Flupenthixol Dihydrochloride Decomposition in Aqueous Solution

R. P. ENEVER ˣ, A. LI WAN PO, and E. SHOTTON

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Abstract □ Flupenthixol dihydrochloride in aqueous solution oxidized to trifluoromethylthioxanthone, ethanol, and piperazine *via* aldehydic and epoxidic intermediates in the presence of air. The formation rate of trifluoromethylthioxanthone increased with increases in pH and oxygen concentration. Buffer ions also affected the decomposition rate. Micelle formation by the drug markedly influenced its oxidation rate.

Keyphrases □ Flupenthixol dihydrochloride—decomposition in aqueous solution □ Decomposition—flupenthixol dihydrochloride in aqueous solution □ Tranquilizers—flupenthixol dihydrochloride, decomposition in aqueous solution

The neuroleptic compound flupenthixol dihydrochloride is unstable to light and heat (1). The drug is closely related chemically to phenothiazines, which are susceptible to oxidative decomposition (2). Many phenothiazines also form micelles in aqueous solution (3), and there is evidence that the degradation kinetics of promethazine are influenced by micelle formation (4).

The objectives of the present work with flupenthixol dihydrochloride were to identify its decomposition products, to establish the degradation pathway in aqueous solution, and to examine some factors influencing the appearance rate of the main decomposition product trifluoromethylthioxanthone. The effect of drug concentration on the decomposition kinetics is also reported and related to the observed micelle-forming properties of flupenthixol dihydrochloride.

EXPERIMENTAL

At all times, flupenthixol dihydrochloride solutions were protected from light to prevent photodecomposition.

Identification of Decomposition Products—The decomposition products were prepared by sealing 2-ml volumes of aqueous solutions (pH 6.8) of flupenthixol dihydrochloride[1] in 10-ml ampuls and autoclaving at 115–116° for up to 6 hr. This procedure ensured that air was present in the ampuls. The decomposition products were isolated by TLC using the methods and materials previously described for amitriptyline hydrochloride (5). The physicochemical techniques used to characterize the isolated products were also identical to those reported for amitriptyline hydrochloride (5).

Rate Studies of Flupenthixol Dihydrochloride Decomposition—*Flupenthixol Dihydrochloride Assay*—Direct absorbance measurements can be used for assaying decomposing solutions of flupenthixol dihydrochloride at <pH 4 since the decomposition products do not interfere. There was no change in the general shape or shift in the absorption maximum of the UV absorption curve with drug decomposition. In addition, results obtained from absorbance measurements were identical with those obtained using a specific colorimetric assay involving extraction of the base and reaction with palladium chloride (6).

A calibration curve was constructed using solutions of flupenthixol dihydrochloride ranging in concentration from 0.5 to 2.5 mg/ml in McIlvaine citric acid–phosphate pH 3.0 buffer (7). The drug was stable in this buffer at room temperature since no decomposition could be detected even after 1 month of storage. Each solution was diluted by a factor of 100 with 0.1 *N* HCl prior to the absorbance[2] reading at 230 nm. For assay, the test solutions were diluted to within the concentration range of the calibration curve.

Trifluoromethylthioxanthone Assay—The formation rate of trifluoromethylthioxanthone[1] was followed by GLC[3]. A 1.5-m (5-ft) × 0.6-cm (0.25-in.) i.d. glass column was packed with 3% (w/w) OV-25 on Chromosorb W AW/DCMS[4]. The flow rates of hydrogen, air, and nitrogen were 83, 450, and 28.5 ml/min, respectively.

Calibration solutions of trifluoromethylthioxanthone ranging in concentration from 0.2 to 3.0 mg/ml were prepared in ether[5]. A 1-ml aliquot of each solution was added to a 10-ml ampul[6] containing 2 ml of the buffer used in the experiment. A 1-ml aliquot of a 0.5-mg/ml solution of dibenzosuberone[7] in ether was added to each ampul to act as an internal standard, and the contents of each ampul were shaken and rotated for 10 min. Subsequently, 2 μl of the ethereal extract from each ampul was injected into the chromatograph. A calibration plot of the peak height ratio of trifluoromethylthioxanthone to dibenzosuberone against the trifluoromethylthioxanthone concentration was constructed.

Trifluoromethylthioxanthone was stable in the buffers used for the preparation of the calibration curve since there was no detectable decomposition even after 1 month of storage at room temperature. Test solutions were treated by extracting the contents of an ampul with 2 ml of the dibenzosuberone internal standard solution and assaying the resultant ethereal extract.

Formation Rate of Trifluoromethylthioxanthone—The influence of pH, buffer ions, and oxygen concentration on the formation rate of trifluoromethylthioxanthone was investigated. For all experiments, 2 ml of the appropriate solutions was pipetted into 10-ml clear glass ampuls[6] prior to storage at 70° in water baths covered to protect the contents from light. The trifluoromethylthioxanthone concentration was then determined at various intervals by the GLC method.

Decomposition Rate of Flupenthixol Dihydrochloride—The effect of concentration on the decomposition rate of flupenthixol dihydrochloride was investigated by storing a series of solutions ranging in concentration from 0.5 to 10.0 mg/ml in McIlvaine citric acid–phosphate pH 3.0 buffer at 80° in water baths covered to protect the contents from light. The residual flupenthioxol dihydrochloride in the solution then was assayed by the spectrophotometric method.

Critical Micelle Concentration (CMC) of Flupenthixol—The CMC of flupenthixol dihydrochloride in distilled water was determined at 18° by the du Nouy tensiometer[8] method (8), the specific conductance method[9], and pH measurements[10] (9). CMC measurement of flupenthixol dihydrochloride at 25, 40, and 50° in pH 3.0 McIlvaine citric acid–phosphate buffer was carried out by the du Nouy tensiometer method using a water circulator[11] for temperature control of the dish.

RESULTS AND DISCUSSION

With carbon tetrachloride–benzene (3:7 v/v) and silica gel[12] plates, seven compounds, including flupenthixol, were separated. The R_f values were: I, 0.79; II, 0.63; III, 0.55; IV, 0.40; V, 0.20; VI, 0.13; and VII, 0.00. Flupenthixol dihydrochloride did not move off the baseline during the separation and corresponded to VII. With the same system, trifluoromethylthioxanthone was shown to have an R_f value identical to that of IV. Comparison of their mass fragmentation patterns, as well as UV, IR, and NMR spectra, confirmed that the two compounds were identical.

[1] Lundbeck Ltd., Luton, Bedfordshire, England.
[2] Pye Unicam SP1800 recording spectrophotometer. Pye Unicam, Cambridge, England.
[3] Pye Unicam 105 gas chromatograph equipped with flame-ionization detector.
[4] Perkin-Elmer Ltd., Beaconsfield, Bucks, England.
[5] B.D.H. Ltd., Poole, Dorset, England.
[6] Aldelphi Tubes Ltd., London, England.
[7] Koch Light Ltd., Colnbrook, Bucks, England.
[8] Cambridge Instrument Co., Cambridge, England.
[9] Zeta Meta Inc., New York, N.Y.
[10] Pye 290 Mk 2 pH meter, Pye Unicam, Cambridge, England.
[11] Gallenkamp Compenstat, Gallenkamp Ltd., London, England.
[12] Camag DSF-5 grade, Camag, Switzerland.

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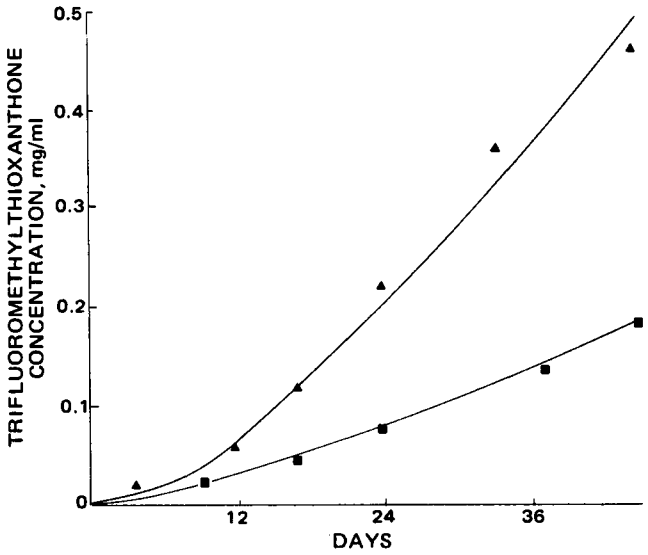


Figure 1—*Influence of oxygen on the formation rate of trifluoromethylthioxanthone from 2 mg of flupenthixol dihydrochloride/ml in pH 5.4 Sorensen citrate buffer at 70°. Key: ▲, under oxygen; and ■, under air.*

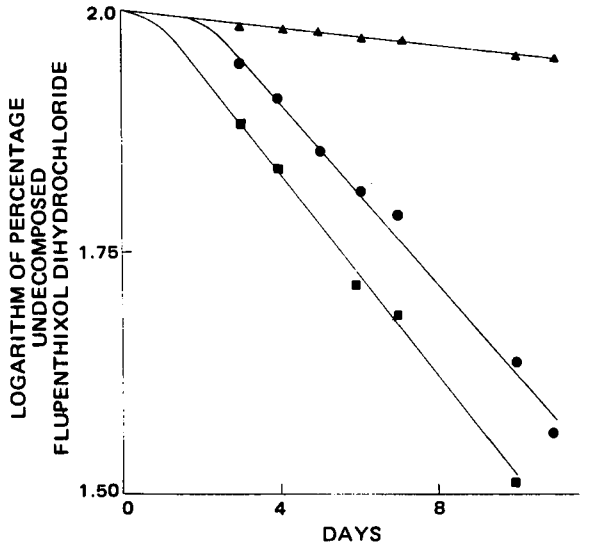


Figure 2—*Effect of drug concentration on the decomposition rate of 5 (▲), 1 (●), and 0.5 (■) mg of flupenthixol dihydrochloride/ml in pH 3.0 McIlvaine citric acid–phosphate buffer at 80°.*

Product V reacted with 2,4-dinitrophenylhydrazine spray reagent to produce a bright-yellow color, indicating the presence of an active carbonyl group. The mass spectrum showed a molecular ion peak at *m/e* 306, corresponding to the molecular formula $C_{16}H_9F_3OS$. The base peak was at *m/e* 305, suggesting a ready loss of proton probably from an aldehyde. A major peak at *m/e* 278, which can be interpreted as β-cleavage accompanied by the loss of an aldehydic function, was observed. Therefore, Structure V was postulated.

The IR spectrum confirmed the presence of a carbonyl function by exhibiting a sharp and intense peak at 1665 cm^{-1}, indicative of a conjugated aldehyde. On exposure to air, TLC showed that the compound was broken down to trifluoromethylthioxanthone.

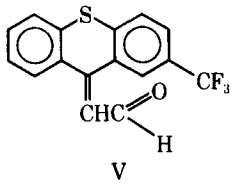
The mass spectrum of VI showed a molecular ion peak with an *m/e* of 336 and a base peak at *m/e* 265, corresponding to one peak in the mass spectrum of V. The greater relative intensity of the latter peak in the spectrum of VI indicated that the side chain attached to the tricyclic nucleus must be more labile than in V. TLC data showed that the compound was more strongly adsorbed than the aldehydic Compound V (R_f 0.13 compared to 0.20) in the nonpolar benzene–carbon tetrachloride system.

From a knowledge of IV and V, the presence of an oxygen atom or an alkene linkage seemed likely. The higher molecular weight relative to IV and V and the lower R_f value indicate the presence of an oxidized alkene linkage. No carbonyl absorption band could be detected in the IR spectrum. Therefore, Structure VI was postulated.

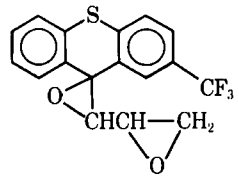
Such a structure would be expected to be very unstable, and exposure to air did indeed lead to the formation of trifluoromethylthioxanthone. Epoxides of similar compounds have been isolated (10).

The mass spectra of I–III showed them to be high molecular weight compounds, which may be dimers of smaller molecules. Such dimerization was described for phenothiazines, which are structurally closely related to flupenthixol dihydrochloride (11).

Piperazine and ethanol were also identified as products of side-chain decomposition. Methods developed by Uda *et al.* (1) were used for identifying piperazine, while ethanol was detected by GLC[3] with a Porapak Q column[13].



V



VI

[13] Waters Associates.

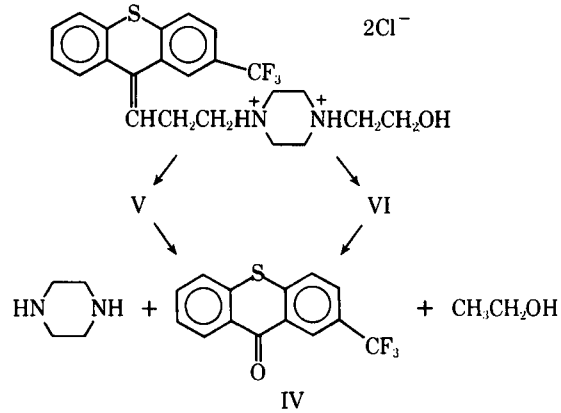
The decomposition pathway shown in Scheme I is postulated for flupenthixol dihydrochloride (VII) and is similar to that determined for amitriptyline hydrochloride (5). Oxidation of the parent compound to the corresponding ketone *via* several intermediates was observed with both drugs. The isolation of an epoxidic intermediate (VI) from the decomposed solution of flupenthixol dihydrochloride, but not from amitriptyline hydrochloride solution, is possibly due to the greater instability of such an intermediate in the latter case. Isolation of V and VI indicates that, in flupenthixol dihydrochloride as with amitriptyline hydrochloride, the alkene bond linking the side chain to the tricyclic nucleus is not the only labile center in the molecule.

The ketone, trifluoromethylthioxanthone (IV), was the major product of decomposition; its formation rate was affected by several factors. When 5 mg of flupenthixol dihydrochloride/ml at 70° in Sorensen citrate buffer solutions (7), adjusted to an ionic strength of 0.3, was used, the formation of the ketone obeyed zero-order kinetics. The rate constants were 3.4 at pH 2.4, 5.95 at pH 3.4, 7.37 at pH 4.4, and 15.3 μg/ml/day at pH 5.4. Thus, an increase in pH markedly accelerated the rate.

The type of buffer system employed also affected the process. With the same drug concentration in pH 4.4 buffers (ionic strength adjusted to 0.2) at 70°, the zero-order rate constants were 9.86 in McIlvaine citric acid–phosphate buffer, 3.99 in Walpole acetate buffer, and 7.37 μg/ml/day in Sorensen citrate buffer again.

Storage of 2-mg/ml solutions of flupenthixol dihydrochloride in pH 5.4 Sorensen citrate buffer under air and oxygen showed, as expected, that the formation rate of trifluoromethylthioxanthone was significantly increased in the presence of oxygen (Fig. 1). Zero-order kinetics were not obeyed at this drug concentration.

The effect of flupenthixol dihydrochloride concentration on its degradation rate is shown in Fig. 2. The process was slowest at the highest



IV

Scheme I

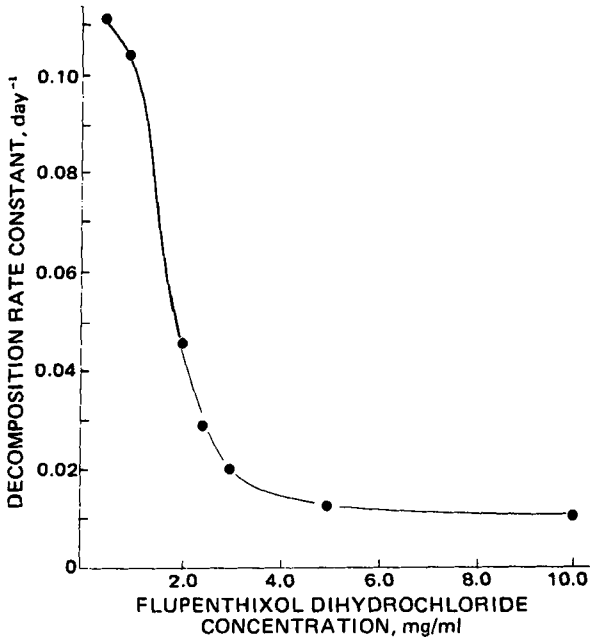


Figure 3—*Relation between first-order rate constant and drug concentration for flupenthixol dihydrochloride in pH 3.0 McIlvaine citric acid–phosphate buffer at 80°.*

concentration and obeyed first-order kinetics. At the lowest concentration, the decomposition also approximated this order of reaction; at intermediate concentrations, *e.g.*, 1 mg/ml, an initial slow rate preceded the more rapid decomposition phase. A control experiment was also carried out by sealing the 1-mg/ml solution under nitrogen and storing it at 80°. There was no detectable decomposition, even after 2 weeks of storage, which confirmed the oxidative nature of the decomposition.

The micelle-forming properties of the drug were investigated in an attempt to explain the phenomenon portrayed in Fig. 2. The three methods used for determining the CMC of the drug in double-distilled water at 18° all gave comparable results (mean value of 3 mg/ml). Thus, the du Nouy method was chosen as the most convenient for determining the effect of temperature on the CMC in buffer solution. The CMC's of flupenthixol dihydrochloride at 25, 40, and 50° in pH 3.0 McIlvaine citric acid–phosphate buffer were 1.25, 1.12, and 1.00 mg/ml, respectively. There was a linear relationship between the logarithm of the CMC and the reciprocal of absolute temperature, and the extrapolated value of the CMC at 80° was estimated to be 0.80 ± 0.05 mg/ml.

The relationship between micelle formation and decomposition can best be seen by plotting the rate constants of flupenthixol dihydrochloride decomposition, calculated from the linear sections of each curve, against initial concentrations (Fig. 3). Where two reaction rate constants were observed for a particular solution, the faster final rate was used in plotting the results. The highest decomposition rate occurred for drug concentrations below the CMC. Thus, micelle formation protected the drug from oxidation; as the drug concentration increased above the CMC, there was a corresponding rise in the relative proportions of the micellar to monomeric forms of the drug and enhancement of this protective effect. Above approximately 3 mg/ml, the rate remained essentially constant (Fig. 3) since the monomeric form of the drug became negligible relative to the total.

The biphasic nature of the data for the decomposition process observed at concentrations between the CMC and 3 mg/ml also can be attributed to micelle formation. Initially, with most of the drug in the micellar form, a slow decomposition rate was observed. As decomposition proceeded, the drug concentration fell below the CMC and the rate was accelerated. Above 3 mg/ml, a single rate of decomposition was observed because, within the time of study, the drug concentration did not fall below the CMC.

The data presented for this class of oxygen-sensitive compounds show that not only pH, oxygen concentration, and buffer composition influence the decomposition rate but also that the ability of the drug to form micellar structures can have a marked effect.

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