N-(Perhydroazepinoalkynyl)- and *N*-(perhydroazocinoalkynyl) succinimides as oxotremorine antagonists

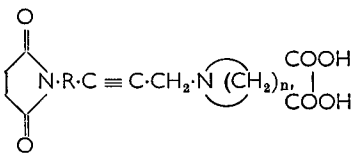
We have reported that some *N*-(4-t-amino-2-butynyl)-substituted succinimides had a blocking action on the motor effects of oxotremorine, but were less active on the peripheral cholinergic effects (Dahlbom, Karlén & others, 1966 a,b). We also found that if the 2-butyne chain was branched with one or two methyl groups or lengthened with a methylene group between the acetylenic bond and the imide nitrogen, the tremorolytic activity was enhanced, some compounds exceeding atropine in this respect (Karlén, Lindeke & others, 1970).

Lévy & Michel-Ber (1967) reported that *N*-(perhydroazepino-2-butynyl)succinimide was an oxotremorine antagonist, and we have investigated analogous modifications of the intermediate 2-butynyl chain of this compound and also some eight-membered cyclic amines. This report deals with the synthesis and pharmacological properties of a series of *N*-(perhydroazepinoalkynyl)- and *N*-(perhydroazocinoalkynyl)succinimides, some of which are much more active than atropine as oxotremorine antagonists.

The compounds were prepared via the Mannich reaction by refluxing a mixture of the appropriate *N*-alkynylsuccinimide (Karlén, Lindeke & others, 1970), formaldehyde, and the cyclic amine in dioxane in the presence of catalytic amounts of cuprous chloride, and they were isolated and purified as the oxalate salt. The compounds prepared and the results of the pharmacological tests for central and peripheral anticholinergic activity are presented in Table 1.

Antagonism of tremor induced by oxotremorine was estimated by determining the median effective dose of oxotremorine necessary to produce an intermittent spontaneous tremor (grade 2 tremor). The intensity of the tremor was graded visually

Table 1. *Physical and pharmacological data for* N-(*perhydroazepinoalkynyl*) *and* N-(*perhydroazocinoalkynyl*)*succinimides*



Compound	R	n	M.p. °C	Formula	*In vivo* dose (μmol/kg) in mice required to produce Oxotremorine blockade†	Mydriasis§
1*	CH_2	6	143–145	$C_{16}H_{22}N_2O_6$	3·9	
2	CHMe	6	113–115	$C_{17}H_{24}N_2O_6$	0·45	5·6
3	CHMe	7	141–143	$C_{18}H_{26}N_2O_6$	4·6	23
4	CMe_2	6	144–146	$C_{18}H_{26}N_2O_6$	1·2	7·7
5	CMe_2	7	122–124	$C_{19}H_{28}N_2O_6$	1·5	9
6	$(CH_2)_2$	6	84–86	$C_{17}H_{24}N_2O_6 \cdot H_2O$	15	>150
7	$(CH_2)_2$	7	140–142	$C_{18}H_{26}N_2O_6$	27	‡
8	$(CH_2)_3$	6	118–119	$C_{18}H_{26}N_2O_6$	22	>75
9	$(CH_2)_3$	7	113–115	$C_{19}H_{28}N_2O_6$	26	180
Atropine					2·8	0·29

* Reported by Levy & Michel-Ber (1967) and included for comparison.

† Dose of test compound required to double the dose of oxotremorine inducing a grade 2 tremor in 50% of the mice.

‡ This compound produced miosis over the entire dosage range tested.

§ Dose of test compound required to double the pupil size relative to the control.

according to a three point system earlier described (Cho & Jenden, 1964). The "up and down" method for small samples described by Dixon (1965) was used to estimate the median effective dose of oxotremorine. Each compound was screened to determine its effective dose range and then four linearly spaced doses including zero were chosen. Female mice, 22 to 26 g in groups of six were given oxotremorine intravenously with or without the test compound (given i.p. 10 min previously)and the median effective dose of oxotremorine determined using a logarithmic series of doses with a spacing of 0·1 units in the $\log_{10}$ dose scale. Tremors were graded 3 min after the oxotremorine injection. Animals with a grade 2 tremor or more were designated positive; others were negative. The median effective dose of oxotremorine was then plotted against the dose of the test compound, and the dose of antagonist which doubled the median effective dose of oxotremorine was estimated graphically.

Mydriatic activity was estimated on mice (groups of 6) by measuring the pupillary diameter before, and 10 min after, the intraperitoneal injection of the test compound. The measurements were made under constant light source using a binocular dissecting microscope with a calibrated eyepiece. The mydriatic dose was estimated graphically as that required to double the pupil size relative to the control.

All the compounds were active in blocking the motor effects of oxotremorine (Table 1), Nos 2, 4 and 5 were more active than atropine, the most active (No. 2) being about six times more potent. The dose producing oxotremorine blockade was always less than that producing mydriasis. This is in marked contrast to atropine, which is less effective in blocking oxotremorine than in producing mydriasis. Consequently the compounds reported here can be regarded as anti-acetylcholine agents with a greater selectivity for the central nervous system than atropine. This property has been shown to be partly due to the low base strength of these amines which favours their distribution to the brain (Karlén & Jenden, 1970).

Activity is enhanced if the parent 2-butyne chain is branched with one or two methyl groups between the acetylenic bond and the imide nitrogen, whereas lengthening of the chain diminishes the activity. The perhydroazepino compounds seem to be more active than the corresponding perhydroazocino compounds.

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