Kimbrough, R., and Gaines, T. B., *Nature*, **211**, 146 (1966).
[2] Chang, S. C., Terry, P. H., and Borkovec, A. B., *Science*, **144**, 57 (1964).
[3] Craig, A. W., Fox, B. W., and Jackson, H., *Biochem. Pharmacol.*, **3**, 42 (1959).
[4] Craig, A. W., and Jackson, H., *Brit. J. Pharmacol.*, **10**, 321 (1955).

Contrasting Endocrine Activities of *cis* and *trans* Isomers in a Series of Substituted Triphenylethylenes

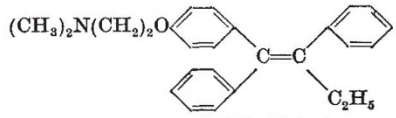
ALTHOUGH triphenylethylene[1,2] and many substituted triphenylethylenes[3] are known to be oestrogenic, more complex endocrine activity has been encountered in some of its basic derivatives. A notable example is clomiphene, 1-(*p*-diethylaminoethoxyphenyl)-1,2-diphenyl-2-chloroethylene (citrate)[4], which has the unexpected property of stimulating ovulation in women with ovulatory failure of certain types[5,6].

A series of analogous 1-(*p*-dialkylaminoalkoxyphenyl)-1,2-diphenyl-2-alkylethylenes has been made here[7] and in many instances the respective isomers isolated in which the unsubstituted phenyl groups are *cis* and *trans* relative to the ethylenic double bond[8]. We have found remarkable and subtle differences in biological properties between the isomeric forms of these compounds, exemplified by *cis*- and *trans*-1-(*p*-dimethylaminoethoxyphenyl)-1,2-diphenyl-2-ethylethylene (I.C.I. compounds No. 47,699 and 46,474 respectively).



I.C.I. 47,699

(*cis*-, melting point, 72°–74° C)



I.C.I. 46,474

(*trans*-, melting point, 96°–98° C)

For biological test, these compounds were administered by gavage as citrates in aqueous suspension. I.C.I. 47,699 was found to behave in all respects as a "conventional" oestrogen, being potent in inducing uterine growth in immature rats and vaginal cornification in spayed rats or mice. Given at low dose levels to intact male rats it causes involution of the prostate and seminal vesicles, as a result of inhibition of pituitary gonadotrophic activity and/or direct anti-androgenic action. Given to pregnant rats during the first 4 days after insemination it is effective in terminating pregnancy by preventing implantation. For this, doses are needed of the same order as induce vaginal cornification in this species, and the effect on pregnancy can be regarded as a manifestation of oestrogenic activity.

The properties of the corresponding *trans* isomer are very different and more complex. In rats it is only weakly and atypically oestrogenic, giving shallow dose response curves with low maxima. It is also anti-oestrogenic, as indicated by its inhibitory effect on the response to exogenous oestrogen of the vaginal epithelium (cornification) and uterus (weight-increase). Given in large daily doses (up to 25 mg/kg) to intact male rats it causes no significant involution of the accessory sex glands and thus would seem not to inhibit hypophyseal gonadotrophic activity. At a daily dose of 1 mg/kg, however, it will completely prevent ovulation in female rats—possibly by a direct action on the ovary. This isomer is extremely effective in terminating early pregnancy in rats. The dose by mouth required to prevent 50 per cent of the eggs shed from implanting is 0·030 mg/kg/day given on the second, third and fourth days of pregnancy, or 0·12 mg/kg given only on the fourth day. These are mere fractions of the daily dose required to cause signs of vaginal cornification in spayed rats. We suggest that in minimal effective doses the compound prevents implantation by counteracting the "oestrogen surge", which is believed to occur on the fourth day of pregnancy and to be necessary for implantation in rats.

Table 1. COMPARISON OF BIOLOGICAL ACTIVITIES OF I.C.I. 46,474 AND I.C.I. 47,699 IN RATS

Type of action	Median effective dose: mg/kg/day (of citrate) per os	
	46,474	47,699
Inhibition of ovo-implantation (*a*)	0·03	0·28
Vaginal cornification in spayed rats (*b*)	41·0	0·2
Uterotrophic action in immature rats	3·6	0·2
Anti-uterotrophic action in immature rats	0·13	*n*
Involution of accessory organs in intact males	~25	~0·5
Inhibition of ovulation in pubescent rats	0·25	1·0
Ratio (*b*)/(*a*)	1,367	0·7

n, No detectable anti-uterotrophic effect.

The contrast in biological properties of these two isomers is clearly apparent from Table 1. A full account of these studies with details of the methods used to obtain the figures shown will appear elsewhere[9].

We would add that although in rats I.C.I. 47,699 is much more potent as an oestrogen than I.C.I. 46,474 (by which its uterotrophic action can be inhibited), both isomers seem to be purely oestrogenic and the *trans* isomer (46,474) the more potent in this respect in mice.

M. J. K. HARPER
A. L. WALPOLE

Research Department,
Imperial Chemical Industries, Ltd.,
Pharmaceuticals Division,
Alderley Park,
Macclesfield, Cheshire.

[1] Robson, J. M., and Schönberg, A., *Nature*, **140**, 196 (1937).
[2] Dodds, C. E., Fitzgerald, M. E. H., and Lawson, W., *Nature*, **140**, 772 (1937).
[3] Grundy, J., *Chem. Rev.*, **57**, 281 (1957).
[4] Holtkamp, D. E., Greslin, J. G., Root, C. A., and Lerner, L. J., *Proc. Soc. Exp. Biol. N.Y.*, **105**, 197 (1960).
[5] Greenblatt, R. B., *Fertil. Steril.*, **12**, 402 (1961).
[6] Kistner, R. W., *Obstet. Gynec. Survey*, **20**, 873 (1965).
[7] U.K. Patent No. 1,013,907.
[8] U.K. patent application No. 30755/65. Bedford, G. R., and Richardson, D. N., *Nature* (in the press).
[9] Harper, M. J. K., and Walpole, A. L., *J. Reprod. Fertil.* (in press).

Inhibitory Effect of Chlorpromazine on Alterations in Electroencephalograms induced by Lysergic Acid Diethylamide in Dogs

IN the past decade the derivatives of phenothiazine (for example, chlorpromazine), among other tranquillizing drugs, have taken an important role in the palliative treatment of spontaneous psychosis[1–4], especially schizophrenia, as well as in the treatment of the acute reversible psychosis, experimentally induced in volunteers and animals, by psychotomimetic drugs such as lysergic acid diethylamide (LSD-25)[5–8].

One of the methods for the objective and quantitative evaluation of the effect of these two groups of psychotropic