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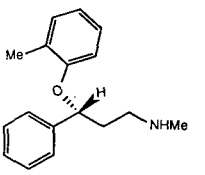
Letter to the Editor

Tomoxetine and the stereoselectivity of drug action

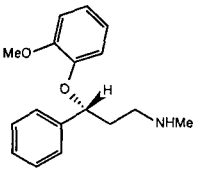
ROBERT OBERLENDER, DAVID E. NICHOLS*, P. V. RAMACHANDRAN†, MORRIS SREBNIK†, *H. C. Brown & R. B. Wetherill Dept of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, and †Laboratories of Chemistry, Purdue University, West Lafayette, Indiana 47907, USA*

The phenoxypropylamine derivative tomoxetine has been shown to inhibit noradrenaline (NA) uptake into synaptosomes from rat hypothalamus (Wong et al 1982). Differences in the potencies of the resolved optical isomers, (−)-tomoxetine (I) and (+)-tomoxetine were also noted, the (−)-isomer being more potent than the racemate or the (+)-isomer in-vitro and in-vivo.

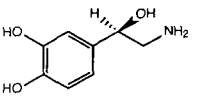
Our attention was caught by the use of the term 'stereoselectivity' in the discussion of NA uptake inhibition by Wong et al (1982). The relative potencies of the (+)- and (−)-isomers of tomoxetine and amphetamine (IV is the more potent (+)-isomer of amphetamine) shown were compared, even though the asymmetric centres for these molecules are not similar. In addition, the stereoselectivity of tomoxetine and NA (III is the biologically relevant (−)-isomer of NA) was discussed with reference to their signs of optical rotation, without regard to absolute configuration. Finally, it was stated that the stereoselectivity of nisoxetine (II is the more potent (+)-isomer), a close



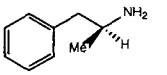
I



II



III



IV

analogue of tomoxetine in which an *ortho*-methoxy group replaces the *ortho*-methyl group in the latter, was reversed relative to tomoxetine. If both compounds interact with the same acceptor sites in noradrenergic nerve terminals, which seems likely from their similarity

* Correspondence.

in chemical structure, then a reversal in stereoselectivity would be extremely unusual. Instead, we considered the possibility that while the sign of optical rotation of the more potent stereoisomers of tomoxetine and nisoxetine is different, their absolute configurations may in fact be identical.

Using a recently developed asymmetric synthesis (H. C. Brown et al, unpublished) that employs the optical isomers of B-chlorodiisopinocamphenylborane, the individual enantiomers of tomoxetine and nisoxetine have been synthesized. This method allows unequivocal assignment of the absolute configurations of these optically pure products. After measuring their optical rotations we find that the more potent (−)-isomer of tomoxetine and the (+)-isomer of nisoxetine share the same absolute configuration, designated *R* by the Cahn-Ingold-Prelog sequence rules.

Furthermore, the comparison (Wong et al 1982) between *R*-(−)-tomoxetine and *R*-(−)-NA is not valid due to the change in priorities in numbering the groups attached to the chiral centres of these two molecules. Thus the biologically relevant *R*-(−)-isomer of NA has the same configuration as the less active *S*-(+)-isomer of tomoxetine and *S*-(−)-isomer of nisoxetine. Since the β-hydroxy-oxygen of *R*-(−)-NA is oriented toward the opposite face of the molecule, relative to the phenoxy-oxygen of *R*-(−)-tomoxetine, the speculation by Wong et al (1982) concerning the stereospecificity of the natural carriers to transport [^{3}H]NA in noradrenergic terminals may need revision.

Many biologically active compounds demonstrate stereoselectivity in their pharmacological activities. Although other factors are sometimes involved, this selectivity usually derives from the discriminatory capacity of the molecular site of action, which depends on its degree of chemical complementarity to the individual stereoisomers (Ariens 1984). It is often useful, in structure-activity relationship studies, to compare stereoselectivity in a series of compounds. Confusion may arise, however, when molecules are compared only with respect to the direction in which they rotate plane polarized light. Discussions of drug stereoselectivity in pharmacology should be based on *absolute configurations* at the same chiral centres. While '(+)' and '(−)' provide convenient labels for optical isomers, their use in such discussions may be misleading and confusing.

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