used immediately in the next reaction. Compounds II*a*, II*b*, and II*d*–II*f* were prepared similarly. The crude products were not analyzed.

***S*-Carboxymethyl-(4-nitrothiobenzoyl)piperidinium Bromide (II*g*)**—Bromoacetic acid (20.8 g, 0.15 mole) was added to a warm solution of I*g* (25.0 g, 0.1 mole) in dry ethylene dichloride (200 ml). After 2 days at 40°, the crystalline solid was filtered off, washed (dry ether), and dried *in vacuo* over phosphorus pentoxide to give the product (37 g, 98%). With benzene as the solvent at room temperature, previous workers (4) failed to prepare this compound.

***S*-Carboxymethyl-(4-phenylazothiobenzoyl)piperidinium Bromide (II*h*)**—A solution of I*h* (30.9 g, 0.1 mole) and bromoacetic acid (20.9 g, 0.15 mole) in dry benzene (600 ml) was kept for 2 days at room temperature. Workup as described for II*g* gave the product (31.4 g, 70%). Compound II*i* was obtained similarly; II*j* was prepared in dry chloroform.

Carboxymethyl Undecanecarbodithioate (III*c*)—A slow stream of dry hydrogen sulfide was passed for 3–4 hr through a stirred solution of II*c*, freshly prepared from I*c* (22.7 g, 70 mmoles), in dry dimethylformamide (85 ml). After 16 hr at 0–5°, the reaction mixture was poured into a threefold volume of ice water with stirring to give a yellow precipitate (14.8 g, 73% based on I*c*), mp 64.5–66° (methanol–water); ν_{max} 3000–2500 and 1710 (COOH) and 1224 (C=S) cm^{-1}; δ 10.4 (1H, s, COOH), 4.05 (2H, s, SCH_2), 3.00 (2H, t, J = 7.8 Hz, CH_2CS), 1.8 (2H, m, CH_2CH_2CS), 1.25 [16H, distorted s, $CH_3(CH_2)_8$], and 0.86 (3H, distorted t, CH_3). Compounds III*a*, III*b*, and III*d*–III*f* were obtained similarly. Attempts by previous workers (4), using ethanol as the solvent, failed to produce these compounds. Compounds III*g*–III*i* were prepared in absolute ethanol. Compounds III*a*–III*i* were shown to be homogeneous (single spot on TLC, silica gel).

***S*-Carboxymethyl 4-Nitrobenzenecarbothioate (IV*g*)**—Compound II*g* in 10 parts of water, after 16 hr at room temperature, gave the product as colorless needles. Compounds IV*h*–IV*k* were obtained similarly. Compounds IV*g*–IV*k* were shown to be homogeneous (single spot on TLC, silica gel).

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COMMUNICATIONS

Stereochemistry of Geometric Isomers of Clomiphene: A Correction of the Literature and a Reexamination of Structure–Activity Relationships

Keyphrases □ Clomiphene—stereochemistry of geometric isomers, structure–activity relationships □ Structure–activity relationships—clomiphene, geometric isomers

To the Editor:

The B-isomer of clomiphene[1] hydrochloride (I-HCl), 2-[*p*-(2-chloro-1,2-diphenylvinyl)phenoxy]triethylamine hydrochloride (IA-HCl, mp 156.5–158°; IB-HCl, mp 149–150.5°), was designated *cis* (Z) since it exhibits a UV λ_{max} attributed to a *trans*-*p*-alkoxystilbene chromophore at a higher wavelength than the A-isomer (1). A comparison of dipole moment, UV, IR, and PMR data of I geometric isomers, 2-[*p*-(2-bromo-1,2-diphenylvinyl)phenoxy]triethylamine (II) and *p*-(2-bromo-1,2-diphenylvinyl)anisole (III) (2), supported this conclusion. However, this conclusion rests on a tenuous stereochemical assignment for geometric isomers of III (3, 4).

In fact, based on a comparison of the dipole moments and spectra of isomers of I–III with those of isomers of 2-[*p*-(1,2-diphenyl-1-butenyl)phenoxy]-*N*,*N*-dimethylethylamine (IV), these assignments were inconsistent with the unequivocal crystallographic proof of stereochemistry for isomers of IV (5, 6). In addition, structure–activity relationships for these compounds were inconsistent since the *cis*-isomer of IV induces conventional estrogenic responses and is the more potent isomer in these respects (7–10), while IA, which had been assigned the *trans*-geometry, exhibits the conventional estrogenic responses and is the more potent isomer of I in these respects (11–21). Furthermore, while the *trans*-isomer of IV exhibits antiestrogenic actions (7–10), IB, previously designated *cis* (1, 2), is the antiestrogenic

[1] Clomid, Merrell-National Laboratories, Division of Richardson-Merrell Inc., Cincinnati, Ohio, is the citrate salt of an isomeric mixture.

isomer (11–21). For these reasons, an unequivocal determination of the stereochemistry of isomers of I was undertaken by X-ray diffraction of IB-HCl and IA-HI. The details of these crystal structures will be published elsewhere.

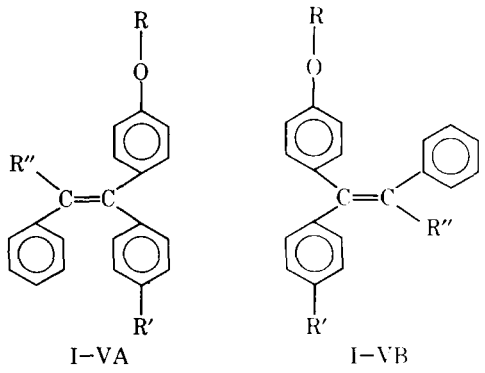
The space group of IB-HCl is $P2_1/c$. There are four formula weights per unit cell and one per asymmetric crystallographic unit. That is, all four molecules have the same conformation. The structure was solved by direct methods. Atomic, positional, and thermal parameters were refined by a full matrix procedure, which converged at a weighted reliability index of 4.0% for this structure. The torsion angle defining the orientation of the unsubstituted rings is 174.4°.

The space group for IA-HI is P1. There are four formula weights per unit cell, which is the asymmetric crystallographic unit. That is, all four molecules have different conformations. The structure was solved by direct methods. The atomic, positional, and thermal parameters for nonhydrogen atoms were refined by a full matrix procedure, which converged at a reliability index of 10% for this structure. The torsion angles defining the orientations of the unsubstituted rings are 10.3, 5.3, 5.1, and 12.7°.

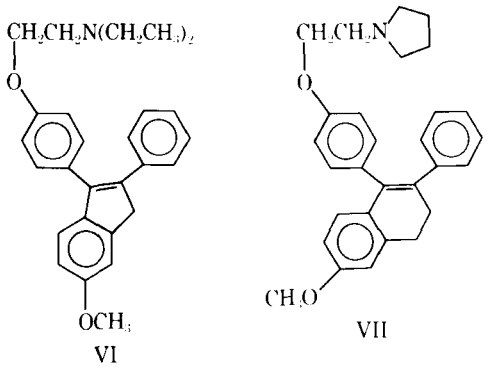
The correct structures (IA and IB) are the reverse of those previously assigned to isomers of I. Thus, the physical data as well as the relationships between geometric isomerism and these biological actions are now consistent. It is the stereochemical assignment for isomers of III that is incorrect (3, 4) and that lent support (2) to the original incorrect assignment of stereochemistry to isomers of I (1).

A suitably oriented basic residue is a consistent feature of many antiestrogenic and estrogenic agents patterned on the triphenylethylene prototype (22). From the results described here, it now appears that a *trans*-disposition of "unsubstituted" benzene rings *favors* antiestrogenic action, although the *trans*-isomers of both I and IV exhibit estrogenic effects as well. While IB (*trans*) has three times the uterotropic (estrogenic) activity (ED_{50}) of IA, it is only 60% as effective (height of the dose–response curve) (12).

It has also been shown that the more estrogenic *cis*-isomers of I and IV have lower affinities than the antiestrogenic *trans*-isomers for the estrogenic receptor (70:1 and 20:4, respectively) (10). This finding is in accord with a lower intrinsic activity for the antiestrogenic *trans*-isomers (B) of I and IV. The antiestrogenic effect on the hypothalamus is primarily responsible for initiation of the ovulatory cycle (18, 23). This effect arises by antagonism of the effects of estrogen, which inhibits the release of follicle-stimulating hormone-releasing factor. Later phases in the development of an ovum are estrogen supported. The *unique* ovulation-inducing properties of IB (12, 23) would appear to be related more to tissue distribution patterns and/or metabolism than to the extent of the inhibition of binding of estrogen to its receptors (10, 24) since the association constant for IB is *only* 3.5 times larger than that for IVB (10). However, the reverse is more likely, as suggested by the magnitudes of the *trans–cis* ratios of the association constants of I and IV. These ascribe a higher degree



I: R = $CH_2CH_2N(CH_2CH_3)_2$, R′ = H, R″ = Cl
II: R = $CH_2CH_2N(CH_2CH_3)_2$, R′ = H, R″ = Br
III: R = CH_3, R′ = H, R″ = Br
IV: R = $CH_2CH_2N(CH_3)_2$, R′ = H, R″ = CH_2CH_3
V: R = $CH_2CH_2(NC_4H_8)$, R′ = *p*-CH_3O, R″ = NO_2



of biological selectivity to I. Furthermore, a mixture of IA and IB is apparently more effective than IB alone.

Thus, while the antiestrogenic effect is responsible for initiation of ovulation, the estrogenic effect is apparently desirable or necessary as well in a later estrogen-dependent phase of the ovulatory cycle. This suggests that the antiestrogenic–estrogenic ratio of the *trans*-isomer (or of the *cis–trans* mixture), as well as the actual magnitude of the antiestrogenic activity, is of paramount importance. Finally, while it may seem enigmatic that I induces ovulation as a result of both its antiestrogenic and estrogenic qualities, it may be pertinent that the estrogenic potency ratios for isomers of IV vary markedly, depending on the tissue used as the biological test system (7). This fact suggests that these tissues have differing sensitivities to antiestrogen as well. Accordingly, the unique ovulation-inducing effects of I perhaps may be ascribed to the unique balance of antiestrogenic and estrogenic effects.

These considerations may have a bearing on the biological effects of such analogs of I as 1-[2-[*p*-[1-(*p*-methoxyphenyl)-2-nitro-2-phenylvinyl]phenoxy]ethyl]pyrrolidine (V), 2-[*p*-(6-methoxy-2-phenylindene-3-yl)phenoxy]triethylamine (VI), and 1-[2-[*p*-(3,4-dihydro-6-methoxy-2-phenyl-1-naphthyl)phenoxy]ethyl]pyrrolidine (VII) (23). This suggests that desmethoxy analogs of these (and similar) prototypes, suitably functionalized in the alicyclic segment to provide optimal tissue distribution, may also exhibit

high affinity for the estrogenic receptor and a suitable balance of antiestrogenic and estrogenic effects associated with induction of ovulation by IB.

In summary, the establishment of the stereochemistry of isomers of I has corrected an error in the literature, permitted a consistent explanation of the biological and physical data available on isomers of I and IV, and provided insight into the molecular mechanisms of action and direction for additional studies in this area.

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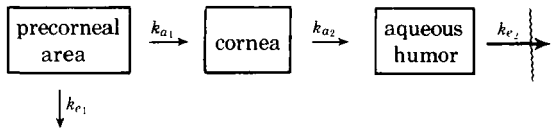
Corneal Drug Absorption: An Illustration of Parallel First-Order Absorption and Rapid Loss of Drug from Absorption Depot

Keyphrases □ Corneal drug absorption—pharmacokinetics, pilocarpine nitrate, rabbits □ Absorption, corneal—pharmacokinetics, pilocarpine nitrate, rabbits □ Pilocarpine nitrate—pharmacokinetics, corneal absorption, rabbits

To the Editor:

While studying corneal drug transport of pilocarpine nitrate, we encountered what at first appeared to be rapid permeation of drug into the cornea and aqueous humor but what, in fact, was a slow absorption process. The short time to achieve peak drug concentration in ocular tissues from an applied dose is caused by a rapid parallel elimination process from the absorption depot. This type of process was reported previously (1–3) but has not been reported as being applicable to the eye. The present communication presents evidence, using pilocarpine nitrate in rabbits, that corneal uptake of this drug and, presumably, other ocular drugs is not as rapid as the ocular tissue drug concentration *versus* time profile appears to indicate.

Ocular tissue drug level *versus* time profiles for most topically applied drugs have two common characteristics relative to the absorption phase: a low fraction of dose absorbed and a short time to achieve a peak drug level in either corneal tissue or aqueous humor (4, 5). The time of peak aqueous humor drug levels is generally in the range of 20–30 min postinstillation of drug, and the fraction of drug absorbed into the anterior chamber is usually less than 0.1 and often less than 0.01. The time of peak drug level in aqueous humor following instillation of an aqueous pilocarpine nitrate solution is around 20 min, and the fraction of dose absorbed is 0.002–0.003 (5). Figure 1 presents the corneal and aqueous humor drug levels *versus* time profiles for pilocarpine nitrate, illustrat-



Scheme I