ANTIFERTILITY AGENTS

C. W. EMMENS
Department of Veterinary Physiology, The University of Sydney, Sydney, Australia

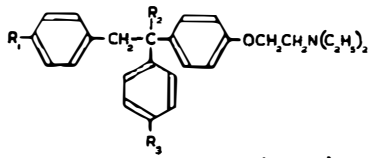
There are many recent reviews of this very active field of work, three in this review within the last six years (1–3). These have dealt in considerable detail with oral contraceptives, intrauterine devices, and substances active in the male, and in less detail with agents affecting the hypothalamic-pituitary-gonadal axis, fertilisation, the passage of ova down the female tract, and implantation. These are covered in the present review, and since agents influencing post-coital events have been the most intensively investigated and may offer a successful and acceptable means of controlling human fertility, more attention is centred on them than on other topics. The review is therefore not comprehensive.

EFFECTS ON THE CENTRAL NERVOUS SYSTEM

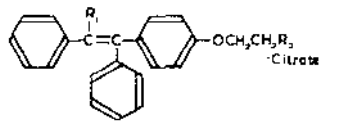
Martini (4) postulates a single "clock," controlling the release of the follicle stimulating hormone releasing factor, FSH-RF, in the spontaneously ovulating mammal. When this release occurs, it is followed by the release of sufficient FSH to stimulate follicular maturation (5, 6). The follicle then responds to circulating LH (7) by the secretion of estrogen, which in turn inhibits further release of FSH-RF and therefore of FSH (6, 8), while the release of LH-RF is increased (9). The consequent peak of LH secretion causes ovulation. Progesterone suppresses synthesis of FSH-RF (8), so that during the luteal phase, FSH is at a low level in the blood. The estrous cycle is terminated by luteolytic activity, believed by Clegg & Doyle (10) to involve both pituitary and uterine factors. The consequent fall in blood progesterone allows new synthesis of FSH-RF to occur and to be available when the biological block signals its release. While it is possible that more than one clock exists, there seems no reason to postulate it.

In certain circumstances spontaneous ovulators may be induced to ovulate as does the cat or rabbit, in response to external stimuli (11–14), and this may apply to women.

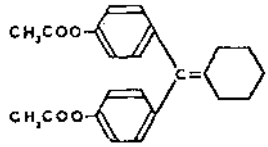
Compounds acting on the CNS may obviously interfere with the processes described above, by upsetting the clock, by blocking pathways in the brain, or by preventing the accumulation or release of FSH-RF or LH-RF, or of luteotrophin where this factor exists as a separate entity. It seems



Ia. R_1=OCH_3, R_2=OH, R_3=H (MER-25)
Ib. R_1=OCH_3, R_2=R_3=H (MRL-37)
Ic. R_1=Cl, R_2=OH, R_3=CH_3 (Triparanol)



IIa. R_1=Cl, R_2=$N(C_2H_5)_2$ (Clomiphene, MRL-41)
IIb, R_1=NO_2, R_2=N
IIc, R_1=C_2H_5, R_2=$N(CH_3)_2$ cis and trans



III. (F-6066)

FIG. 1

likely that various steroidal or other substances may act in one or more of these ways when they exert antifertility effects, but that the main action of steroids is on the hypothalamus. Thus, estrogens reduce the concentration of both FSH-RF and LH-RF in the hypothalamus of female castrate rats (15, 16), while progesterone reduces it in both normals and castrates (8, 16). The clock is believed to be sited outside the hypothalamus, and nonsteroidal agents may block neural mechanisms or pathways from it (17, 18) to the hypothalamus. Such substances as anaesthetics, tranquillizers, and cholinergic or adrenergic blocking agents do this, but their use as antifertility agents is clearly limited. A variety of catecholamine, monoaminoxydase, and serotonin depletors or blocking agents has been investigated, and shown in some cases to affect gonadotropin release, but none has been suggested as useful in man. The practical use of ovulation blockage in the human is so far confined to substances having hormonal activities; if not steroids, they resemble them in action. It is important that FSH-RF and LH-RF have now been demonstrated to act in man, although those used were of bovine origin (19). A review of the human situation is given by Diczfalusy (20).

Much of the action of oral contraceptives containing estrogen and progestagen seems to be due to their estrogen content, and the development of sequential pills, containing estrogen alone during the early part of the menstrual cycle, has followed recognition of this fact. Diethylstilbestrol (DES) alone is surprisingly efficient (21); when it was administered in a dose of 2 mg per day over days 1 to 20 of the cycle, three pregnancies resulted in 105 woman-years. Side effects were nausea in 11 of 86 women, and breakthrough bleeding in 38, severe in five. More effective and consistent control seems possible with DES than with natural estrogens (22).

Walpole (23) reviewed a series of synthetic estrogens or antiestrogens, or both, which have been found to inhibit gonadotropin release (or to lower

blood levels) in various experimental animals and man. These include MER-25 (ethamoxytriphetol, Ia, Fig. 1) and MRL-41 (clomiphene, Ib, Fig. 1); while ICI-22,365 (a dithiocarbamoylhydrazine derivative, $H_2N \cdot CS \cdot NH \cdot NH \cdot CS \cdot NH_2$), and ICI-33,828 ($CH_2 = CH \cdot CH(CH_3) \cdot NH \cdot CS \cdot NH \cdot NH \cdot CS \cdot NHCH_3$), not reported to be estrogens, were potent inhibitors of gonadotropin production or release in animals and man. However, all of these compounds have multiple actions, and MER-41 at least may stimulate gonadotropin release in lower doses (24). ICI-33,828 has been found to reduce urinary excretion of gonadotropins in men and women (22, 23) in doses of from 1 to 10 mg/kg, and was used similarly to the Pincus pill (25), without disturbing the menstrual cycle. Side effects were anorexia, nausea, lethargy, somnolence, and disturbance of thyroid function. These preclude the likelihood of further clinical trials with this particular compound.

Einer-Jensen (26) reports that F-6066 (bis-(*p*-acetoxyphenyl) cyclohexylidene-methane, III, Fig. 1), a weak estrogen, reduces fertility in male and female rodents by antigonadotropic actions, and reduces urinary gonadotropins and estrogens almost to nil in men and women. Both this compound and ICI-33,828 would seem to merit further study.

Effects on Peripheral Mechanisms Associated with Ovulation

The effects of various natural steroids directly on the ovary are not well understood, even less are the effects of synthetic substances. Thus, oöcyte loss appears to occur independently of hormonal events, and neither estrogens nor progestational compounds appear to affect primary follicular degeneration (27–29). Circulating gonadotropins, responsible for ovulation, can however be neutralised by various means, and this is also accompanied by changes in steroid production.

There seems little new to report on plant extracts affecting gonadotropin action, or on immunological methods of attack in this particular context. On the other hand, radio-immunoassay is becoming an important means of investigating circulating and other gonadotropins and promises to provide more accurate information about FSH and LH levels at various stages of the cycle and pregnancy than is now available. The technique for such assays may in the end provide potent specific antigonadotropins. Other aspects of immunology are discussed below.

Although the synthetic estrogens presumably act at the same sites—e.g., the hypothalamus—as do the natural estrogens, there is evidence that diethylstilbestrol may act directly on the ovary in the human (30).

Pincus (31) has reported on the local effects of a series of compounds, many of which were already known to act centrally. They were tested in the mouse, using PMS and HCG to induce ovulation in immature females. Lysozyme, perphenazine (Trilafon) Laxitol, prochlorperazine (Compazine), meprobamate (Equanil), reserpine, and morphine proved effective in inhibiting ovulation to varying degrees, reserpine being the most potent. Similar effects were seen with reserpine in hypophysectomised rats superovulated with PMS and HCG. In another study, Kar et al. (32), using induced ovu-

lation in the immature rat, found chloroacetocatechol, vanillin, 2,3,5-trimethylhydroquinone, and 4-methyl uracil to be effective, the first compound having the greatest potency. However, it did not prove to have antifertility potency in the rat.

Inhibition of Fertilisation

Apart from the classical spermicidal agents, there are few drugs which interfere directly with fertilisation. Many do so indirectly, by causing obstruction of the passage of either sperm or ova in the female reproductive tract or by upsetting the timing involved. Chang (33) showed that progestagens, including progesterone, interfere with sperm transport and capacitation in the rabbit, but accelerated transport of eggs also occurred and could be responsible for some of the effects seen. However, human clinical experience confirms that low doses of progestagen change the consistency of cervical mucus, making it hard for the spermatozoa to penetrate, while possibly at the same time inhibiting the transport of such spermatozoa as arrive in the uterus. The progestagen may be given by injection (34, 35) or orally (36). Menstruation occurs naturally and side effects appear to be minimal.

Immunological control of fertilisation has been a subject for conjecture for some considerable time but no clear advances seem recently to have been made. Weil (37) has reviewed the field of seminal antigens, but which steps in fertilisation are affected is not known. Circulating antibodies to spermatozoa have been demonstrated frequently in female animals, and appear in the fluid of the genital tract, but it is not certain where they are produced. Tyler et al. (38) may be consulted for another recent review. There seems to be some way to go before active immunisation as a means of fertility control becomes feasible.

Effects on Tubal Transport and Implantation

Earlier work on changes induced in tubal transport of ova was done with estrogens, and there is little doubt that the effects seen with new compounds may often be due to their estrogenicity. Normal implantation depends on the correct timing of the arrival of the blastocyst in the uterus, and thus disturbances of tubal transport tend to be accompanied by failure of implantation. It may take a lot of experimentation to decide whether a compound is depressing fertility because of an action on tubal transport, on the uterus, or because of some other action such as zygotoxicity.

Estrogens occupy a peculiar place in fertility control in mammals. They are at one phase or another essential in the normal processes of mating and early pregnancy, yet they prevent conception at practically all stages in most mammalian species investigated. In primates, including man, their action does not extend far into pregnancy, but their effectiveness if given shortly after coitus has been demonstrated by Morris & van Wagenen (39). Diethylstilbestrol in doses of 1 to 25 mg for six days after mating in the rhesus monkey prevented pregnancy in all of 321 matings. Similar results were ob-

tained with 10 mg per day of estradiol. A dose of 50 mg per day for four to six days after rape in women, mostly near mid-cycle, resulted in no pregnancies in a small series of cases (number not stated), while volunteers (number not stated) who had intercourse near mid-cycle and then received 5 to 50 mg of diethylstilbestrol or 0.5 mg of ethynyl estradiol experienced no pregnancies. These subjects showed a counteraction of the normal thermogenic effect of progesterone and endometrial changes generally suggestive of inhibition of the later, proliferative phase of the cycle. These limited human trials were stated by the authors to be of no statistical significance as yet.

The mechanism of action of estrogens and related substances when given post-coitally has been the subject of considerable discussion. In laboratory rodents, a balance between estrogen and progesterone seems to be needed for the normal course of events, and Shelesnyak and his colleagues (40, 41) believe that a surge of estrogen occurs during the course of day 4 of pregnancy (day 1 = day of finding a vaginal plug or spermatozoa) and, either via histamine release or by some other mechanism, is responsible for implantation. Administration of MER-25, one of the earliest known synthetic antiestrogens, prevents implantation in rats, and hence the concept arose and has been widely explored that disturbance of the estrogen balance on either side of its optimum might result in failure of implantation. Thus, both tubal transport and implantation might well be upset, either by estrogens or by antiestrogens (42). However, despite the need for estrogen early in pregnancy in the rodent, it is by no means certain that a surge occurs (43, 44) and it is not necessary experimentally in the mouse, in which Humphrey (45) has shown that a constant daily dose of estradiol is followed by implantation in the progesterone-treated ovariectomised mouse at the normal time. The supposed role of histamine in implantation (40, 41) has not received much support from other laboratories, and it now seems unlikely either that an estrogen surge occurs in rodents or that histamine is concerned with the action of estrogen. It should be noted that there is evidence that estrogen is not necessary for implantation in the rabbit, guinea pig, or hamster, and that the situation in the larger domestic animals and primates is not known. In the hamster (46), various antiestrogenic compounds do not prevent implantation.

The general situation is therefore, that both estrogens and antiestrogens of various types prevent early pregnancy in various species, but since many antiestrogenic compounds are themselves estrogenic at a higher dosage level, it is difficult to decide whether a particular compound is antifertility in action because it is an estrogen, antiestrogen, or something else besides. Detailed studies by Emmens and his colleagues have shown that dimethylstilbestrol (DMS, IV, Fig. 2) (47), probably U-11,100A (Va, Fig. 2) (48), and possibly MER-25 (49) act because they are estrogenic; whereas U-11555A (Vb, Fig. 2), U-10997 (VI, Fig. 2), and MRL-37 do not seem to be sufficiently estrogenic to explain their antifertility actions (42). Other com-

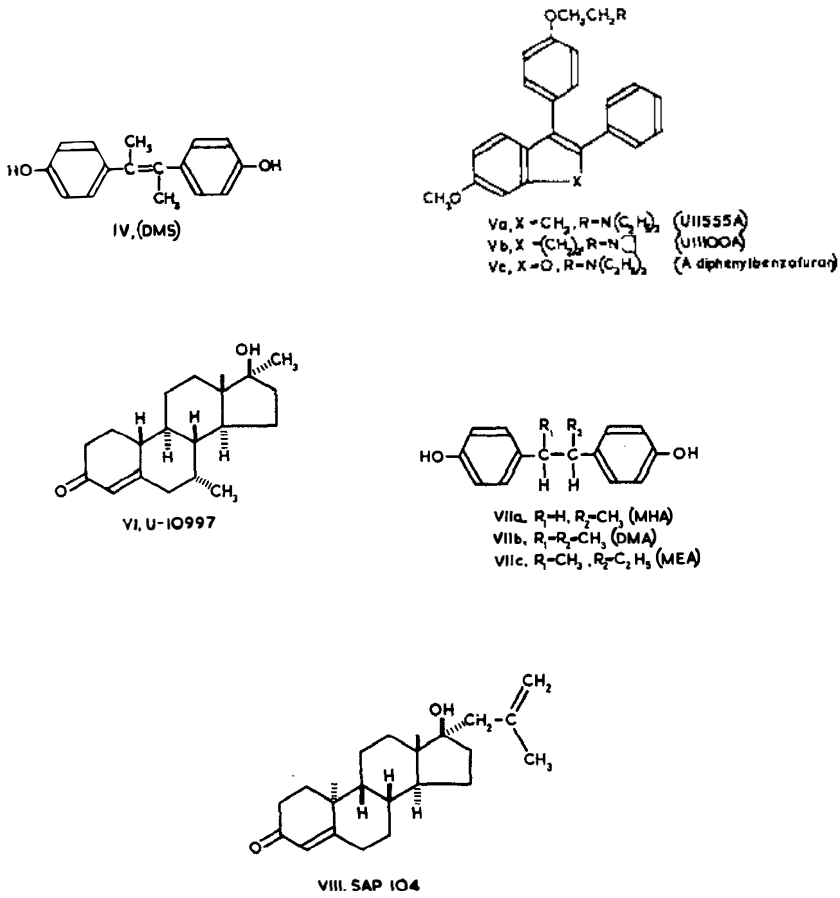


FIG. 2

pounds, such as *meso*-DMA (VIIb, Fig. 2) and *erythro*-MEA (VIIc, Fig. 2) (50) are potent estrogens, yet have antifertility actions at a lower dosage level than can reasonably be explained by their conventional estrogenic activity. Considerable dissociation of estrogenic or antiestrogenic activity from antifertility activity is seen in a number of such compounds, which leads to speculation about the possibility of discovering substances with little or no hormonal activity at levels at which they exert an antifertility effect. The interesting example of SAP-104 (VIII, Fig. 2), a 9β,10α-steroid which as far as is known is antiestrogenic and nothing else, has been discussed recently (51). This compound prevents mating in rodents, but not pregnancy if given after mating. The steroid U-10997 prevents mating and also prevents pregnancy if given after mating, but not if administration is delayed

until the time of implantation (51). U-10997 is androgenic and anabolic and may owe its antifertility properties to the former activity. In contrast, MRL-37 prevents pregnancy when given at any time from prior to mating until the time of implantation, even preventing it when given only prior to mating in a dose which does not stop mating from occurring. MRL-37 has no known hormonal activities. Thus, antiestrogens which are either extremely weak estrogens or not estrogenic may act as antifertility agents, by preventing mating or by disturbing tubal transport or implantation.

A more detailed survey of the relevant compounds is given below.

Zygotoxic Activity

Recent work by Humphrey (52, and unpublished data) has demonstrated that with a variety of estrogenic and antiestrogenic compounds, no toxic action could be seen on the fertilised zygote, with doses causing failure of implantation in mice. MER-25, specifically implicated in earlier work, was included in the study. Donor mice were treated with active compounds, or with vehicle alone for three days after mating, blastocysts were harvested on day 4 after mating and transplanted simultaneously from controls and treated mice into the left or right uterine horn of pseudopregnant recipients. The latter were either treated from day 1 of pseudopregnancy with the compounds concerned, or with vehicle alone (controls). In all cases, a normal percentage of the blastocysts implanted into control recipients, irrespective of whether their donors had been receiving an active compound or not, while very few implantations occurred in treated recipients, again irrespective of the origin of the blastocysts. Thus, with all compounds investigated, the uterus was affected, but not the zygote.

With MER-25, which causes tubal retention of about 50 per cent of ova in the mouse, separately collected tubal and uterine blastocysts were equally able to implant into normal host uteri, casting doubt on the belief that the rate of passage through the Fallopian tube affects the survival or viability of the fertilised ovum. Although interference with normal tubal transport in both the rodent and rabbit (53) is detrimental to implantation, the effect of such timing disturbances would appear to be uterine, not directly on the blastocyst.

Relationships Between Estrogenic, Antiestrogenic, and Antifertility Activity

As indicated above, considerable interest has centered on the linkage between estrogenic, antiestrogenic, and antifertility activity, in particular postcoital antifertility activity. Emmens (54) found that, in a series of 12 steroids chosen to exhibit various levels of estrogenic and antiestrogenic potency, none had antifertility effects post-coitally in mice which were not explicable by estrogenicity, while no relationship was found between antiestrogenicity and antifertility effects. In a series of 15 nonsteroids, similarly chosen, a far less significant correlation was found, and it was suggested that in

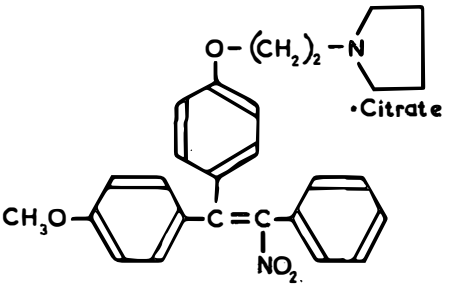
some cases post-coital antifertility effects might well be due to estrogen antagonism. This links up with the earlier finding (55) that steroidal antiestrogens typically act late in the cycle of events following the administration of an estrogen to the castrate rodent, whereas the general run of nonsteroidal antiestrogens appear to act as if they were competitive inhibitors, preventing such early events as vaginal tetrazolium reduction (56) and mitosis (57). If interference with, say, implantation required disturbance of early estrogen action in the uterus, steroids might fail to achieve this.

Kincl & Dorfman (58) reported on 53 steroids and concluded that, while the majority furnished evidence only of a linkage between estrogenic and antifertility activities in the rat, several tetrahydropyranyl ethers derived from estradiol, and synthetic steroids lacking a 3, or a 17 oxygen function showed a separation. Unfortunately, the substances were given from the pro-estrus preceding mating through to implantation, and so ovulation, fertilisation, transport, or nidation could all be implicated, and the results therefore do not demonstrate a post-coital dissociation of hormonal and antifertility potencies. Pincus and his colleagues (59) studied the relationship in another set of steroids of uterotropic, "antiprogestational," and post-coital antifertility activity in the rat, and again found dissociations, but neither of the first two is necessarily a true measure of estrogenic activity. It seems that a dissociation between estrogenic and post-coital antifertility actions has yet to be demonstrated in a steroid which is not a frank androgen or similar compound.

With nonsteroidal compounds, more has been established. During the investigation of series of drugs such as those described below, it has become apparent that nonsteroids may elicit not only unusual types of response, when viewed from the point of view of the normal actions of steroid hormones, but may show less of a spectrum of activities and perhaps promise more in the way of clinical use. It is too early to speculate further. Humphrey & Martin (60), while concluding that the effects of various "antiestrogens" on ovum transport in the mouse are really an expression of estrogenicity, describe different effects for different compounds, and Humphrey (61) finds that the anti-implantation effects of some of them may reflect an antiestrogenic action. No doubt dosage levels affect findings, but it is fairly clear that DMS, MRL-37, MER-25, U-11,100A, U-11,555A, and U-10,997 had estrogen-like actions on tubal transport and the deciduoma reaction; yet in experiments involving delayed implantation, U-10997 induced implantation in almost all mice, MER-25, MRL-37, U-11,100A, and U-11,555A induced implantation in some mice yet prevented estradiol induction of implantation, while DMS induced implantation in 15 per cent of mice and did not prevent estradiol-induced implantation.

Prasad & Kalra (46) present an attempted analysis of the modes of action of various nonsteroidal antifertility agents, essentially in rodents, and conclude as follows:

(*a*) The compounds may increase tubal motility and uterine motility as



IX. (CN-55945-27)

FIG. 3

do estrogens, resulting in expulsion of ova or blastocysts (DMS- MER-25, MRL-41, U-11,100A, U-11,555A).

(*b*) They may be cytotoxic and affect the viability of the ova or blastocysts (MER-25).

(*c*) They may inhibit estrogen uptake by the uterus and interfere with the decidual cell response (MER-25, MRL-41, U-11,555A, CN-55,945-27, IV, Fig. 3).

(*d*) They may inhibit the estrogen-induced action of histamine on the uterus and subsequent decidualisation (U-11,555A, MRL-41, U-11,100A).

(*e*) They may inhibit the decidual cell response by blocking estrogen-dependent enzymes (MER-25) or estrogen dependent DNA, RNA, and protein synthesis (U-11,634, XVII, Fig. 6).

(*f*) They may enhance the secretion of LH, which causes luteolysis, lowering progesterone levels (CN-55,945,27).

Mechanisms (*b*) and (*d*) would appear not to have been unequivocally demonstrated, but the others would seem to be implicated in various different instances.

The observations of Miller & Emmens (62, 63) on the early action of some of the antiestrogens would suggest that the key to the peculiarities of many of the nonsteroidal compounds may be the period of time they occupy receptors in the uterus or other target organs. Studies of the uptake of tritiated uridine by the ovariectomised mouse uterus after single or multiple injections show that some so-called antiestrogens are probably no more than short-acting estrogens, displacing estradiol in the authors' tests when given simultaneously with it, but leaving the site of action thereafter without completing the stimulus necessary for the later manifestations of estrogenic activity such as uterine growth or vaginal mitosis and cornification. With this type of antiestrogen, the exact effects on reproduction might depend on dosage, duration of or mode of administration, and on the particular response of the target organ. The antifertility effect might thus be due to estrogenic activity in some instances, but to displacement of natural estrogen in others.

From what has just been said, it will be seen that investigations of post-coital antifertility compounds have centred on the steroids and on the synthetic estrogens and their antagonists. It would be nice to have a completely new start, with quite unrelated compounds of no hormonal activity, but nobody has produced them.

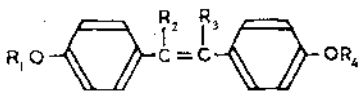
Two main types of compound have been so far extensively reported. They are (*a*) stilbene and bibenzyl derivatives, including some basic ethers, related to the potent synthetic estrogens, diethylstilbestrol and hexestrol, and (*b*) basic ethers of some phenolic triarylethylene, -ethane or -ethanol derivates and their ring-fused analogues.

Stilbene and Bibenzyl Derivatives

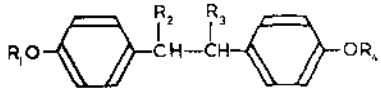
Like the natural estrogens, the α, α'-dialkylstilbene-4,4'-diols, many of which were originally made by Dodds and his co-workers (64) in their search for synthetic estrogens, the most active of which is diethylstilbestrol, disturb tubal transport and implantation. Emmens and his colleagues (65–67) found a remarkable parallelism between estrogenic, antiestrogenic, and antifertility potency in these compounds and eventually concluded that their antifertility effects must be assigned to their estrogenic action. On the other hand, the 4,4'-dihydroxybibenzyls (VII Fig. 2) showed evidence of divergence between these activities (50). Separation of stereoisomers was achieved in some instances. According to the nature of the compound a member of the series may exist as a single *dl* pair of optical isomers (MHA, VIIa, Fig. 2), a *meso-* form and a *dl* pair (DMA, VIIb, Fig. 2) or as two *dl* pairs, the *erythro-* and *threo-* isomers (MEA, VIIc., Fig. 2). Diastereoisomers may differ considerably in estrogenic, antiestrogenic, or antifertility potency, but the ratios between these activities tend to remain similar. Thus, *meso*-DMA has MEDS of approximately 60, 0.3, and 5 μg for the three activities respectively, *dl*-DMA has MEDs of 600, 3, and 100 μg, although both *l*-DMA and *d*-DMA are slightly weaker than their mixture in both estrogenic and antifertility potencies (ca 1 mg and 0.5 mg respectively for each compound). *Erythro*-MEA is much more potent than *threo*-MEA (50) in all respects, and is the most active antifertility compound of this type so far reported other than simple estrogens, with a daily post-coital MED of less than 1 μg by injection in the mouse. Its *d*— and *l*— isomers differ in potency, but not greatly (68). *Erythro*-MEA approaches estradiol in antifertility potency in the mouse or rat, but has less than one hundredth of its estrogenic potency. It is virtually nontoxic in rodents, but shows evidence of estrogenic stimulation in high dosage (69).

Basic Ether Derivatives of DMS and Related Compounds

Emmens et al. (70), have recently examined several series of stilbene and bibenzyl derivatives which in some ways link DMS and MER-25. The probable higher risk of harmful side effects with triarylalkane and -alkene derivatives made it seem advisable to explore other types of compound more fully. Only a few such substances had previously been reported, and were



Xa. $R_2 = CH_3$, $R_3 = H$
Xb. $R_2 = R_3 = CH_3$
Mono- and di-methylstilbenes



XIa, $R_2 = CH_3$, $R_3 = H$
XIb, $R_2 = R_3 = CH_3$
Mono- and di-methylbibenzyls

FIG. 4

examined for other reasons. The basic ether groups attached were 2(N, N-dimethylamino)ethyl-; 2(N,N-diethylamino)ethyl-; 2(N-pyrrolidino) ethyl-; 2(N-piperidino)ethyl-; and 2(N-morpholino)ethyl-. The synthesis of the compounds was described elsewhere (71). A series of trans-α-methylstilbene derivatives (Xa, Fig. 4) showed no estrogenic or antifertility activities in the mouse in doses of up to 1 mg, but varying degrees of local antiestrogenic potency (MED 50–1000 μg). A series of *trans*-α,α'-dimethylstilbene derivatives (Xb, Fig. 4) showed no antifertility potency, varying degrees of local antiestrogenic activity (MED 6–1000 μg), and a few were estrogenic at the 1 mg level. Some α-methylbibenzyl derivatives (XIa, Fig. 4) showed no estrogenic or antifertility potencies, but both weak parenteral and local antiestrogenic potency (MED 150–1000 μg). Finally, several of a series of α,α'-dimethylbibenzyl derivatives (XIb, Fig. 4) exhibited weak estrogenic potency, accompanied by antifertility activity (MED 200–1000 μg/day) and varying degrees of local antiestrogenic activity (MED 2–1000 μg). One compound had five times the antifertility potency that would be expected from its estrogenic activity, but the parallelism was otherwise close.

The basic triarylethanol derivative MER-25 was the first compound of type (*b*) above to be described as an estrogen antagonist (72) and antifertility agent (73). Although weakly active as either an estrogen or antiestrogen, it has the advantage of being active orally and by injection. It was inactive as an antiestrogen in intravaginal assays in the mouse (74). A large number of compounds similar to MER-25 have been synthesised, of which MRL-37 and clomiphene are the best known. Clomiphene, however, did not prevent pregnancy in the rhesus monkey when given after mating in doses of 40 mg/kg daily by mouth for six days (75, 76), or when given continuously every fourth day by injection of 2.5 mg/kg (77). It was also teratogenic in rabbits. The related substance, triparanol (Ic, Fig. 1) caused reproductive defects and was teratogenic in rats (78). The α-trinitrotriarylethylene derivative CN-55,945-27 is another antiestrogen which shows antifertility action in the rat (79).

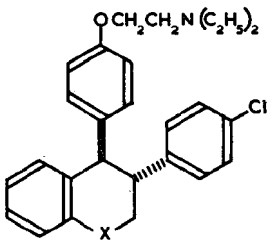
Most of the triarylethylene compounds investigated have been mixtures of geometrical isomers. Harper & Walpole's (80) work with the *cis*- and *trans*-isomers of 1-(*p*-β-dimethylaminoethoxyphenyl)-1,2-diphenylbut-1-ene (IIc, Fig. 1) warns of the possibility of quite different activities in such isomers and in different species. The *cis*-isomer, ICI-47,699, is a potent estro-

gen in rats and mice, with no antiestrogenic activity, and appears to act as an estrogen in causing failure of implantation post-coitally. The *trans*-isomer, ICI-46,474, is a more potent estrogen than ICI-47,699 in the mouse, with no antiestrogenic activity, and highly potent as an antifertility agent (120 μg/kg per day orally *post coitum*). In the rat, it is weakly estrogenic, strongly antiestrogenic yet also highly potent as an antifertility agent (30 μg/kg per day orally *post coitum*).

U-11,100A, U-11,555A, AND SIMILAR COMPOUNDS

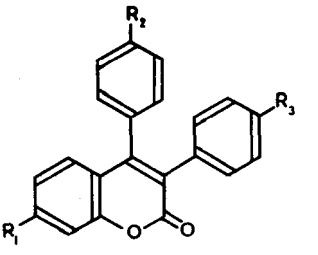
Lednicer and colleagues have made other compounds, some mentioned in Jackson & Schnieden's review (3). Basic ethers of the 2,3-diphenylindenes (81) showed a peak of antifertility activity at 25 μg/rat per day, and compound U-11,155A, active at 100 μg/rat per day when given for 7 days after coitus, has been extensively investigated. Series of dihydronaphthalenes (cf U-11,1000A), and tetrahydronaphthols were also made (82). In both the indenes and the new series, the addition of a 6-methoxy group as seen in V, Fig. 2, and the substitution of a pyrrolidino for the diethylamino group at the para position increased antifertility activity manyfold. Bencze et al. (83, 84) studied some tetrahydronaphthalenes and found peak antifertility activity in basic phenolic ether (XIIa, Fig. 5), which prevented pregnancy in all rats at 20 μg/kg per day when given on days 1 to 4 after coitus. This compound was also estrogenic. In this series, the addition of a 6-methoxy group increased uterotropic activity and decreased antifertility effects, the substitution of pyrrolidino or other groups for diethylamino decreased antifertility potency, and halogenation increased antifertility activity, whereas in the indenes it decreased it.

Active in the post-ovulatory, preimplantation period, U-11,100A and U-11,555A are supposed to be implicated in antagonising the estrogen surge in the rat or mouse, but comparisons of their properties by Emmens and his colleagues (48, 85) show that the two compounds are quite different in biological effects. U-11,100A is estrogenic in vaginal smear tests in rats and mice with a subcutaneous MED of ca 500 μg and 50 to 100 μg per animal respectively. It is also estrogenic orally and intravaginally and in the tetrazolium reduction test. However, in all test systems the dose-response line turns down at higher dosage levels without reaching 100 per cent. It is also weakly antiestrogenic at intermediate dosage levels by subcutaneous injection in mice, but at higher dosage levels it synergises with estradiol. Intravaginally, only antagonism is seen. As an antifertility agent in mice U-11,100A shows a post-coital potency explicable in terms of its estrogenicity (MED 50 μg/day on days 1 to 3 or 4 to 6 *post coitum*). In contrast, U-11,555A is estrogenic in vaginal smear tests in mice with a subcutaneous MED of not less than 5 mg. It was not tested in the rat. It is weakly antiestrogenic in similar tests, with an MED of about 200 μg, either subcutaneously or intravaginally, and exhibits no such interactions as U-11,100A. The antifertility MED post-coitally in the mouse is ca 100 μg/day (days 1 to 3) or 300 μg/day (days 4 to 6 *post-coitum*). In the rat U-11,555A has a constant MED on



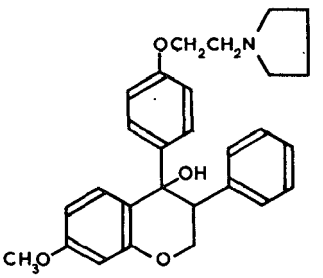
XIIa, X = CH_2 (A diphenyltetrahydronaphthalene)

XIIb, X = O (A diphenylchroman)



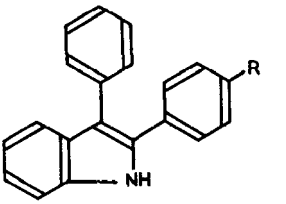
XIII

Diphenylcoumarins



XIV

A 3,4-diphenylchromanol



XV

Diphenylindoles

FIG. 5

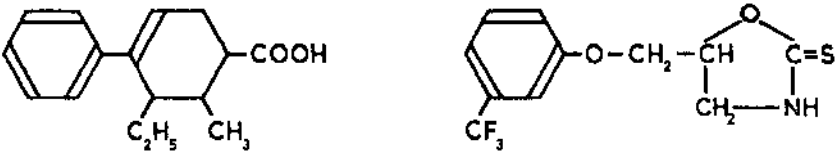
days 1 to 3 or 4 to 6 of 400 μg. A very similar situation is thus seen to the results with ICI-47,699 and ICI-46,474, in that estrogenic action may explain the results with one compound but not with the other. It is unfortunate that U-11,555A is both unstable and causes photosensitization in the human (78).

OTHER SUBSTANCES

Various heterocyclic analogues of Va, Vb, XIIa, and XIIb have shown weak antifertility activity. Lednicer et al. (86) investigated basic ethers of 3,4-diphenylcoumarins (XII, Fig. 5), Carney et al. (87) some diphenychromanes (cf. XIIb, Fig. 5), Gopalachari & Iyer (88) a 2,3-diphenylbenzofuran, Grover et al. (89) and Kar et al. (90) the diphenylbenzofurans (cf. Vc, Fig. 2), and Landquist & Marsden (91) and Iyer & Gopalachari (92) some 2,3-diphenylindoles (XV, Fig. 5). Of these, the most potent compound is 2-phenyl-3*p*-(β-pyrrolidinoethoxy)phenyl-6-methoxybenzofuran hydrochloride, effective at 4 mg/kg per day post-coitally in the rat. This compound is

mildly estrogenic, not antiestrogenic, and its antifertility properties were assigned to its estrogenicity.

Kar and his colleagues have reported antifertility activity in the rat with several further series of compounds. Among these, *p*-nitro-*p'*-ethylaminodiphenylsulphide, *p*-*p'*-diaminodiphenylsulphide, and *p*-*p'*-diaminodiphenylsulphoxide (93) have shown activity at levels of 100 to 200 mg/kg per day, given on days 1 to 5 *post-coitum*. A number of 2,3-diphenylacrylophenones are active at levels below 15 mg/kg per day in similar tests (94), the most active being 3-*p*-chlorophenyl-2-phenyl-4'-β-pyrrolidino ethoxyacrylophenone, at 1 mg/kg per day. Another compound, ORF-3858, 2-methyl-3-ethyl-4-phenyl-Δ^4 cyclohexene-carboxylic acid, (XVI, Fig. 6) was found to be effective post-coitally in primates (77). It showed no evidence of toxicity or teratogenicity in rabbits and seems a promising compound for further development. It is effective in the rhesus monkey at ca 2 mg/kg per day, given for 6 days after mating.



XVI, (ORF-3858) XVII, (U-11,634)

FIG. 6

CN-55,945-27, 1-(2-(*p*-α-(*p*-methoxyphenyl)-β-nitrostyryl)-phenoxyl)-ethyl)pyrrolidine monocitrate (IX, Fig. 3) has been found to prevent pregnancy in mice, rats, and dogs when given in the diet in doses of from 50 to 500 μg/kg per day continuously (79).

U-10,293, 2,8-dichloro-6,12-diphenyldibenzo (b,f) (1,5) diazocine inhibited pregnancy in rats given orally or subcutaneously on days 1 to 7 after mating (95) and a single dose prior to implantation was effective. U-10,293 is estrogenic, antigonadotropic, of low toxicity, and reputedly not teratogenic.

U-11,634, in a series of 5-(phenozymethyl)-2-oxazolidinethiones made by Youngdale et al. (96), is 5(α,α,α-trifluoro-m-tolyloxymethyl)-2-oxazolidinethione (XVII, Fig. 6). It prevents implantation in the rat if given orally or subcutaneously at 2.5 mg/rat for 7 days commencing at proestrus, and a single dose of 10 mg/rat was effective on days 3 to 6 post-coitally, but not earlier. This compound is of particular interest in being without uterotropic, antiestrogenic, or other hormonal properties (97, 98), but blocks many uterine responses to estrogens or progesterone. At the antifertility dose level, it is not toxic or teratogenic, but at higher dosage levels it inhibits thyroid function and causes hepatitis.

Very recently 66/179, 2-phenyl-3-*p*-(β-pyrrolidinoethoxy)phenyl-2:1

(b) naphthofuran has been reported as an antifertility agent by Kamboj et al. (99). The MED orally in rats when given on days 1 to 5 *post-coitum* is 2 mg/kg; and a single dose of 10 mg/kg on any day from 1 to 3 *post-coitum* causes 100 per cent sterility. The same dose is effective in rhesus monkeys, but rabbits require 30 mg/kg. Some uterotropic but no direct estrogenic effects were seen. Tubal transport, fertilisation, and ovum development are unaffected, and the action of the compounds is said to be antiprogestational, preventing deciduoma formation. As it is not toxic at antifertility doses, the compound shows promise.

The early work of Shelesnyak (100), showing that various ergot alkaloids prevent implantation in the rat has not seen clinical application, but a recent report (101) of a study of ergolene and ergoline derivatives claims that, in nontoxic doses, D-6-methyl-8-cyanomethylergoline (6605-VUFB) prevents pregnancy in the rat up to the 7th day *post-coitum* after a single dose of 10 mg/kg. Toxicity has been a difficulty with those compounds, and the possibility of an effective agent of low toxicity may revive interest in them.

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