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Cholinesterase Inhibitors: Structure of Eserine

ESERINE (physostigmine) was first isolated from the Calabar bean in the latter half of the last century¹, but it was not until much later that its activity on the heart was demonstrated to be due to inhibition of acetylcholinesterase^{2,3}. It is one of the few compounds that are equally active as inhibitors of both true and pseudo-cholinesterase and has been used by many workers as a reference standard in the evaluation of new cholinesterase inhibitors. The chemical structure of this alkaloid was elucidated by Stedman⁴ and the absolute configuration has relatively recently been confirmed by use of the nuclear Overhauser effect (NOE) in NMR spectroscopy⁵. As part of our study of the geometry of molecules affecting cholinergic nervous transmission, we have determined the crystal structure.

ment with the results of the NOE study⁵. In solution there is no inversion of configuration by C18 and the lone pair on N5 (ref. 5), but the second pyrrolidine ring may be expected to be conformationally rather flexible because of inversion through N7. In the crystal, the lone pair on N7 is also *cis* to the hydrogen atom on C6. The carbamate group is planar, with the hydrogen on N16 *trans* to the keto oxygen, and will remain so in solution because of the partial double bond C14–N16. In the crystal, the torsion angle C12–C1–O13–C14 is observed to be -72° , but an examination of CPK space-filling atomic models indicates that this angle may range -30° to -150° and $+30^\circ$ to $+150^\circ$: the value of 31.8 observed by us in the crystal structure of neostigmine bromide⁷ is clearly a lower bound and no sign of a similar interaction between the *ortho* aromatic proton and the keto oxygen exists in the present structure.

Chothia and Pauling⁸ have postulated a particular conformation of acetylcholine as being the conformation relevant to interaction with the esterase, and Pauling and Petcher⁷ have pointed out the similarity between this postulated conformation and the observed solid-state conformation of neostigmine. It is difficult to correlate the conformation of eserine with these two because of the *para* relationship of N5 and the carbamate group in eserine. The observed conformations of eserine and neostigmine are, however, similar in some respects. The N5–C14 and N5–O15 distances are 638 and 620 pm respectively, compared with 605 and 647 pm in neostigmine. AChE appears to be relatively insensitive to molecular shape as far as reversible inhibition is concerned, provided that three necessary groups are present, these being a carbamate group bonded to an aromatic ring which must carry an alkyl substituted nitrogen atom in the *meta* or *para* position.

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Fig. 1 Perspective drawing of eserine, projected on the plane of N5–N7–C9–C11. The absolute configuration corresponds to that of the natural alkaloid.

Crystals of eserine (BDH Ltd), as clear tabular plates, are orthorhombic, space group $P2_12_12_1$, with $a=1458$ (1), $b=1435$ (1), $c=727.1$ (6) pm. Three-dimensional intensity data were measured on a computer-controlled⁶ four-circle diffractometer using graphite monochromatized MoK_α radiation. 2,658 measurements for $2\theta \leq 60^\circ$ yielded 2,556 symmetry-independent observations, of which 1,520 were significantly above background ($I \geq 3\sigma(I)$). The structure was solved by application of multi-solution direct methods and refined by block-diagonal least squares using anisotropic temperature factors for C, N and O, and isotropic vibrations for hydrogen. The present values of R are 0.060 over the 1,520 significant reflexions and 0.097 over all 2,531 data.

The conformation of the molecule is shown in Fig. 1, in the absolute configuration corresponding to that of the natural alkaloid. The two pyrrolidine rings are *cis*-fused, and that adjacent to the aromatic ring is practically flat, while the other is in the half-chair (C_2) conformation with the two-fold axis passing through C8 and the centre of the C6–C10 bond. Both ring nitrogen atoms are tetrahedral, but N5 is rather flattened and has more sp^2 character, judging from the bond angles. The C18 methyl group is *cis* to the hydrogen on C6, in agree-

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