DISPUTANDUM

Stereoselective activity of chiral neuroleptics*

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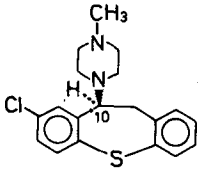
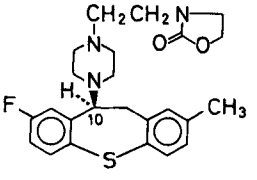
Summary. Attention is drawn to the evidence in favour of the stereoselective activity of chiral neuroleptics. The results reported by Gupta et al.[1], which suggest that their chiral dibenzothiepins do not fit in with that evidence, are questioned.

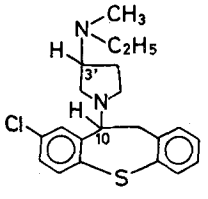
The stereoselective activity of chiral neuroleptics has been demonstrated in 3 cases so far. Of these, butaclamol has been studied in greatest depth. Pharmacological[2–4], biochemical[5,6], and dopaminergic receptor binding studies[7–9] have all shown that the neuroleptic action of butaclamol resides in the (+),S-enantiomer. Using pharmacological tests (apomorphine- and amphetamine-antagonism and cataleptic action in the rat), we have demonstrated[10] that the neuroleptic activity of octoclothepin (**1**) is due to its (+),S-enantiomer. More recently, Aschwanden et al.[11] have reported that for the dibenzothiepin **2**, which structurally is closely related to octoclothepin, it is again the (+),S-enantiomer that is neuroleptically active in their pharmacological and biochemical models.



1 (+)-S-Octoclothepin



2 (+)-S



3 (10S, 3'S)
4 (10R, 3'R)
5 (10R, 3'S)
6 (10S, 3'R)

In view of this clear evidence for the stereospecific activity of neuroleptics, the reports by Witiak and his associates[1,12], according to which there are no significant differences in neuroleptic activity between the dibenzothiepin enantiomers **3** and **4**, and **5** and **6**, respectively, are somewhat surprising. In the more recent of their publications[1], these authors claim that their results are in agreement with those originally reported for octoclothepin (**1**) by Protiva and co-workers[13]. They appear to have overlooked the statement made in our report on the neuroleptic effects of octoclothepin[10] that the Czech workers, in a personal communication, had confirmed our findings, and their new results correcting their earlier claims[13] have since been published[14].

Before searching for reasons why the aminopyrrolidinyl-dibenzothiepins **3–6** should fail to conform to the pattern, one has to be certain that these structures do in fact possess specific neuroleptic properties. Referring to the more recent report by Gupta et al.[1], the described method of measuring amphetamine antagonism is open to question. Our main criticism is that the method differs in several important respects from any of the 3 reference methods cited. There are various marked differences in the dose of agonist, the frequency of observation and the test duration, for example. In particular, it could be suspected that the prolonged observation period of 4 h employed might include non-specific changes.

This doubt receives further support from the authors' own earlier findings for the neurotoxic effects in the rotarod test and for the inhibition of conditioned avoidance[12]. The effective doses were virtually identical for each pair of enantiomers in both tests. From this data we would deduce, not that there was no stereospecificity in the neuroleptic action of the enantiomers, but rather that they lacked a clearly specific neuroleptic action. In this context, we would also refer to Metyšová and Protiva[14] who stated that the lack of stereoselectivity originally reported by them for octoclothepin related only to the central depressant effects, whereas the neuroleptic effects were highly stereospecific.

* *Comments on the publication of* Gupta et al.[1].

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