Antagonism of amphetamine stereotyped behavior by diastereoisomeric dihydrodibenzothiepin neuroleptics[1]

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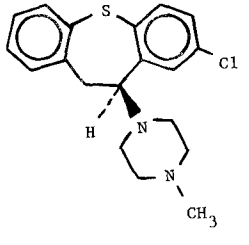
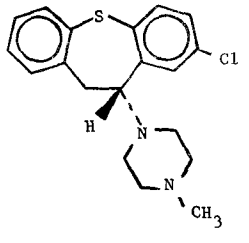
Summary. Differences in neuroleptic activity were observed between the diastereoisomers of a dihydrodibenzothiepin derivative, while no potency differences were seen between their respective enantiomorphs.

The stereoselective biological activity of the neuroleptic compounds butaclamol[2,3] and octoclothepin[4] has been reported. *(+)-Butaclamol has* been observed to be at least 100 times more potent than its (−)-enantiomer in its ability to antagonize amphetamine-induced stereotyped behavior in rats[3], while (+)-S-octoclothepin[8-chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[b, f]-thiepin] was 36 times more potent than its (−)-R-enantiomer in this test[4].

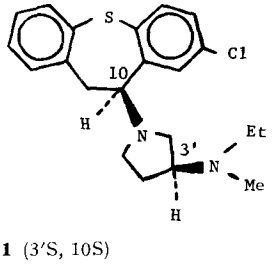
We have recently reported the synthesis, stereochemistry and biological properties of 4 chiral isomers [3′S, 10S (**1**); 3′R, 10R (**2**); 3′S, 10R (**3**); 3′R, 10S (**4**)] of 8-chloro-10-(3′-methylethylaminopyrrolidino)-10,11-dihydrodibenzo[b,f]thiepin, synthesized from amino acids of known absolute configuration[5]. In view of the close chemical similarity between our chiral isomers[5] and octoclothepin[4,6] (see figure), it was of interest to re-examine our compounds to determine whether enantiomorphic and/or diastereomeric differences in neuroleptic activity exist.



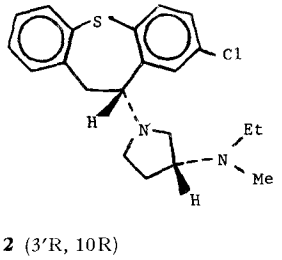
(+)-S-Octoclothepin



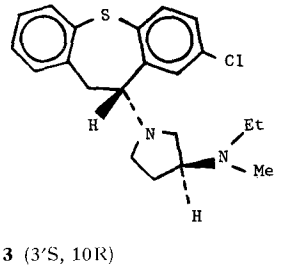
(-)-R-Octoclothepin



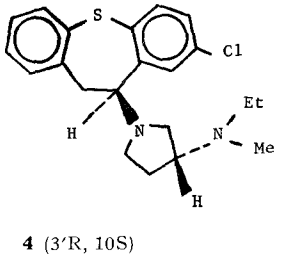
1 (3′S, 10S)



2 (3′R, 10R)



3 (3′S, 10R)



4 (3′R, 10S)

Little or no differences in potency were found between enantiomorphs **1** and **2**, or between **3** and **4**, while **1** and **2** were found to be 13.7 and 8.3 times more active than their respective diastereoisomers **3** and **4** in their ability to antagonize amphetamine-induced stereotyped behavior (see table). Similarly, in our earlier report, we observed diastereoisomeric differences (1.8–1.9fold) but no enantiomorphic differences in the ability of these chiral isomers to block conditioned-avoidance responding in mice[5]. These findings are at variance with those of Petcher et al.[4], but consistent with Jílek et al.[6]; the latter group observed no enantiomorphic differences in the pharmacological activity of octoclothepin.

[1] Supported by USPHS grant NS-10203.

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Comparative neuroleptic activities of dihydrodibenzo[b, f] thiepin isomers and chlorpromazine[a]

Compound	ED50[b]
1 (3′S, 10S)	0.54 (0.23–1.27)
2 (3′R, 10R)	1.10 (0.49–2.45)
3 (3′S, 10R)	7.4 (3.4–16.1)
4 (3′R, 10S)	9.1 (5.2–16.0)
Chlorpromazine	3.7 (2.6–5.3)

[a] Adult, male Sprague-Dawley rats were injected with (+)-amphetamine (10 mg/kg, i.p.) and administered test compounds 15 min later. Stereotyped behavior was rated at 15 min intervals for 4 h[7–9]. [b] The intensity of stereotyped behavior after administration of test compounds at doses of 0.315–15 mg/kg was determined in groups of 4 rats, and the dose which produced a 50% blockade of stereotypies (ED50 and 95% confidence limits) determined[10].