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Polymorphism and possible intramolecular bonding in benperidol

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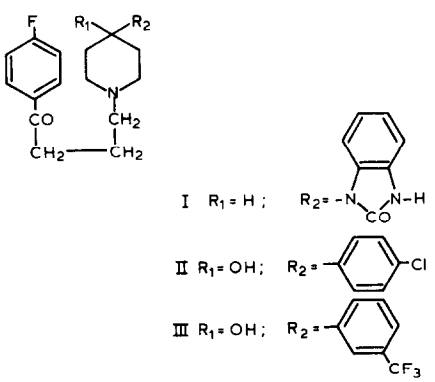
Summary

The existence of two polymorphs and two solvates of benperidol has been confirmed by IR spectrophotometry and differential scanning calorimetry, but an amorphous form and a possible third polymorph have been shown to be mixtures of the other two polymorphs. UV absorption indicates that benperidol can behave as an acid, through the dissociation of the enol form of its amide group. Internal neutralisation occurs, and polymorphic form I was identified as the amide, while polymorphic form II is the zwitterion. BHW plots of keto carbonyl stretching frequencies suggest than an intramolecular charge transfer occurs in haloperidol and trifluperidol hydrochlorides, and also in benperidol base, but not in haloperidol or trifluperidol bases. It is suggested that the differences between the conformations of amide and internally bonded zwitterion may be responsible for the polymorphism of benperidol.

Introduction

Azibi et al. (1982) reported that benperidol (I) exists in three polymorphic forms, all stable at room temperature. Form I was the original commercial form, form II was obtained by crystallisation from isopropanol and form III by crystallisation from *n*-heptane. Two solvated forms were obtained, one by crystallisation from ethanol, and the other from a mixture of water and acetone, together with an amorphous form, obtained by melting and cooling. No mode of interaction was suggested. There is no evidence in the literature to suggest that haloperidol (II) or trifluperidol (III) form polymorphs. Spectroscopic and other evidence are presented below and used to suggest why benperidol forms polymorphs and solvates, while the other two compounds do not.



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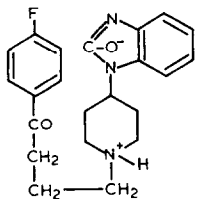


IV

Experimental

Materials

Benperidol, haloperidol and trifluperidol hydrochloride were gifts from Janssen Pharmaceuticals, and 4-fluoroacetophenone of 99% purity obtained from Fluorochem. Solvents were of the highest purity available. All were dried over sodium wire or calcium chloride, and distilled before use.

Haloperidol hydrochloride was prepared by dissolving 100 mg of haloperidol in 8 ml of isopropanol at 50°C, then adding 8 ml of 36% hydrochloric acid and 4 ml of acetone. This mixture was maintained at 50°C for 5 min then cooled, first at room temperature, then in an ice-bath and finally to − 20°C. The crystals were filtered off and dried under vacuum at 60°C. The product consisted of colourless crystals, m.p. 220–221°C (Okkerse et al., 1971).

Trifluperidol was prepared by dissolving 100 mg of trifluperidol hydrochloride in 75 ml of deionised water, adjusting to pH 8–9 with 25% ammonia, and extracting with four 25 ml portions of chloroform. The extracts were combined, dried over anhydrous sodium sulphate and filtered. Chloroform was removed by rotary evaporation, and the residue recrystallised from isopropanol and dried at 40°C. The product was obtained as colourless crystals, m.p. 94°C (Okkerse et al., 1971).

Preparation of polymorphs and solvates of benperidol (Azibi et al., 1982)

Form II was prepared by crystallisation of benperidol from isopropanol. 200 mg were dissolved in 25 ml isopropanol at 60°C and cooled to −10°C for 2 days. The crystals which separated were removed by filtration and dried, first at room temperature and then under low vacuum at 50°C. The product consisted of colourless crystals, m.p. 166°C.

Form III was obtained by heating 100 mg of benperidol at 50°C with 50 ml of *n*-heptane, under reflux. The solution was cooled in a refrigerator for 1 day, and the crystals removed by filtration and dried, first at room temperature and then under low vacuum at 50°C. The product was off-white crystals, m.p. 161°C.

Form I was considered to be the original sample, m.p. 173°C.

Benperidol ethanolate was prepared by dissolving 100 mg of benperidol in 80 ml of ethanol at 50°C, then refrigerating for 2 days. The crystals which separated were filtered off and dried, first at room temperature, then under low vacuum at 50°C. Colourless crystals, m.p. 140°C were obtained.

Benperidol hydrate was obtained by dissolving 300 mg of benperidol in a mixture of 20 ml water and 20 ml acetone, and refluxing at 60°C for 30 min. The clear solution was cooled to room temperature, then refrigerated for 1 day. The crystals which separated were filtered off and dried, giving off-white crystals, m.p. 127°C.

Amorphous benperidol was prepared by melting 50 mg in an oven at 277°C and leaving to cool at room temperature. Brownish-white plates were obtained, mp 160°C.

Differential scanning calorimetry. Thermograms of the polymorphs of benperidol were recorded on a Perkin Elmer DSC 2C differential scanning calorimeter. The instrument was calibrated using purified indium, tin, benzoic acid and salicylic acid. 2 to 6 mg samples were used. Results are shown in Fig. 1.

Infrared spectra were recorded using a Perkin Elmer 681 spectrophotometer, from potassium bromide discs (Fig. 2), and from a range of different solvents. Solutions were examined in 0.1 and 1.0 mm cells.

Ultraviolet spectra were recorded on a Pye Unicam SP 1800 spectrophotometer and quantitative measurements at fixed wavelengths made on a Pye Unicam SP 500 spectrophotometer.

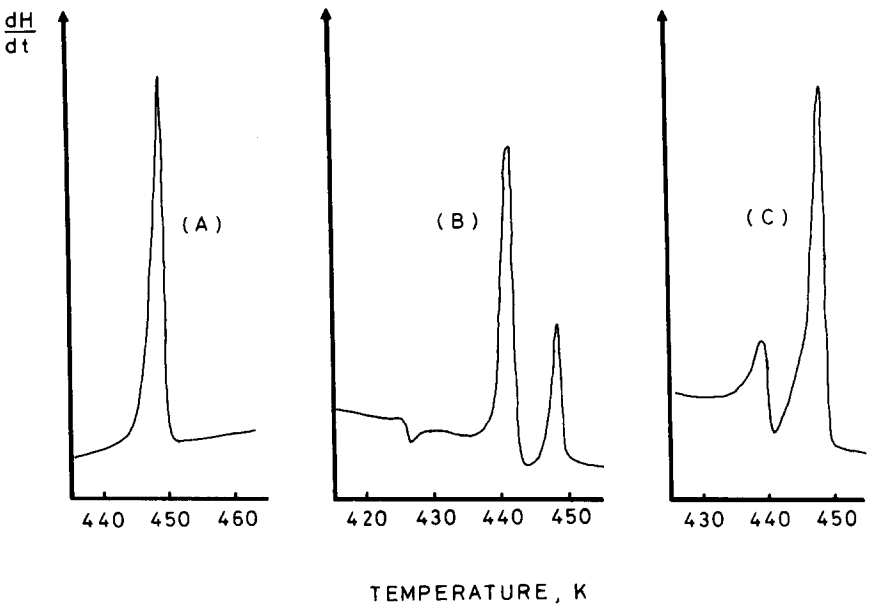
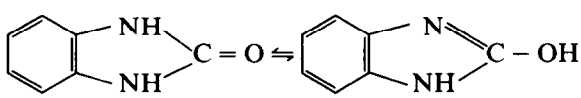


Fig. 1. DSC thermograms of benperidol. A: commercial product (form I). B: crystallised from isopropanol (form II). C: crystallised from *n*-heptane (form III).

Results and Discussion

Recrystallisation of haloperidol hydrochloride and trifluperidol hydrochloride from a range of solvents revealed no evidence of polymorphism. DSC thermograms of Forms I to III of benperidol are shown in Fig. 1 and are similar to those described by Azibi et al. (1982). Form I gave a single, sharp endotherm at 448K, while form II gave endotherms at 442 and 448K, with an exotherm at 443K, indicating that the molten form II crystallises to give form I. Form III gave a similar thermogram to form II but the relative peak heights were reversed, suggesting that form III is a mixture of forms I and II. The infrared spectra of the polymorphs are shown in Fig. 2. Form I gave two carbonyl stretching bands, ketone at 1685 cm^{-1} and amide at 1710 cm^{-1}, together with an NH stretching band at 3110 cm^{-1}, all in accordance with the structure of benperidol (I). In contrast, form II gave only one carbonyl stretching band, ketone at 1685 cm^{-1} and no NH stretching in the 3100 region. Efros and Eltsov (1957) have shown that benzimidazolone enolises as follows:



If the enol group in the benzimidazolone fragment of benperidol ionises, a zwitterion, as shown in (IV) is possible, and would give the IR spectrum obtained with form II. That forms I and II are keto and zwitterion, respectively, is supported by the absence of hydroxyl stretching peaks from both spectra. The spectrum of form III showed absorption at 3110, 1710 and 1685 cm^{-1}, but the NH stretching band was considerably reduced in comparison with form I, and the amide band was only a shoulder. These observations support the opinion that form III is a mixture of forms I and II. The amorphous form gave a similar spectrum, suggesting that this is also a mixture of forms I and II.

The ethanolate and hydrate spectra are similar to that of form II, but the hydrate has a hydroxyl stretching band at 3540 cm^{-1} and the ethanolate

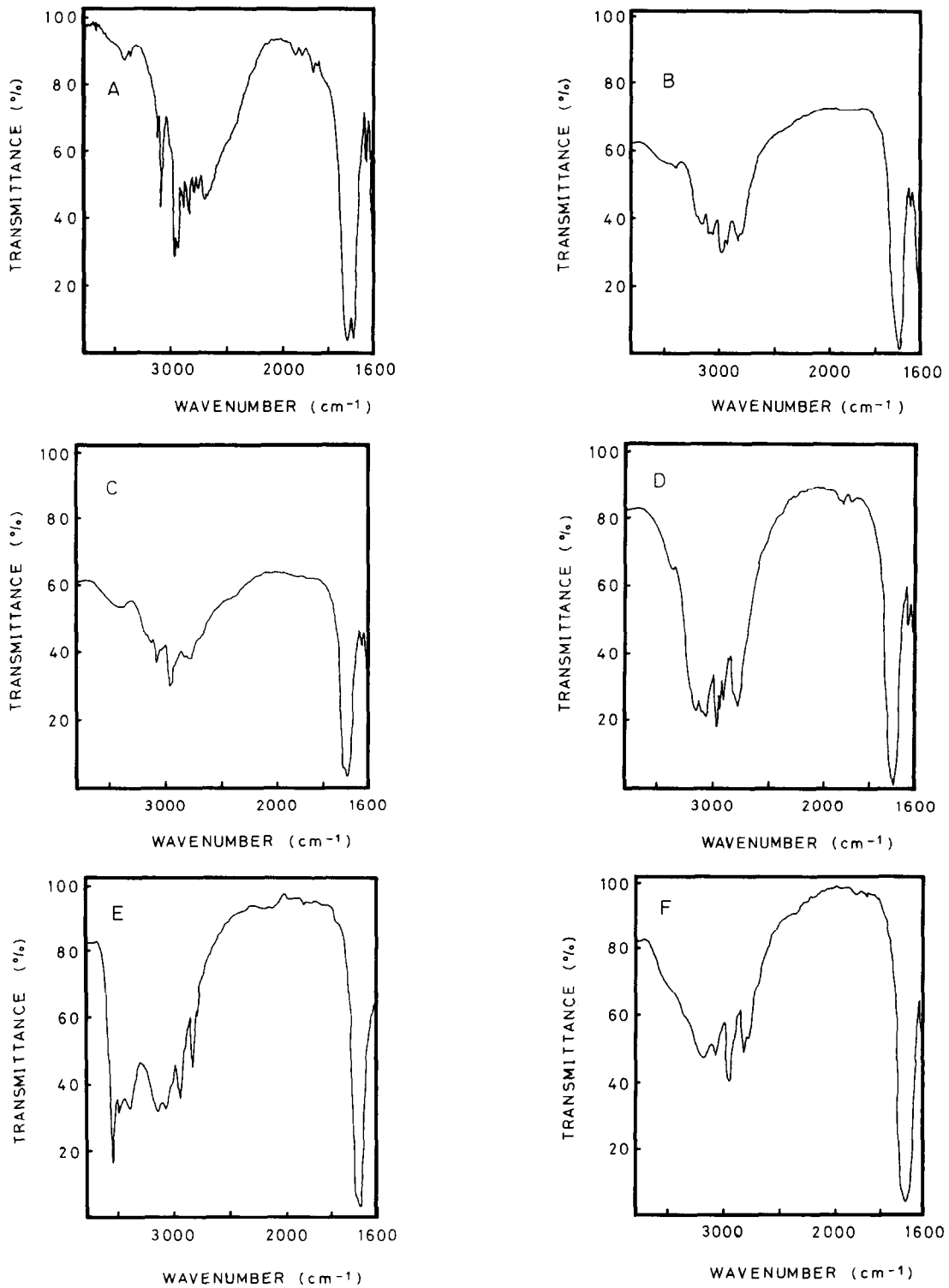


Fig. 2. Infrared spectra in KBr discs. A: form I. B: form II. C: form III. D: ethanolate. E: hydrate. F: amorphous.

does not. This suggests that the hydroxyl group of ethanol and one of the hydroxyls of water are hydrogen bonded to the amide oxygen. Electronic spectra, shown in Fig. 3, confirm that the benzimidazolone group in benperidol ionises. The benperidol molecule consists of two chromophores, a 4-fluoroacetophenone group and a benzimidazolone group, joined by a non-resonating link. The chromophores therefore function independently. Difference spectra, with 4-fluoroacetophenone or benzimidazolone solutions as blanks, indicated that absorption at 249 nm was due partly to the 4-fluoroacetophenone chromophore, but the peaks in the 260–310 nm region were due solely to the benzimidazolone chromophore. The maxima in the 260–310 nm region varied with pH and passed through an isosbestic point at 280 nm. Only two spectra are shown, but spectra at intermediate pH values fitted the general pattern. Spectra at low and intermediate pH values followed the same path, indicating that the behaviour represented acid ionisation. Basic ionisation would have no influence on the UV spectrum because the basic group of benperidol occurs in the transparent region of the molecule.

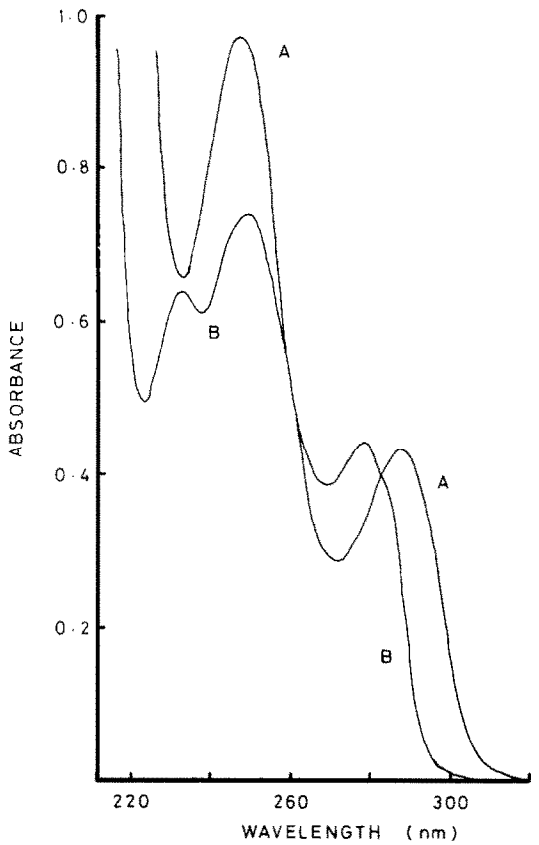


Fig. 3. Ultraviolet spectra for 5.5×10^{-5} M benperidol in (A) 0.1 M sodium hydroxide and (B) water.

Bellamy et al. (1958) examined the solute–solvent interactions of functional groups by plotting the frequencies in a range of solvents with the frequencies obtained with a standard solute having the same functional group. A rectilinear plot with unit slope indicated that the group behaved the same way in both solvents, and any solvent which did not fall on or near the line behaved in an abnormal manner. A typical plot for the keto carbonyl frequencies of trifluperidol, using 4-fluoroacetophenone as standard, is shown in Fig. 4, and indicates that solute–solvent interactions are the same in the two compounds. Similar results were obtained with haloperidol. However, the frequencies of trifluperidol and haloperidol hydrochlorides were insensitive to solvent changes, as shown in Fig. 5. The corresponding plot for benperidol is shown in Fig. 6; the results

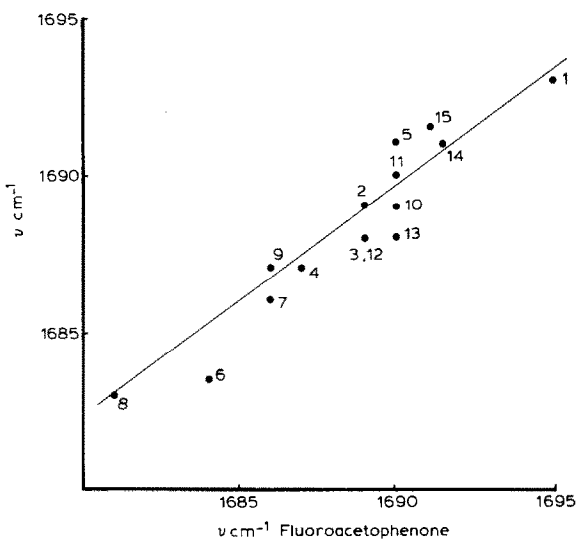


Fig. 4. BHW plot of carbonyl stretching frequencies of trifluperidol against 4-fluoroacetophenone. Solvents: (1) diethylether; (2) 1,4-dioxane; (3) methoxybenzene; (4) nitrobenzene; (5) tetrahydrofuran; (6) chloroform; (7) dichloromethane; (8) bromoform; (9) 1,2-dichloroethane; (10) trichloroethylene; (11) benzene; (12) bromobenzene; (13) chlorobenzene; (14) toluene; (15) xylene.

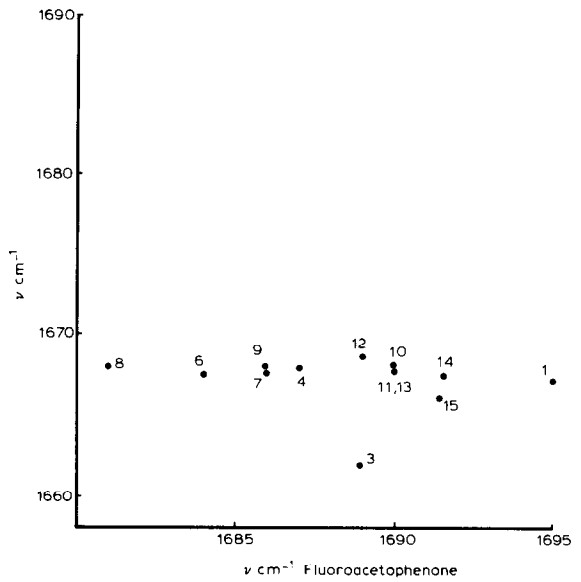


Fig. 5. BHW plot of carbonyl stretching frequencies of trifluperidol hydrochloride against 4-fluoroacetophenone. Solvent code as in Fig. 4.

are scattered, taking a form intermediate between Figs. 4 and 5. It is suggested that in the hydrochlorides the protonated piperidyl nitrogen is involved in a charge transfer with the ketone group, forming an intramolecular six-membered ring. The ketone group thereby loses its ability to interact with solvents, with a resulting insensitivity of the carbonyl stretching frequency. In haloperidol and trifluperidol bases the nitrogen is not protonated, and there is no intramolecular interaction. Benperidol takes on an intermediate position between the bases and the salts, because its acidic group is weaker than hydrochloric acid. An intramolecular interaction of this type in the zwitterion form of benperidol would have a different conformation from the amide form, accounting for the observed polymorphism.

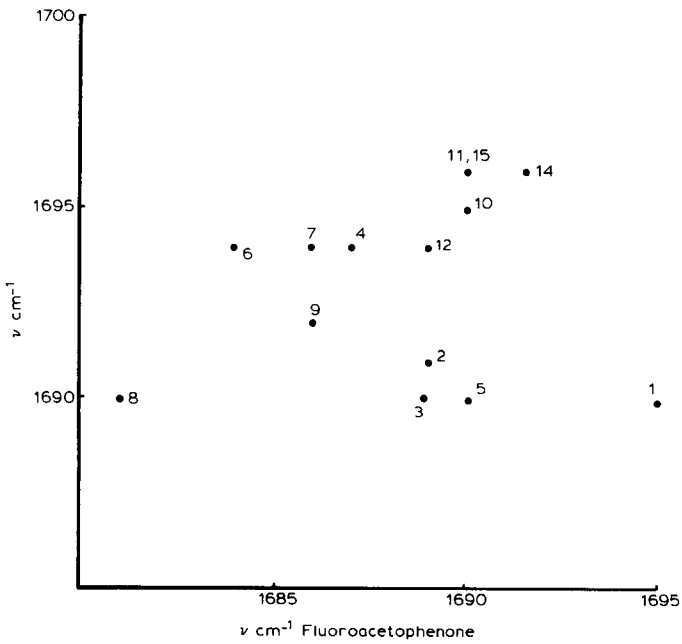


Fig. 6. BHW plot of carbonyl stretching frequencies of benperidol against 4-fluoroacetophenone. Solvent code as in Fig. 4.

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