usually effects a sustained contraction of the guinea-pig ileum which may reach 70–100% of the maximal height produced by the agonist furtrethonium. The contraction of the guinea-pig ileum produced by RTMP is generally unaffected by hexamethonium (3×10^{-4}M), Neobenodine (3×10^{-6}M) or the serotonin antagonist xylamidine tosylate (3×10^{-6}M). However, it may be partly or completely eliminated by lachesine (10^{-4}M), procaine (3×10^{-3}M), morphine (1.25×10^{-3}M), magnesium chloride ($1–3 \times 10^{-2}$M), aging at room temperature or the absence of calcium ion in the Tyrode solution. Hemicholinium (1.75×10^{-3}M) generally has no effect on the initial RTMP contraction but accelerates the onset of tachyphylaxis following repeated doses. During RTMP tachyphylaxis, sensitivity of the guinea-pig ileum to the indirect cholinomimetic phenyl acetate (Takagi, Takayanagi, Ishida and Moritoki, 1965) ($1–3 \times 10^{-3}$M) is markedly reduced while that due to furtrethonium or pentyl trimethylammonium iodide (3×10^{-5}M) is relatively little decreased. Antagonism by RTMP to furtrethonium, methylfurtrethonium and pentyl trimethylammonium iodide has been demonstrated on rat intestine and guinea-pig ileum which were negligibly responsive to the spasmogenic action of the chelate, and similar pA_2 values have been obtained against each agonist in both preparations. Combined competitive and non-competitive antagonism is produced by still higher doses of RTMP.

It is tentatively concluded that: (1) RTMP releases ACh from the postganglionic cholinergic nerve terminals of the guinea-pig ileum and probably rat intestine; (2) RTMP inhibits acetylcholine esterase and is also a competitive and non-competitive antagonist of typical cholinomimetic drugs, the cholinergic receptors of both rat intestine and guinea-pig ileum responding to RTMP in a similar manner; (3) RTMP lacks a region of high charge density and other characteristics usually present in more potent cholinergic drugs and its multiple actions must all be mediated by the simple physical forces inherent in the cation.

REFERENCES

HENDERSON, P. TH., ARIËNS, E. J. & SIMONIS, A. M. (1968). Differentiation of various types of cholinergic and other spasmogenic actions in the isolated guinea-pig ileum. *Eur. J. Pharmac.*, in the Press.

SHULMAN, A. & DWYER, F. P. (1964). Metal chelates in biological systems. In *Chelating Agents and Metal Chelates*, ed. Dwyer, F. P. & Mellor, D. P., pp. 383–439. New York: Academic Press.

TAKAGI, K., TAKAYANAGI, I., ISHIDA, Y. & MORITOKI, H. (1965). Effects of phenyl acetate and its analogues on isolated guinea-pig small intestine. *Archs. int. Pharmacodyn. Thér.*, **158**, 354–359.

VAN ROSSUM, J. M. (1963). Cumulative dose-response curves. II. Techniques of making dose response curves in isolated organs and the evaluation of drug parameters. *Archs. int. Pharmacodyn. Thér.*, **143**, 299–330.

VAN ROSSUM, J. M. & VAN DEN BRINK, F. G. (1963). Cumulative dose-response curves. I. Introduction to the technique. *Archs. int. Pharmacodyn. Thér.*, **143**, 240–247.

Some derivatives of tropine and *pseudo*tropine

R. B. BARLOW* and M. G. MUSTAFA, *Department of Pharmacology, University of Edinburgh, Scotland*

The benzilic esters of tropine and *pseudo*tropine were described by Forster, Goodford & Ing (1957), who reported that benzilyltropine methiodide and ethiodide and benzilyl-*pseudo*tropine methiodide were all as active as atropine in antagonizing acetylcholine on the isolated guinea-pig ileum. In the test, however, the compounds

did not appear to have had time to come into equilibrium with the tissue. Because we thought it unlikely that they were all equiactive, we have measured their affinity constants for the muscarine-sensitive acetylcholine receptors in the tissue by methods in which time was allowed for equilibrium to be established between the antagonists and the receptors. The procedure used was a recently described modification (Edinburgh staff, 1968) of the method of Barlow, Scott & Stephenson (1963).

The results (Table 1) also include values for benzilyl and diphenylacetyl esters of choline and for derivatives of piperidin-4-ol described by Abramson in a communication to the Society at Bristol (1964). There are two isomeric forms of the ethiodides (Fig. 1); we believe that the ethyl group is equatorial (Fig. 1a) in our derivatives though it may be axial in the simple tropine and *pseudo*tropine ethiodides (Fódor, 1965).

TABLE 1. *Log. affinity constants for muscarine-sensitive acetylcholine receptors of the guinea-pig ileum*

	Methiodide	Ethiodide
Tropine	3·166	3·162
*Pseudo*tropine	3·142	3·142
Benzilyl tropine	10·373	9·085
Benzilyl *pseudo*tropine	9·761	8·119
Benzilylcholine	8·511	
Diphenylacetyltropine	8·669	7·864
Diphenylacetyl*pseudo*tropine	8·231	6·873
Diphenylacetylcholine	7·159	
3(Diphenylacetyl)-N-methylpiperidine	7·094	7·226
4(Diphenylacetyl)-N-methylpiperidine	0·064	9·080

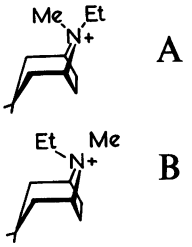

FIG. 1. Isomeric forms of tropane ethiodides.

Although diphenylacetyl esters of tropine and *pseudo*tropine are more potent than esters of choline, derivatives of piperidin-4-ol are more potent still, indicating that the differences in affinity between the tropine and *pseudo*tropine isomers arise from interference by the pyrrolidine ring with binding at the receptors.

REFERENCES

BARLOW, R. B., SCOTT, N. A. & STEPHENSON, R. P. (1963). An attempt to study the effects of chemical structure on the affinity and efficacy of compounds related to acetylcholine. *Br. J. Pharmac. Chemother.*, **12**, 509–522.

EDINBURGH STAFF (1968). *Pharmacological experiments on isolated preparations*, p. 26. Edinburgh: E. and S. Livingstone.

FÓDOR, G. (1965). In Fódor, G., Nador, K. & Torgov, I. V., *Recent Developments in the Chemistry of Natural Carbon Compounds*, vol. 1, p. 128. Budapest: Akademiai Kiado.

FOSTER, R., GOODFORD, P. J. & ING, H. R. (1957). Further new tropine derivatives. *J. chem. Soc.*, 3575–3578.