The comparative activity of arecoline and arecoline *N*-metho salt

SIR,—Arecoline is well known as one of the relatively few tertiary amines that have high activity as a muscarinic agent. Indeed this activity has been underestimated in the past because the pKa of arecoline is 7·61 (35°) so that it is incompletely ionised at blood pH and even more so in Ringer-Locke or Tyrode's. Recently, we have found that the activity of the arecolinium ion on the guinea-pig ileum was 1·4 times as great as carbachol and had a similar slope and maximum and it was also about equal to acetylcholine although differing in slope. We thought it of interest to see whether the quaternary arecolinium *N*-metho salt (the methiodide prepared by the method of Wilstätter, 1887) had an even greater activity. However, it was only one fortieth of the activity of the tertiary arecolinium ion itself. On the other hand, when tested on the frog rectus abdominis, the tertiary arecolinium ion had only 1·1% of the activity of carbachol whereas the quaternary *N*-metho salt was a little more active than carbachol (Table 1).

TABLE 1. RELATIVE ACTIVITY OF ARECOLINE AND ITS *N*-METHO SALT.

	Molar potency relative to carbachol		Relative potency
	Arecolinium	*N*-methylarecolinium	Arecolinium / *N*-Methylarecolinium
Guinea-pig ileum	1·42	0·034	42
Frog rectus abdominis ..	0·011	1·39	0·008

These results point to the conformation of the nitrogen in tetrahydropyridine being such that at the muscarinic receptor a better fit is obtained when the free groups are a methyl and a hydrogen than when both free groups are methyl. This suggests that when the nitrogen is constrained within the ring the additional methyl prevents optimal interaction possibly by increasing the separation of the positive nitrogen from an anionic group in the receptor and so reducing the coulombic attraction. This behaviour is in contradistinction to the effect of quaternisation in acetylcholine, muscarine, dioxolanes and other substances where the quaternary group is in an aliphatic chain capable of assuming several rotational conformations in solution and in which the addition of a methyl group increases muscarinic potency by a factor of 10^2—10^3.

On the other hand at the nicotinic receptor arecoline and its *N*-metho derivative behave in conformity with other tertiary-quaternary pairs and the increase in activity on quaternising is not dissimilar to the difference between 2-dimethylaminoethyl acetate and acetylcholine at this receptor. However, nicotine is actually slightly more active than *N*-methyl nicotinium (Hamilton, 1963). It seems as though the geometry of the nicotinic receptor is less stringent in the conformation required around the nitrogen than is the muscarine receptor. Study of the activity of acetylcholino-mimetic substances derived from heterocycles differing in ring size and conformation seems to offer a fruitful way of studying the detailed geometry of the cation combining site at these receptors.

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August 6, 1964

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