rats. In contrast, the injection of 25 mg/kg of mescaline into cats produced peak levels in the brain of 4 μg/g after 30–60 min and the brain-plasma ratio was approximately 4[8]. Injection of the same quantity of mescaline into dogs produced cortical levels of 13 μg/g after 4 h and the brain-plasma ratio was approximately 2[9]. These data could indicate a species difference in the accumulation of mescaline in the CNS.

The physiological disposition of 4-methoxyphenylethylamine (M-1) and 3,4-dimethoxyphenylethylamine (M-2) in the rat is known[10,11]. A comparison of these data with those obtained with 3,4,5-trimethoxyphenylethylamine (M-3) or mescaline in this paper shows the following differences: First, after the injection of comparable amounts, M-1, M-2, and M-3 can be detected in the brain for approximately 30, 45, and at least 210 min. Second, the injection of increasing doses of M-1 and M-2 produces an increase in brain levels, whereas M-3 shows saturation in the CNS. Third, peak levels after the injection of 40 mg/kg i.p. of M-1, M-2, and M-3 are approximately 17, 8, and 3 μg/g, respectively. Ratios of the concentrations in the brain and plasma are approximately 4, 2, and 0.6, respectively. The number of methoxy groups seems to decrease the penetration of these compounds into the CNS. Fourth, the presence of M-1 and M-2 in the CNS correlates fairly well with the time of abnormal behavior whereas no such correlation is apparent for M-3; rats appear normal after approximately 2 h[4] although brain levels of M-3 are still as high as at times of abnormal behavior. Finally, the smallest doses of M-1, M-2, and M-3 which will show abnormal behavior in rats are approximately 40, 25, and 12.5 mg/kg, respectively. At these doses brain levels of M-1, M-2, and M-3 are approximately 17, 3, and 0.5 μg/g, respectively. A comparison of the injected doses of M-1 and M-3 shows that M-3 is approximately 3 times more potent than M-1. However, a comparison of the brain levels of both compounds at these doses reveals that M-3 produces abnormal behavior at 1/34 the concentration at which M-1 is effective[12].

Table II. Concentrations of mescaline in rat brain, liver and plasma as a function of dose injected

	Dose (mg/kg) 20	40	80
	μg/g or ml		
Brain	0.9 ± 0.4	3.2 ± 0.7	2.7 ± 0.6
Liver	6.1 ± 4.2	22.1 ± 2.1	52.5 ± 13.8
Plasma	2.6 ± 1.0	4.9 ± 2.0	10.2 ± 1.9

Each value is the mean ± the standard deviation from at least 3 animals. Rats were killed 30 min after i.p. administration of mescaline × hemisulfate.

Zusammenfassung. Eine Schnellmethode zur Bestimmung von Meskalin in Geweben und biologischen Flüssigkeiten wird beschrieben. Nach der Injektion (40 mg/kg, i.p.) sinken die Konzentrationen von Meskalin in Leber und Plasma während der folgenden 2 h rasch ab, während die Verbindung im Gehirn (ca. 1,5 μg/g) bis zu 3,5 h unverändert verbleibt. Ein Vergleich zwischen Meskalin und zwei verwandten Verbindungen wurde angestellt.

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N-(t-Aminoalkynyl)-Substituted Pyrrolidones as Oxotremorine Antagonists

The high degree of muscarinic potency of oxotremorine, 1-(2-oxopyrrolidino)-4-pyrrolidino-2-butyne, peripherally[1] as well as centrally[2], has stimulated the interest in structural modifications of this agent. A number of compounds closely related to oxotremorine have been synthesized by BEBBINGTON et al.[3] and NEYMEYER et al.[4], but it was found that all structural changes resulted in compounds which were either less active than oxotremorine or inactive.

In 1966 we observed that replacement of the 2-oxopyrrolidino moiety of the oxotremorine molecule by a succinimide group led to compounds with antagonistic properties[5,6], and it was found later that slight modifications in the 2-butyne chain could lead to compounds which were about one hundred times more active as antagonists than the parent compound[7]. We found it of interest to investigate how similar modifications of the 2-butyne chain of oxotremorine would influence the pharmacological properties, and we now wish to report on the synthesis and pharmacological properties of a series of compounds closely related to oxotremorine in which the 2-butyne chain has been branched with 1 or 2 methyl groups or lengthened with 1 methylene group between the acetylenic bond and the lactam

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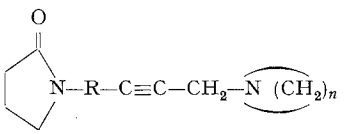
Physical and pharmacological data for N-(*t*-aminoalkynyl)-substituted pyrrolidones



Compound	R	*n*	Derivative	Melting point/°C	Formula	In vivo dose (μmoles/kg) in mice required to produce	
						Oxotremorine blockade[a]	Mydriasis[b]
I	$CH(CH_3)$	4	Sesquioxalate	117–119	$C_{16}H_{23}N_2O_7$	0.44	1.65
II	$CH(CH_3)$	5	Oxalate	144–145	$C_{16}H_{24}N_2O_5$	0.89	5
III	$CH(CH_3)$	6	Oxalate	116–117	$C_{17}H_{26}N_2O_5$	0.82	4.85
IV	$CH(CH_3)$	7	Oxalate	123–125	$C_{18}H_{28}N_2O_5$	3.45	19.5
V	$C(CH_3)_2$	4	Hydrochloride	121–123	$C_{14}H_{23}ClN_2O$	15.4	65
VI	$(CH_2)_2$	4	Sesquioxalate	119–121	$C_{16}H_{23}N_2O_7$	8.3	33
VII	$(CH_2)_2$	5	Perchlorate	114–116	$C_{14}H_{23}ClN_2O_5$	95	[c]
VIII	$(CH_2)_2$	6	Dihydrochloride	126–130 dec.	$C_{15}H_{26}Cl_2N_2O$	31.2	>75
Atropine						2.8	0.29

[a] Dose of test compound required to double the dose of oxotremorine inducing a grade 2 tremor in 50% of the mice. [b] Dose of test compound required to double the pupil size relative to the control. [c] This compound produced miosis.

nitrogen. Variations of the size of the cyclic amine were also made.

The new compounds were prepared through the Mannich reaction by refluxing the appropriate N-alkynylpyrrolidone, formaldehyde and the cyclic amine in dioxane in the presence of catalytic amounts of cuprous chloride. The N-alkynylpyrrolidone was obtained by ring closure of the corresponding 4-alkynylaminobutyric acid.

When the new compounds were tested pharmacologically, we found surprisingly that all of them were devoid of oxotremorine-like properties but were instead antagonists to oxotremorine, some of them being even more active than atropine. The compounds prepared and the results of the pharmacological tests are presented in the Table.

Antagonism to 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 according to a three-point system earlier described[8]. The 'up and down' method for small samples described by DIXON[9] was employed to estimate the median effective dose of oxotremorine. Each compound was screened initially to determine the dose range in which it was effective; 4 linearly spaced doses including zero were then chosen. Groups of 6 female mice weighing 22–26 g were administered oxotremorine with or without the test compound and the median effective dose of oxotremorine was determined. A logarithmic series of doses of oxotremorine with a spacing of 0.1 in the $\log_{10}$ dose scale was used. Tremors were graded 3 min after the administration of oxotremorine. The test compounds were administered i.p. 10 min before the i.v. administration of the oxotremorine. Animals with a grade 2 tremor or more were designated positive; others were designated 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 diameter relative to the control.

It is evident from the Table that all the compounds were effective in blocking the motor effects of oxotremorine, 3 of them (I–III) being more active than atropine. The most active compound (I), which differs from oxotremorine in structure only by a methyl group, was more than 6 times as active as atropine in this respect. The dose required to produce oxotremorine blockade was in every case less than that which produced 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 anticholinergic agents with a greater selectivity for the central nervous system than atropine.

Zusammenfassung. Eine Anzahl von Antagonisten zu Oxotremorin wurden durch kleine Modifikationen der Struktur des Oxotremorins erhalten. Die aktivste Verbindung, N-(1-Methyl-4-pyrrolidino-2-butinyl)pyrrolidon, ist mehr als sechsmal wirksamer als Atropin und hat eine grössere Spezifizität mit Bezug auf das Zentralnervensystem.

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