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PSYCHOTROPIC PROPERTIES OF N-(1-ADAMANTYL)-N'-SUBSTITUTED PIPERAZINES

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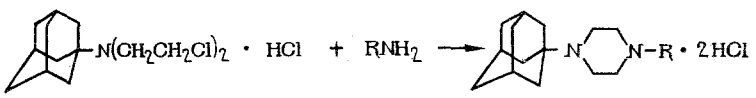
It is known that the dihydrochlorides of N-(1-adamantyl)-N'-substituted piperazines display experimental antiviral activity against a number of influenza viruses, vaccinia, poliomyelitis virus, and Sendai paramyxovirus [1]. On the other hand, it is also known that 1-aminoadamantane hydrochloride (midantan), while having fairly pronounced antiviral activity, also has an effect on the central nervous system and is currently used as an antiparkinsonism medicament [2].

We have studied the action of adamantylpiperazines on the central nervous system for the first time.

We prepared the N-(1-adamantyl)-N'-substituted piperazines by reaction of 1-[bis(2-chloroethyl)amino]adamantane hydrochloride with various primary amines [3]:



I-XVI

where R = H (I), CH_3 (II), C_2H_5 (III), C_3H_7 (IV), iso-C_3H_7 (V), C_4H_9 (VI), iso-C_4H_9 (VII), t-C_4H_9 (VIII), C_5H_{11} (IX), cyclopentyl (X), cyclohexyl (XI), cyclooctyl (XII), 1-adamantyl (XIII), C_6H_5 (XIV), $C_6H_5CH_2$ (XV), or CH_2CH_2OH (XVI).

EXPERIMENTAL

The experiments were performed on BALB/c mice of both sexes weighing 18-25 g and on nonlineal female rats weighing 180-250 g.

The test substances were administered intraperitoneally in increasing doses 15-30 min before carrying out the experiment. Control animals were given the corresponding volume of physiological saline solution.

The experimental data were processed statistically to calculate the mean effective (ED_{50}) and lethal (LD_{50}) doses and the arithmetic means and standard deviations of these means (M ± m). Differences were considered significant at the P = 0.05 level [4].

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TABLE 1. Pharmacological Activity of N-(1-Adamantyl)-N'-Substituted Piperazine Hydrochlorides

Compound	LD_{50}, mg/kg	LD_{50}, mg/kg			Activity alteration index				
		rotating rod	"tube" test	hypothermia (3° or more)	hexenal*	medinal	chloral hydrate*	nicotine*	arecoline*
I	185 (176–194)	80 (62–104)	80 (62–104)	57 (36–76)	2,45†	3,24†	1,79†	—	1,19
II	220 (170–286)	80 (62–104)	80 (62–104)	29 (21–39)	2,15†	4,61†	1,32	1,63	3,11
III	170 (148–196)	135 (116–157)	135 (116–157)	57 (36–76)	3,00†	3,19†	1,96†	—	0,87
IV	70 (54–91)	—	—	32 (22–46)	0,80	1,06	2,06†	—	1,47
V	84 (57–122)	85 (77–93)	85 (77–93)	42 (28–63)	0,82	1,05	1,05	—	1,64
VI	70 (62–78)	28 (22–35)	33 (25–43)	33 (22–47)	1,08	1,18	1,71†	—	1,56
VII	39 (31–48)	—	—	—	0,79	1,26	0,81	—	1,96
VIII	135 (111–165)	78 (66–92)	100	30 (15–45)	1,14	0,92	0,87	2,34	1,47
IX	72 (55–95)	33 (22–47)	25 (17–36)	29 (21–38)	0,85	0,82	0,69†	1,18	1,67
X	35 (26–46)	—	—	—	0,76	0,84	0,48†	1,22	2,22
XI	45 (36–56)	25 (17–36)	33 (22–47)	29 (21–38)	1,43	0,84	0,97	2,38	1,60
XII	70 (54–91)	—	—	—	1,22	0,56†	1,25	2,08	1,33
XIII	90 (74–109)	31 (22–43)	31 (22–43)	37 (29–49)	0,89	1,31	1,04	1,38	1,47
XIV	195 (157–231)	60 (44–82)	60 (44–82)	42 (28–63)	2,27†	1,41	1,77†	1,42	1,56
XV	105 (89–124)	56 (43–73)	56 (43–73)	32 (22–46)	1,49†	1,10	1,48†	—	1,78
XVI	325 (277–380)	100 (50–200)	100 (50–200)	45 (24–86)	4,25†	1,51†	1,43†	—	2,67

*Dose of compound 20 mg/kg.
†$\Delta < 0.05$.

The substances were studied using various tests.

1. Their effect on coordination and muscle tonus was tested by the rotating rod method [5] and the "tube" test [6].

2. Their effect on exploratory reaction (ER) and motor activity (MA) was evaluated in an actometer [7]. The ER was determined in the first 5 min after placing the animals in the actometer, and MA was registered over 1 h. Amphetamine (10 mg/kg) was administered 10 min before the experiment, and reserpine (3 mg/kg) was administered 18 h before the experiment.

The experimental data were evaluated relative to the control, which was taken as unity.

3. Their effect on the action of hypnotics was tested on hexenal (70 mg/kg, iv), medinal (150 mg/kg, ip), and chloral hydrate (300 mg/kg, ip). The duration of sleep (in min) was determined from the moment at which the "turnover" reflex was lost to the moment at which it was regained. In addition, these experiments were used to determine the indices by which the narcotic effect of the hypnotic agents was altered (the ratio of the mean sleep time in the test animals to the mean sleep time in control mice).

4. Their analgesic action was studied using the hot-plate test [8].

5. Their spasmolytic action was determined by the maximum electroshock test [9] and the corazol spasm test (0.5% solution, iv, at a rate of 0.01 ml/sec) [10].

6. Their effect on the central m- and n-choline receptors was determined from their ability to prevent tremors induced by nicotine (0.01% solution, iv, at a rate of 0.01 ml/sec) and arecoline (by determining the tremor-inducing ED_{50} of arecoline).

7. Their effect on the central adrenergic and dopaminergic processes was investigated

by the amphetamine stereotypy method [11].

8. Their hypothermic action was determined in experiments on mice by measuring the rectal temperature before and at 30-min intervals after administering the test substances, over a period of 4 h. The ED_{50} was determined as the dose giving a hypothermic effect of 3°C or more.

9. The acute toxicity of the compounds was determined in experiments on white mice.

The main results of the investigations are given in Table 1.

RESULTS AND DISCUSSION

The N-(1-adamantyl)-N'-substituted piperazines have a considerable effect on the central nervous system. Thus, almost all of the compounds had a hypothermic effect, altered the hypnotic effects of hexenal, medinal, and chloral hydrate, displayed center m- and n-cholinolytic properties, and influenced the effects of amphetamine and reserpine. Some of the compounds (III, XV, and XVI) displayed analgesic activity [ED_{50} 80 (53-90), 25 (17-36) and 200 (127-265) mg/kg, respectively]. Spasmolytic activity was not detected in the maximum electroshock test, and corazol antagonism was insignificant.

The behavior of the experimental animals did not change significantly when they received the test compounds in doses up to 10-20 mg/kg. At higher doses we observed increased motor activity and loss of coordination (see Table 1). At doses close to the lethal dose, the animals displayed Straub's symptom and suffered tremors and clonic spasms alternating with periods of sluggishness and immobility. Death occurred within 0.5 day.

The test substances can be divided into two groups with respect to their mean lethal doses: less toxic compounds (I-III, VIII, XIV-XVI) having an LD_{50} of 105-325 mg/kg; and more toxic compounds (IV-VII and IX-XIII) having an LD_{50} of 35-70 mg/kg.

The compounds of the first group (I-III, XIV-XVI) prolonged the hypnotic effects of hexenal, medinal, and chloral hydrate, while the compounds of the second group (IV-VII, IX-XIII) had no effect or shortened drug-induced sleep.

Except for the N'-phenyl and N'-benzyl derivatives (XIV and XV), the N-(1-adamantyl)-N'-substituted piperazine dihydrochlorides increase the psychostimulant action of amphetamine on the exploratory reaction in mice by a factor of 3 to 10. At doses of 2.5 to 25 mg/kg they increase the duration of amphetamine-induced stereotypy in white rats by 5-20%.

At a dose of 5-20 mg/kg, all of the substances gave a 30-50% decrease in exploratory reaction and locomotor activity in reserpine-treated mice. They have no significant effect on the hypothermic action of reserpine.

The adamantylpiperazines displayed some central m-cholinolytic activity, and compounds II and XIII-XIV also displayed n-cholinolytic activity (see Table 1).

The investigations show that the adamantylpiperazine derivatives have a broad spectrum of central activity. Some of the central effects are common to all the compounds investigated, while others are characteristic of only some of the substances.

Of the common central properties, we should note the following: ability to interfere with coordination and muscle tonus, hypothermic activity, central cholinolytic effects, potentiation of the depressant effect of reserpine on exploratory reaction and locomotor activity, and also potentiation of amphetamine-induced stereotypy and of the action of amphetamine on exploratory reaction (except for compounds XIV and XV).

It is interesting to note that the compounds with the lowest toxicity (I-III, VIII, and XIV-XVI) induce the above reactions, as a rule, at considerably lower doses than the more toxic compounds (IV-VII and IX-XIII).

Another common feature of all the adamantylpiperazines is that they do not potentiate the hypothermic effect of reserpine, do not display spasmolytic properties in the maximum electroshock test, and are weak corazol antagonists.

The reactions characteristic of only some of the adamantylpiperazines include analgesic activity and the ability to prolong the action of hypnotics (mainly hexenal and medinal).

The former effect is displayed by compounds III, XV, and XVI, and the latter by compounds I-III and XIV-XVI.

Thus, on the basis of an analysis of the spectrum of central effects displayed by the adamantylpiperazines as a function of their structure, we can note that N-(1-adamantyl)-piperazine (I) and its N'-methyl (II), ethyl (III), phenyl (XIV), benzyl (XV) and hydroxyethyl (XVI) derivatives are superior in both the strength and the spectrum of their action compared with compounds having a longer hydrocarbon or alicyclic grouping (IV-VII and IX-XIII).

The active compounds that we have found are difficult to assign to any particular class of drugs since they possess both stimulant and pronounced depressant properties (this applies especially to compounds I-III and XVI). By analogy with known drugs, however, these compounds may be expected to have antiparkinsonism and antidepressant activity.

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2,5-TETRAHYDROFURANDYL-BIS(4'-HYDROXYIMINOMETHYLPYRIDINE) DICHLORIDE AND ITS PHARMACOLOGICAL ACTIVITY

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The quarternary salts of 4-hydroxyiminomethylpyridine have been studied because they are known to reactivate cholinesterase which has been inactivated by organo-phosphorous compounds. One of the most effective cholinesterase reactivators so far described is toxogonin the dichloride of bis-4'-hydroxyiminomethylpyridine-1 methyl ether (I). It has been suggested [1] that toxogonin is effective because in the monobetaine form of this compound the –C–O–C– angle of the dimethylether link has minimum strain and the molecule assumes a sandwich structure facilitating access to the phosphorylated cholinesterase.

To investigate the effect of steric factors on the reactivating and general pharmacological properties of these compounds, diquarternary hydroxyiminomethylpyridine salts were prepared in which the ether oxygen is in a tetrahydrofuran ring system and not in the aliphatic

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