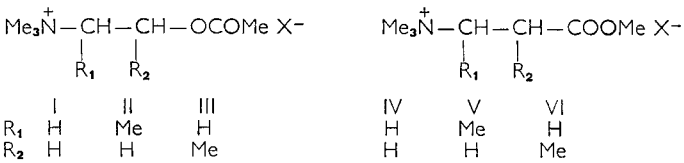
The muscarinic and nicotinic activities of some esters related to acetylcholine

Schueler & Keasling (1951) reported that the reversed carboxyl analogues of acetyl-α-methylcholine and acetyl-β-methylcholine, namely methyl 3-dimethylaminobutyrate methiodide (V) and methyl 3-dimethylamino-2-methylpropionate methiodide (VI), possessed less than one ten-thousandth of the muscarinic activity of their respective acetylcholine analogues (II and III). Methyl 3-dimethylaminopropionate methiodide (IV), which is the reversed carboxyl analogue of acetylcholine (I), is reported to possess at least one-tenth the activity of, and at most to be equipotent with, acetylcholine (Bass, Schueler & others, 1950; Barrass, Brimblecombe & others, 1968). In view of this high activity shown by the ester (IV) compared with compounds V and VI, we have synthesized and re-examined the muscarinic and nicotinic activities of all three esters (IV, V and VI).



	I	II	III	IV	V	VI
R_1	H	Me	H	H	Me	H
R_2	H	H	Me	H	H	Me

For the preparation of esters IV-VI, equimolar quantities of anhydrous dimethylamine were reacted with solutions of methyl acrylate, methyl crotonate or methyl methacrylate respectively, in anhydrous methanol. The cooled amine solution was slowly added with stirring to the cooled solution of the ester and the resulting mixture maintained at 0° for 2 h, then maintained at room temperature for 24 h. The resulting tertiary amines were purified by fractional distillation and characterized by analysis, and by their nmr and infrared spectra.

The methiodides (IV-VI) were obtained by dissolving each tertiary amine in acetone and adding an excess of a solution of methyl iodide in acetone. The purified products were characterized by their infrared, nmr and mass spectra.

The muscarinic activity of each compound was examined on the blood pressure of the anaesthetized rat and on the guinea-pig ileum. The molar potency of each compound, relative to acetylcholine, was determined in the absence and in the presence of a ganglion blocking agent to exclude possible interference from any nicotinic activity the compounds might have. The results are summarized in Table 1. All the compounds were less active than acetylcholine but compounds V and VI were much more active than reported previously (Schueler & Keasling, 1951). Compounds II (acetyl-α-methylcholine), IV and V showed a marked increase in potency in the presence of the ganglion blocking agents. In the rat, hyoscine methiodide (5 mg/kg) intravenously abolished the fall in blood pressure caused by all compounds. Similarly, the contractile effect of the compounds on the guinea-pig ileum was abolished by hyoscine methiodide (0·1 μg/ml). These results indicate that the compounds have a muscarinic action.

The nicotinic activity of the compounds was studied on the blood pressure of the rat pre-treated with hyoscine methiodide (5 mg/kg) intravenously and on the frog rectus muscle. The results are in Table 2. Compounds II, IV and V possessed significant nicotinic activity on both test preparations; compounds III and VI had little or no nicotinic activity as previously reported (Schueler & Keasling, 1951; Beckett, Harper & Clitherow, 1963). A comparison of the muscarinic and nicotinic activities of the

Table 1. *The muscarinic activities of some acetylcholine analogues and related esters.* Molar potencies (±s.e.) were determined relative to acetylcholine = 1·00.

Compound	Rat blood pressure n = 4	Rat blood pressure (Pre-treated with pentolinium tartrate (5 mg/kg)) n = 2	Guinea-pig ileum n = 4	Guinea-pig ileum (In presence of hexamethonium, 100 μg/ml) n = 2
II	0·02 (±0·01)	0·04	0·03 (±0·01)	0·05
III	0·40 (±0·11)	0·40	0·86 (±0·17)	0·88
IV	0·11 (±0·03)	0·50	0·30 (±0·15)	0·30
V	0·11 (±0·01)	0·03	0·05 (±0·03)	0·06
VI	0·02 (±0·01)	0·01	0·03 (±0·01)	0·02

Table 2. *The nicotinic activities of some acetylcholine analogues and related esters.* Molar potencies (±s.e.) were determined relative to acetylcholine = 1·00.

Compound	Frog rectus muscle n = 4	Rat blood pressure (Pre-treated with hyoscine methiodide (5 mg/kg)) n = 4
II	0·17 (±0·06)	0·80 (±0·10)
III	<0·001	<0·01
IV	0·97 (±0·31)	0·85 (±0·07)
V	0·12 (±0·03)	0·75 (±0·17)
VI	<0·001	<0·01

compounds suggested that II, IV and V have more specific nicotinic action than acetylcholine. However, the specificity was much less marked with compound IV. It was noteworthy that methyl 3-dimethylaminobutyrate methiodide (V) was slightly more potent than acetyl-α-methylcholine (II).

The activities shown by compounds V and VI in our experiments were much higher than those reported by Schueler & Keasling (1951). Perhaps these workers were using impure compounds; we were unable to obtain pure compounds by their method of preparation.

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