# The photochemical stability of *cis*- and *trans* - isomers of tricyclic neuroleptic drugs

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The irradiation of the tranquillizers flupenthixol, clopenthixol and chlorprothixene has been found to induce rapid *cis-trans* isomerization. The composition of the photostationary mixture is not that of the batch drug and hence this process may affect the activity. Further decomposition to a thioxanthone derivative occurs rapidly in the presence of air. Exclusion of oxygen, however, does not prevent further degradation and a slower secondary isomerization is observed on prolonged irradiation. Doxepin and dothiepin also undergo analogous reactions but the isomerizations are much slower and the oxidative degradation yields many products.

Flupenthixol (I), clopenthixol (II), chlorprothixene (III) and thiothixene (IV) are representatives of a group of major tranquillizers based upon the thioxanthene nucleus. The presence of a substituent at the 2-position of these drugs allows the existence of geometrical isomers about the exocyclic olefin

cis R_3 R_2 (a)
trans R_2 R_3 (b)
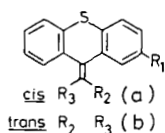
Flupenthixol Ia $R_1=CF_3$ $R_2=CH_2-CH_2-N\bigcirc N-CH_2-CH_2OH$ $R_3=H$
Clopenthixol IIa $R_1=Cl$ $R_2=CH_2-CH_2-N\bigcirc N-CH_2-CH_2OH$ $R_3=H$
Chlorprothixene IIIa $R_1=Cl$ $R_2=CH_2-CH_2-N(CH_3)_2$ $R_3=H$
Thiothixene IVa $R_1=SO_2N(CH_3)_2$ $R_2=CH_2-CH_2-N\bigcirc N-CH_3$ $R_3=H$

cis R_1 R_2 (a)
trans R_2 R_1 (b)
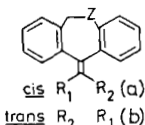
Doxepin Va $R_1=H$ $R_2=CH_2-CH_2-N(CH_3)_2$ $Z=O$
Dothiepin VIa $R_1=H$ $R_2=CH_2-CH_2-N(CH_3)_2$ $Z=S$

function at position 9 and both *cis*-[α- or Z] (Ia, IIa, IIIa, IVa) and *trans*-[β or E] (Ib, IIb, IIIb, IVb) forms have been described. There is considerable theoretical interest in the structure-activity relationships in this series of compounds (Horn et al 1975). Studies in vitro involving the inhibition of the dopamine-stimulated adenylate cyclase activity in homogenates of rat brain (Horn et al 1975; Miller et al 1974) or the competition with [³H]haloperidol for the dopamine receptor (corpus striatum) in synaptic

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receptor binding studies (Enna et al 1976; Burt et al 1976) mirror the in vivo result (Møller Nielsen et al 1973) and show that the *cis*-isomer is a potent drug whereas the *trans*-compound has a relatively low activity (Enna et al 1977). Similar results have been reported for doxepin (Bloom & Tretter 1964).

Despite these observations there appears to be a wide variation in the *cis-trans* ratio of these drugs (Table 1) and apart from the manufacturer's control

Table 1. Percentage of more active *cis*-isomer in tricyclic neuroleptics.

Drug	% Cis-Isomer	Ref.
Flupenthixol	50	Møller Nielsen et al 1973
Chlorprothixene	100	Martindale 1977a
Thiothixene*	37	Muren & Bloom 1970
Doxepin	15	Hobbs 1969
Dothiepin	mainly *trans*-	Martindale 1977b

* 100% cis-isomer formulated in capsules.

at the production point no in-use standards for isomeric composition and hence overall activity are laid down. We have recently reported a high pressure liquid chromatographic procedure which enables the resolution of the *cis*- and *trans*-isomers of these compounds and which has revealed the presence of batch to batch variation in these drugs (Li Wan Po & Irwin 1979). Here we wish to report the effect of exposure to light on these drugs and to show that a rapid change in the isomeric composition, as well as further degradation, may result.

MATERIALS AND METHODS

Apparatus

Analyses were performed using a high-pressure liquid chromatograph constructed from an Altex

100A constant flow solvent metering pump, a Rheodyne 7120 valve injector fitted with a 20 μl loop, and a Cecil 212 variable wavelength ultraviolet monitor, equipped with an 8 μl flow cell and operated at 260 nm with a sensitivity of 0·5–2 AUFS.

Chromatography was performed using a 25 cm ×4·6 mm i.d. spherisorb (5 μm spherical totally porous silica) with a mobile phase consisting of ethyl acetate (85), methanol (15) and 3% w/v ammonia (1) delivered at 1 ml min^{-1} at a pressure of 70 bar.

Mass spectra were determined by means of a Micromass 12B mass spectrometer by direct probe insertion at 280 °C with an ionizing voltage of 70 eV, a trap current of 100 μA and an accelerating voltage of 3KV. ^{1}H n.m.r. spectra were determined in deuterochloroform for free bases and D_2O for hydrochlorides with a Varian A60A spectrometer.

Artificial irradiation was achieved by means of an Hanovia 100W medium-pressure mercury arc lamp fitted with a quartz sleeve or a Microscal light fastness tester equipped with a 400W mercury tungsten lamp. T.l.c. data were obtained using silica-gel GF 254 [250 μm thick] with a mobile phase of benzene–carbon tetrachloride (7:3 v/v), the R_F of 2-trifluoromethylxanthone was 0·40.

Materials. Solutions of the hydrochlorides of *cis*- and *trans*-flupenthixol, clopenthixol, doxepin and dothiepin (0·5 mg ml^{-1}) were prepared in distilled water and 2 ml of each solution was packed into a series of clear glass ampoules. Chlorprothixene, available as the free base, was dissolved and packed using two equivalents of HCl. Similar series of ampoules were prepared using deoxygenated water (boiled and cooled in ice three times in a continuous nitrogen stream) with a nitrogen atmosphere. These ampoules, containing either an air or nitrogen atmosphere, were subjected to:—(i) autoclaving (115 °C for 30 min), (ii) storage at room temperature (20 °C) in the dark, (iii) storage on a window ledge for four days, (iv) irradiation using the Microscal light fastness tester or (v) irradiation using the Hanovia photochemical reactor.

Solutions were assayed by taking 1 ml of the exposed solution, basifying this by the addition of aqueous sodium hydroxide (5M, 1 ml) and extraction of the liberated bases into ethyl acetate (2 ml). The supernatant ethyl acetate layer (20 μl) was injected onto the h.p.l.c. column. The composition of the flupenthixol solutions was determined by adding promazine (0·25 mg ml^{-1}, 1 ml) as an internal standard and interpolating onto a calibration curve

produced from known amounts of the *cis*- and *trans*-isomers (0·5 → 0·05 mg ml^{-1}).

RESULTS AND DISCUSSION

Although the photochemical instability of thioxanthenes has been reported (Uda et al 1970; Gantes et al 1969) and the manufacturers recommend that samples be protected from light, no comprehensive studies on the nature of the degradation have been reported. To provide further information we have irradiated solutions of flupenthixol (I) clopenthixol, (II) and chlorprothixene (III) using a Microscal light fastness testing cabinet. This apparatus is rated at 3·4 times the intensity of sunlight and was chosen to give a repeatable level of irradiation rather than reliance being placed upon the varying intensities of natural daylight. Samples were held in clear glass ampoules which are effectively transparent to wavelengths longer than 300 nm (Dimbleby 1953; Lachman et al 1976). The photochemical degradation of *cis*-flupenthixol dihydrochloride in aqueous solution in this system may be monitored readily by h.p.l.c. and typical traces are shown in Fig. 1. Initially, only one peak, due to the pure *cis*-isomer, is observed (Fig. 1A) but on exposure to light, with the exclusion of oxygen, a rapid *cis- trans* isomerization is initiated. After 15 min (Fig. 1B) considerable degradation of the sample had occurred and the ratio of *cis*- and *trans*-isomers (1:1) was close to the composition of the batch and formulated samples of flupenthixol (Li Wan Po & Irwin 1979).

In those samples which were irradiated without the exclusion of air, two modes of decomposition were evident (Fig. 1D). *Cis- trans* isomerization was still a major component of this degradation and a photostationary equilibrium ratio was again rapidly set up. The presence of oxygen, however, led to the light-initiated oxidation of both *cis*- and *trans*-flupenthixol to yield 2-trifluoromethyl thioxanthone (VII). This product may be observed (Fig. 1D) as a non-retained peak in the chromatogram. As this is somewhat poor evidence for identity, the structure of the degradation product was confirmed by t.l.c. and mass spectrometric comparisons with authentic material.

The rates of isomerization of *cis* and *trans*-flupenthixol were determined separately by monitoring the degradation caused by the Hanovia lamp. This more powerful lamp increased the rate of isomerization and under these conditions both isomers were found to decay at the same rate with a half-life of 5 min.
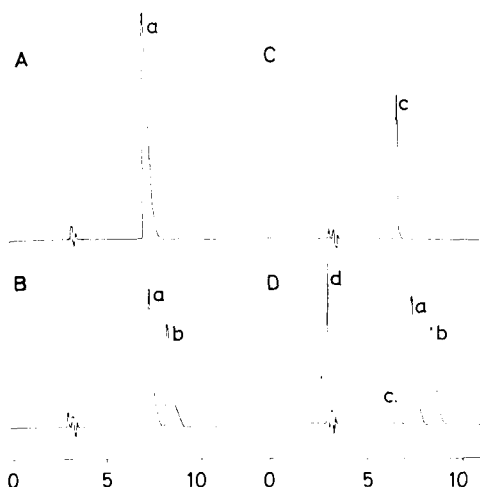
FIG. 1. Photochemical degradation of flupenthixol solutions (A) *cis*-isomer; (B) *cis*-isomer exposed to light (N_2) for 15 min; (C) *cis*-isomer exposed to light (N_2) for 24 h; (D) *cis*-isomer exposed to light (Air) for 1 h. Identified peaks are (a) *cis*-flupenthixol, (b) *trans*-flupenthixol, (d) 2-trifluoromethylthioxanthone.

Control samples of the *cis*- or *trans*-isomers which were stored in the dark or autoclaved with either an atmosphere of air or nitrogen, underwent no detect-

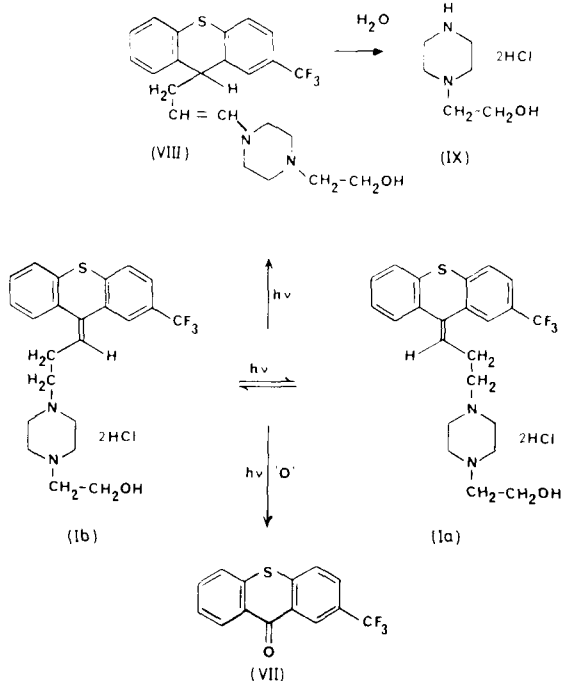Scheme 1. Photochemical degradation of *cis*-flupenthixol in solution.

able decomposition showing that the observed degradations were photochemical in origin.

On longer irradiation of the flupenthixol solutions under nitrogen, the photostationary equilibrium mixture of isomers was seen to undergo further degradation (Fig. 1C, Scheme 1) and eventually total conversion into a new product (VIII) was achieved. Decomposition of this compound in light and air yielded 2-trifluoromethylthioxanthone and 1-hydroxyethylpiperazine (IX) [confirmed by ^{1}H nmr spectroscopy of the hydrochloride, with methylene absorptions at τ 6·25 and τ 7·35 (CH_2–CH_2–OH) and at τ 6·72 and τ 7·14 (ring protons)]. This evidence and the retention time on the column (many weak bases and neutral compounds were totally unretained with this system) indicate that the major structural features of flupenthixol were still intact. Further, this product was detected (h.p.l.c.) as a single peak which suggested that either no geometrical isomers were possible in this structure or else one isomer is considerably more stable than the other. Unfortunately, the stability of this product, which rapidly yields the thioxanthone (VII) on attempted isolation, has proved insufficient for unambiguous structural determination to date. It would appear, however, that isomerization of the exocyclic olefin in the alkylamino side-chain to the enamine (VIII) is a possibility.

The corresponding h.p.l.c. data for the decomposition of clopenthixol is shown in Fig. 2. Analogous degradation occurs and a photostationary phase is again produced. However, in this instance, the composition of the equilibrium mixture differs from the batch composition in that more *cis*- isomer is present. This trend is more evident with chlorprothixene which is formulated as the *cis*- isomer (Fig. 3). Here, exposure to light rapidly causes a reduction in the proportion of this isomer until equilibrium is attained. It appears from this study, therefore, that the photochemical equilibrium ratio of *cis*- and *trans*-isomers and the batch composition may differ considerably, particularly with a liquid preparation, and to monitor possible changes isomer-specific quality control procedures should be used.

Further irradiation under nitrogen caused the slow degradation of the *cis*- and *trans*-isomers of both clopenthixol and chlorprothixene and the appearance of the new product may clearly be seen (Figs 2C, 3C).

In the presence of air, irradiation also caused clopenthixol and chlorprothixene to yield, in this case the same, thioxanthone. The degradation of these drugs therefore parallels that of flupenthixol.
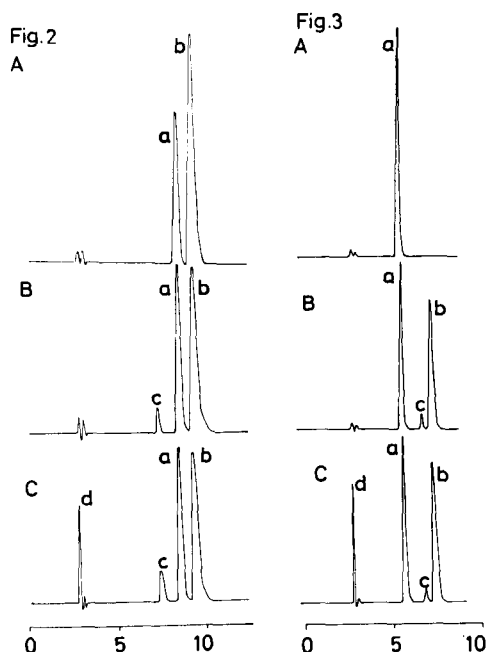
FIG. 2. Photochemical degradation of clopenthixol solutions. (A) batch sample, (B) after exposure to light (N$_2$) for 1 h, (C) after exposure to light (air) for 1 h. Peaks are (a) cis- and (b) trans-isomers. (d) 2-chlorothioxanthone.

FIG. 3. Photochemical degradation of chlorprothixene solutions. (A) cis-isomer, (B) after exposure to light (N$_2$) for 1 h, (C) after exposure to light (Air) for 1 h. Peaks are (a) cis, (b) trans-isomer. (d) 2-chlorothioxanthone.

FIG. 4. Photochemical degradation of doxepin solutions. (A) batch sample, (B) after exposure to light (N$_2$) for 1 h, (C) after exposure to light (N$_2$) for 24 h, (D) after exposure to light—Hanovia Lamp (air) for 24 h. Peaks are (a) cis- and (b) trans-isomer.

The decomposition is largely mediated by light and different profiles result depending upon whether air has been excluded or not.

The decomposition of doxepin was found to be considerably slower than that of the thioxanthenes (Fig. 4). Irradiation of solutions under nitrogen nevertheless caused changes in the isomer ratio (cis-isomer increasing) and also in the production of another rearrangement product.

Irradiation in the presence of air (Fig. 4D) initiates oxidative decomposition and the further possibilities of degradation of the oxepine ring (compared to the thioxanthenes) lead to a most complex oxidation profile. The photochemical stability profile of dothiepin (Fig. 5) parallels that of doxepin closely.

Although it is difficult to relate decomposition induced by artificial illumination to real conditions, these results illustrate that, in particular, the thioxanthene tranquillizers may be degraded quite rapidly by light. This is of clear importance when solutions of
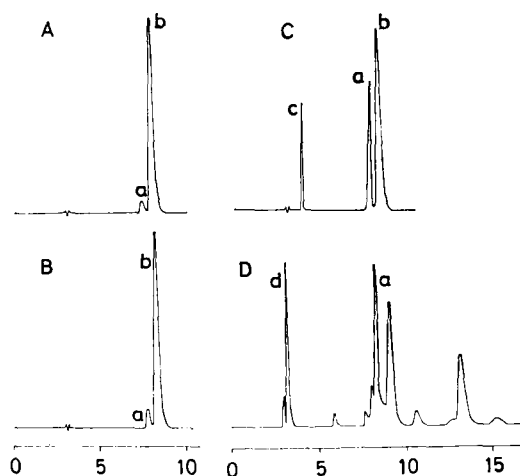
these drugs are handled during analytical or pharmaceutical procedures. In properly formulated and stored solid dosage forms these changes will probably be insignificant but they could be of importance in liquid preparations, which may use a pro-drug form of the cis-isomer formulated as an oily injection. In view of the variation in the isomer composition of these compounds, the possible changes in the isomer
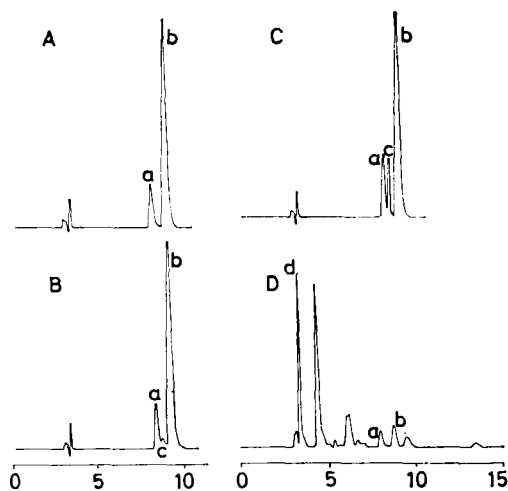

FIG. 5. Photochemical degradation of dothiepin solutions. (A) batch sample, (B) after exposure to light (N$_2$) for 1 h (C) after exposure to light (N$_2$) for 24 h (D) after exposure to light—Hanovia Lamp (air) for 24 h. Peaks are (a) cis-and (b) trans-isomers.

ratio during storage and the difference in activity of the *cis*- and *trans*-isomers we feel that standardization of the *cis-trans* ratio monitored by an isomer-specific assay would be advantageous.

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