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.

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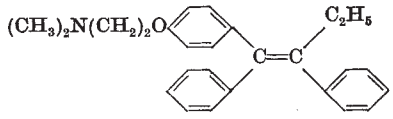
Contrasting Endocrine Activities of *cis* and *trans* Isomers in a Series of Substituted Triphenylethylenes

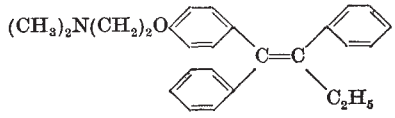
ALTHOUGH triphenylethylene[1,2] and many substituted triphenylethylenes[3] are known to be oestrogenic, more complex endocrine activity has been encountered in some of its basic derivatives. A notable example is clomiphene, 1-(*p*-diethylaminoethoxyphenyl)-1,2-diphenyl-2-chloroethylene (citrate)[4], 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.

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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

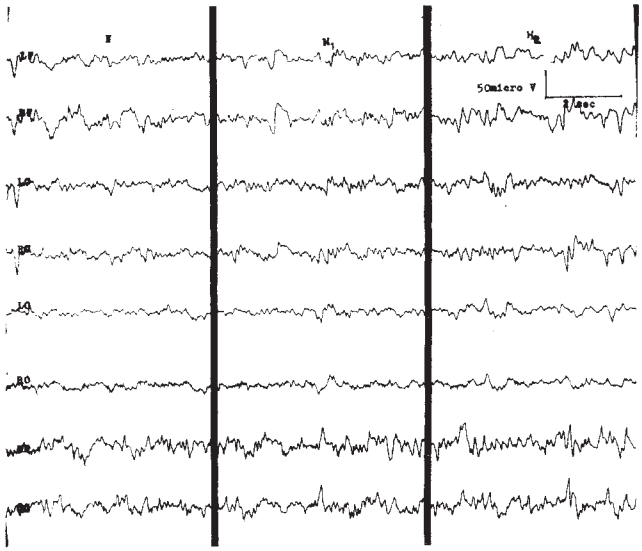

Fig. 1. Three samples of the original electroencephalogram taken on the three occasions (see text).

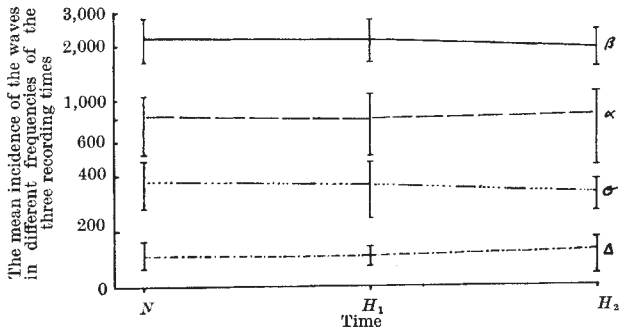

Fig. 2. Graphic illustration of Table 1.

drugs, on the central nervous system, is the study of electroencephalograms[9,10].

In a previous work we showed that LSD-25 causes significant alterations in the electroencephalograms of the dog[11]. In this communication we present the results of a further investigation demonstrating the inhibitory effect of chlorpromazine on alterations in the electroencephalograms induced by LSD-25.

The experiments were performed on ten normal dogs weighing between 1·6 and 3·7 kg. LSD-25 was administered at the dosage of 1 μg/kg. This was followed immediately by an intravenous injection of chlorpromazine (2 mg/kg weight). The electroencephalogram was recorded before the experiment, and 1 and 2 h after the drugs had been administered. On each occasion the recording lasted 3 min, and was performed on an eight-channel apparatus (Offner type *T*), using needle electrodes. A time constant of 0·1 sec was used, and monopolar and bipolar derivations as follows: *LF-RF-LC-RC-LO-RO-FF-OO*. The electrode placed near the ear was chosen as the reference. The total incidence of the waves in different frequency spectra (Δ, θ, α and β) on six monopolar derivations of the first 20 sec of each minute on each of the three occasions (3 min) was computed and compared statistically.

The results are summarized in Table 1.

Table 1. STATISTICAL COMPARISON BETWEEN THE MEAN INCIDENCE OF THE WAVES IN DIFFERENT FREQUENCIES OF THE THREE RECORDING TIMES

	N	H_1	H_2	N-H_1	H_1-H_2	N-H_2
Δ	101·1 ± 55	91·2 ± 31	100·8 ± 63	< 0·60	< 0·60	< 0·90
θ	386·7 ± 121	353·2 ± 117	316·6 ± 58	< 0·50	< 0·40	< 0·10
α	824·4 ± 260	800·9 ± 295	844·1 ± 395	< 0·70	< 0·70	< 0·99
β	2,232·4 ± 615	2,194·1 ± 572	1,998·9 ± 458	< 0·80	< 0·40	< 0·30

N, Normal, before the administration of the drug. H_1, 1 h after the drugs had been administered. H_2, 2 h after the drugs had been administered.

As can be seen, no significant changes in the normal pattern of the electroencephalograms of the dogs occurred after the joint administration of LSD-25 and chlorpromazine. On the other hand, we were able to demonstrate a statistically significant increase in the total incidence of the Δ, θ and α rhythm 1 h after administration of LSD-25.

Our findings indicate that chlorpromazine has an inhibitory effect on the action of LSD-25 in the central nervous system. This effect can be explained on the basis of a probable antagonistic effect between these two psychopharmaceutical compounds in a receptor site in the brain.

B. DJAHANGUIRI
N. GUITI

Department of Experimental Medicine and Pharmacology,
Faculty of Medicine,
University of Tehran.

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Some Pharmacological Properties of a New Adrenergic β-Receptor Antagonist

SEVERAL compounds have now been described as adrenergic β-receptor antagonists including dichloroisoprenaline[1], pronethalol ('Alderlin')[2], propranolol ('Inderal')[3], *MJ* 1999 (ref. 4), and INPEA[5]. Propranolol is about ten times more active than the other compounds in blocking the inotropic and chronotropic actions of catecholamines[6]. Studies with pronethalol and propranolol have shown that adrenergic β-receptor antagonists are valuable in the treatment of various clinical disorders[7–11]. The use of pronethalol was restricted when it was shown to be a potential carcinogenic agent in mice[12]; propranolol is devoid of this action[13]. This communication describes some of the pharmacological properties of a new adrenergic β-receptor antagonist 1-isopropylamino-3-(3-tolyloxy)-2-propanol hydrochloride ('I.C.I. 45,763'), selected from a series of phenoxypropanolamines synthesized by Crowther, Smith and Wood[14].

Increases in heart rate were produced in anaesthetized cats by the constant intravenous infusion for 10 min of isoprenaline at 0·2 μg/kg/min before and after the intravenous infusion for 30 min of 'I.C.I. 45,763' at 1, 5 or 25 μg/kg/min. (All drugs were in the racemic form and are here expressed in terms of the salt.) The effects of 'I.C.I. 45,763' on resting heart rate and on the isoprenaline tachycardia are given in Table 1; these are the averaged results from groups of three cats for each rate of infusion. Table 1 also contains the results obtained in similar experiments with propranolol[15]. Propranolol at all doses produced a bradycardia and reduced the isoprenaline tachycardia. 'I.C.I. 45,763' had a variable effect on resting heart rate; 1 μg/kg/min increased heart rate slightly, 5 μg/kg/min reduced it and with the largest dose there was no change. The blockade of the isoprenaline tachycardia produced by 'I.C.I. 45,763' was similar to that obtained with propranolol.

Further observations were made in two cats anaesthetized with chloralose 16 h after pre-treatment with syrosingopine, 5 mg/kg subcutaneously, to deplete peripheral noradrenaline stores[16]. The intravenous infusion of 'I.C.I. 45,763' at 25 μg/kg/min increased resting heart