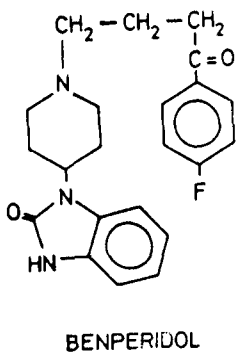
INTRAMOLECULAR BONDING IN SOME BUTYROPHENONES

A.E.H.Gassim, P.Girgis Takla and K.C.James, Welsh School of Pharmacy, UWIST, Box 13, Cardiff CF1 3XF, U.K.

Despite the fact that benperidol forms polymorphs (Azibi et al, 1982) there is no evidence for polymorphism in the related compound haloperidol. Solid benperidol, crystallised from n-heptane, gives two carbonyl stretching frequencies, one for the ketone at 1685 and one for the amide at 1710 cm^{-1}, but the amide carbonyl peak is absent from the i.r. spectra of the other polymorphs. Benzimidazolone is known to be tautomeric, and it is therefore probable that the benperidol polymorphs which do not display amide carbonyl peaks exist in the -N-C(OH)=N- form. Haloperidol contains no amide, which supports the suggestion that polymorphism is involved with this group.

Bellamy and Williams (1959) studied solute-solvent interactions by plotting the i.r. frequencies of a solute functional group, dissolved in a series of solvents, against the corresponding frequencies in a standard solute. A straight line with significant slope indicates that the functional group interacts with the solvents in the same way in both solutes. Haloperidol gave such a plot against 4-fluoroacetophenone, as also did trifluperidol, but benperidol and the hydrochlorides of haloperidol and trifluperidol gave an almost constant ketone carbonyl stretching frequency which was independent of the nature of the solvent. Examples are shown in Fig.1 and 2.



BENPERIDOL

Fig. 1. Trifluperidol

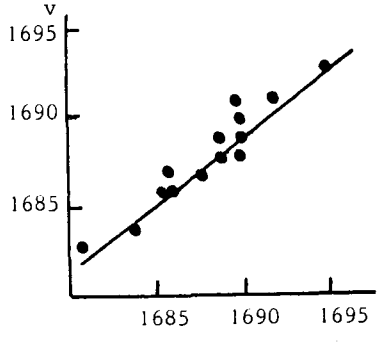
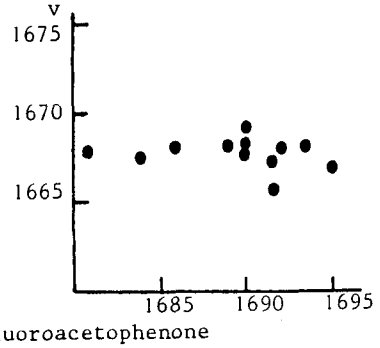


Fig. 2. Trifluperidol Hydrochloride



v 4-fluoroacetophenone

A probable explanation is that the ketone oxygen of benperidol is involved in an intramolecular bond, and atomic models indicate that an interaction with the piperidine ring nitrogen is possible, without creating strain. The enol hydroxide of benzimidazole is capable of ionising, and u.v. spectra of benperidol indicate that it behaves in a similar manner. The amide proton in benperidol can therefore provide the necessary positive charge on the piperidine nitrogen to bond with ketone oxygen, resulting in formation of a 6-membered ring. The hydrochlorides of haloperidol and trifluperidol are capable of the same interaction, for similar reasons.

Azibi,M. et al. (1982) Pharm. Acta Helv. 57 172-188
Bellamy,L.J. & Williams,R.L. (1959) Trans. Faraday Soc. 55 14-18