This work was done during tenure of a grant from the Muscular Dystrophy Group of Great Britain.

REFERENCE

LILEY, A. W. (1956). An investigation of spontaneous activity at the neuromuscular junction of the rat. *J. Physiol., Lond.*, **132**, 650–666.

Conformations and biological activities of cyclic analogues of choline aryl ethers

E. R. CLARK* and C. F. C. SMITH, *Department of Pharmacology, University of Leeds*

In order to stimulate nicotinic receptors, Clark, Dawes & Williams (1968) suggested that choline phenyl ether must adopt a conformation in which the dihedral angle ('angle-of-twist') between the plane containing the benzene ring and the ether oxygen, and the plane containing the ether oxygen and the carbon atom situated β to the quaternary nitrogen must be 0°.

To look further into the problem of relating the conformations of choline aryl ethers with biological activity we have synthesized and studied (8-methyl-chroman-2-ylmethyl)trimethylammonium bromide (I), *cis* (II) and *trans* (III) isomers of N,N,N-trimethyl-2-phenoxycyclohexylammonium bromide, *cis*-N,N,N-trimethyl-2-(2,6-xylyloxy)cyclohexylammonium bromide (IV) and N,N-dimethyl-3-phenoxy-piperidinium bromide (V). The angles-of-twist about the phenyl oxygen bonds, determined using ultraviolet spectroscopy (Clark & Williams, 1967), are I—50°, II & III—48°, IV—75·5°, V—50·5°. The ring structures require a gauche conformation for the (O)C–C($\overset{+}{\text{N}}$) bond in compounds II, III & IV, and a fully staggered conformation in compound V.

On the pithed rat only compound V (300 μg i.v.) elicited appreciable ganglion stimulant activity producing a rise in blood pressure (inhibited by pentolinium, 0·5 mg i.v.) similar in magnitude to that produced by 20 μg of choline phenyl ether. On the guinea-pig isolated ileum, however, no compound elicited a nicotinic response. Examination of molecular models of compounds II, III and V shows that though free rotation about the phenyl-oxygen bond is restricted a conformation can be made in which the 'angle-of-twist' approaches 0° and the measured angles for these compounds are time averaged. If the assumption is made that a small degree of bond distortion occurs and allows compounds II, III and V to adopt a 0° 'angle-of-twist' about the phenyl-oxygen bond then our results suggest that a fully staggered conformation of the (O)C–C($\overset{+}{\text{N}}$) moiety is essential in order to stimulate the ganglionic receptors concerned in producing the pressor response in the rat.

All the test compounds blocked the ganglionic action potential in the rabbit isolated superior cervical ganglion preparation, the concentrations required to achieve a *ca* 50% blockade of the action potential being respectively II—1·1, III—1·3, V—1·6, IV—2·5, I—3·2 μg/ml. The concentration of choline phenyl ether required to achieve the same degree of blockade was, however, only 0·02 μg/ml. The possession of such low-level blocking activity by all the test compounds makes valid conclusions regarding the conformational requirements for blockade of the superior cervical ganglion difficult to draw.

REFERENCES

CLARK, E. R., DAWES, P. M. & WILLIAMS, S. G. (1968). Relationship between the molecular conformation of choline aryl ethers and nicotine-like stimulant activity. *Br. J. Pharmac. Chemother.*, **32**, 113–126.

CLARK, E. R. & WILLIAMS, S. G. (1967). The conformations of aromatic ethers as determined from their ultra-violet absorption spectra. *J. Chem. Soc.* (*B*), 859–866.