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ANTICATALEPTIC ACTIVITY OF 2-AMINOADAMANTANE DERIVATIVES

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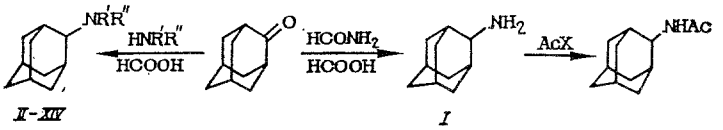
UDC 615.214.3:547.592.1

We have continued our work [1] relating the anticataleptic activity of various types of adamantane derivatives by examining a series of N-alkyl and N-acyl derivatives of 2-aminoadamantane (II-XIV), which we synthesized by the Leuckart reaction starting from 2-adamantanone



II-XIV I

We have described the preparation of 2-aminoadamantane (I) and its N-alkyl and N-acyl derivatives (Table 1) earlier [2]. We prepared 2-(N-benzoylamino)adamantane (XII) and 2-(N-methyl-N-benzoylamino)adamantane (XIV) by refluxing 2-aminoadamantane hydrochloride and 2-(N-methylamine)adamantane hydrochloride (II) respectively with benzoyl chloride in an inert solvent and synthesized 2-(N-p-toluenesulfonylamino)adamantane (XIII) under equivalent conditions from I and p-toluenesulfonyl chloride.

We evaluated the ability of the compounds to prevent the development of catalepsy induced by triphthazine (1.5 mg/kg intraperitoneally) in tests on white mice (weight 18-22 g) and rats (weight 150-220 g). The test compounds were administered as the hydrochlorides intraperitoneally 30 min before administration of the neuroleptic; catalepsy was monitored over a period of 5 h. We have described the methods of evaluating catalepsy elsewhere [1]. We assayed the central n-cholinolytic activity of the compounds by nicotine antagonism with an estimate of the ability of the compounds to prevent convulsions (tonic extensor component) induced in mice by rapid intravenous administration of nicotine (1.65 mg/kg). We also determined the acute 24-h toxicity. Statistical evaluation of the results was carried out with calculation of ED_{50}, the dose that prevents convulsions in 50% of the animals [3, 4], and $ED_{1/2}$, the dose that halves the intensity of catalepsy (by least squares) with $P = 0.05$.

The work revealed [5] that all derivatives of I have high anticataleptic activity in tests on the listed models (Table 1). The derivatives of I are superior to 1-aminoadamantane in terms of ability to prevent the development of catalepsy induced by triphthazine in mice and particularly in rats. An exception was I itself and 2-dimethylaminoadamantane (VI), which in tests on mice show no statistically significant difference in activity from 1-aminoadamantane. We also found that in terms of triphthazine antagonism, the N-acyl derivatives of I have higher anticataleptic activity than the corresponding N-alkyl derivatives (Table 1).

In addition to the ability to eliminate triphthazine catalepsy, the derivatives of I show distinct antagonism toward the cataleptic effect of tetrabenazine, a synthetic analog of reserpine, the mechanism of whose action involves its ability to cause rapid release of brain monoamines. In terms of this model I is almost twice as active as 1-aminoadamantane.

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Scientific-Research Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 14, No. 5, pp. 45-48, May, 1980. Original article submitted October 31, 1979.

0091-150X/80/1405-0313$07.50

TABLE 1. Comparative Activity of 1-Aminoadamantane and Derivatives of I in Preventing the Development of Triphthazine-Induced Catalepsy

Compound	R′	R″	ED_{50}, mg/kg intraperitoneally (tests in mice)	Activity relative to 1-aminoadamantane	ED_{50}, mg/kg intraperitoneally (tests in rats)	Activity relative to 1-aminoadamantane	LD_{50}, mg/kg intraperitoneally (tests in mice)
I	H	H	57,7 (30,8—85,3)	0,57	7,5 (2,3—24,0)	4,25	250,0 (224,1—278,7)
II	H	CH_3	12,5 (5,7—27,5)	4,0	4,5 (3,3—6,0)	7,1	140,0 (133,3—145,6)
III	H	C_4H_9	23,0 (12,4—42,5)	2,2	1,0 (0,4—2,5)	32,0	About 100
IV	H	$CH_2C_6H_5$	35,0 (20,5—59,9)	1,4	8,6 (4,4—16,6)	5,7	145,0 (133,3—158,0)
V	H	CH_2CH_2OH	9,9 (5,2—18,8)	5,0	9,5 (5,9—14,3)	3,3	235,0 (216—254,9)
VI	CH_3	CH_3	74,0 (59,2—92,1)	0,7	7,4 (3,5—15,9)	4,3	120 (112,9—127,4)
VII	$-(CH_2)_5-$		32,0 (23,5—43,5)	1,5	6,8 (5,1—9,0)	4,7	140 (127,8—153,3)
VIII	$-CH_2)_2O(CH_2)_2-$		14,5 (9,6—21,7)	3,4	23,5 (15,2—36,4)	1,3	470 (455—485)
IX	H	CHO	11,0 (4,8—17,1)	4,5	1,8 (0,9—3,6)	17,0	130 (113,1—143,0)
X	H	$COCH_3$	2,7 (1,4—5,2)	18,5	3,1 (1,0—9,6)	10,0	520 (495,2—546)
XI	H	$COOC_2H_5$	14,5 (7,2—29,0)	3,5	1,0 (0,6—2,8)	32,0	1190 (1081,1—1309,1)
XII	H	COC_6H_5	9,0 (4,8—17,1)	5,5	2,0 (0,9—4,2)	16,0	4000 (3644—4280)
XIII	H	$SO_2C_6H_4CH_3$	8,0 (4,2—15,2)	6,2	5,4 (3,8—7,6)	5,9	About 1200
XIV	CH_3	COC_6H_5	7,0 (5,0—9,8)	7,5	6,4 (4,4—9,8)	4,5	About 1200
1-aminoadamantane			50,0 (28,0—120,0)	1	32,0 (21,3—48,0)	1	270,0 (240—294,0)

TABLE 2. Comparative Activity of Adamantane Derivatives

Compound	Prevention of tetrabenazine-induced catalepsy, $ED_{1/2}$, mg/kg	Nicotine antagonism from the prevention of tonic extension, ED_{50}, mg/kg
1-Amino-adamantane	23,9 (20,4—27,9)	20,0 (15,0—26,0)
I	13,5 (11,4—15,9)	14,5 (7,6—27,5)
IX	48,0 (40,0—57,6)	42,5 (34,5—52,3)
X	57,0 (51,3—63,2)	—
XII	21,1 (20,2—22,1)	80,0 (53,0—120,0)
Pediphen	—	4,3 (2,6—7,0)

The introduction of various substituents into the amino group of I reduces the activity (in terms of tetrabenazine antagonism) relative to the unsubstituted amine (Table 2).

Examination of the central n-cholinolytic activity of several derivatives of I in comparison with the n-cholinolytic pediphen revealed that they have slight antagonism toward nicotine convulsions (Table 2).

The toxicity of the test compounds is low. Among the derivatives of I the N-acylamino-adamantanes are least toxic (compounds XI-XIV; Table 1).

The compounds used for the treatment of parkinsonism affect two types of mediator system — cholinolytics (atropine-like compounds, phenothiazine derivatives) and compounds that enhance the functions of the dopamine systems (L-dopa, amantadine) [6-10]. The results of our present study suggest that the mechanism of the anticataleptic effect of the derivatives of I, like that of amantadine, involves their effect on the catecholamine function in the brain and not their central cholinolytic effect.

EXPERIMENTAL CHEMISTRY

2-(N-Benzoylamino)adamantane (XII). A mixture of I hydrochloride (4.7 g) and toluene (16 ml) was refluxed for 30 min under a Dean—Stark trap. Benzoyl chloride (4 g) was added dropwise to the refluxing suspension with vigorous stirring and the mixture was then refluxed until the precipitate had completely dissolved and the evolution of hydrogen chloride ceased. The reaction mixture was cooled to 0°C and filtered to give amide XII (5.3 g). The yield was 94%, mp 163-165°C (from ethanol). Found, %: C 79.61; H 8.37. $C_{17}H_{21}NO$. Calculated, %: C 79.85; H 8.29.

2-(N-p-Toluenesulfonylamino)adamantane (XIII). To a suspension of I hydrochloride (4.7 g) in dry xylene (50 ml) was added p-toluenesulfonyl chloride (10 g). The mixture was refluxed until the evolution of hydrogen chloride ceased and then cooled. The precipitate was filtered off to give amide XIII (8.5 g). The yield was 90%, mp 145-146.5°C (from aqueous methanol). Literature [11]: mp 143-144°C.

2-(N-Methyl-N-benzoylamino)adamantane (XIV). Hydrochloride of II (1.25 g) was refluxed with toluene (10 ml) in a setup under a Dean—Stark trap for 30 min. Benzoyl chloride (1.6 g) was then added and the mixture was refluxed for 5 h (until the evolution of hydrogen chloride ceased). Acetone (10 ml) was added and the mixture was cooled to —30°C and filtered to give amide XIV (1 g). The yield was 59%, mp 110-111°C (from acetone). Found, %: C 80.60; H 8.78. $C_{18}H_{23}NO$. Calculated, %: C 80.26; H 8.60.

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INVESTIGATION OF THE POSSIBILITY OF SEPARATING PLATYPHYLLINE AND SENECIPHYLLINE BY A DISSOCIATIVE EXTRACTION METHOD

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UDC 615.217.34:547.94]:582.998.2].074

The alkaloid platyphylline, which is a valuable and difficultly available drug, is obtained from the above-ground portion of flat-leaved groundsel in which platyphylline (I) is accompanied by the alkaloid seneciphylline (II), which has limited application in medicine at the present time. The quantitative ratio of the contents of (I) and (II) in raw material is variable and oscillates within wide limits depending on many natural factors.

Since (I) is used in medicine as a single substance, all the known methods of obtaining this drug include a stage for separating alkaloids. Appreciable difficulties arose when resolving this problem which were due to the similarity of structures (I) and (II).

All the methods of separating (I) and (II) developed up to the present time are based on the difference in solubility of these alkaloids of, for example, their bases in cyclohexane [1] or pH 7.0 ammonia buffer [2], and tartaric acid salts in alcohol [3].

The stage of separating the alkaloids is always preceded by the extraction of total alkaloids from solid vegetable raw material with any solvent, concentration of the solution, and the obtaining of crude total alkaloids in the solid state. The conduct of each of the numerous stages is linked with appreciable losses of the desired expensive product which occur as a result of the presence, in the crude total, of alkaloids up to 30% (by weight) of extractable substances and the significant content of (II) in it.

The problem of the development of an effective technological method for obtaining this preparation is urgent because of the restriction of the source of raw material to wild flat-leaved groundsel due to unsuccessful attempts to cultivate this plant, and of the medicinal value of platyphylline. A new effective method has been developed by us [4] for the solid phase extraction of total alkaloids from flat-leaved groundsel with a hot 5% alum solution in the presence of Devarda's alloy with the extraction of more than 90% (I) in the aqueous alum extract.

Subsequently, in the process of improving technological methods in the stages of solid phase extraction and alkaloid reduction, it turned out to be expedient to separate the process of reducing N-oxides from the process of solid phase extraction of the alkaloids. In this case the extraction of alkaloids in the reduced and oxidized forms was readily effected with hot water without adding any reagents, and the reduction of alkaloids proceeds effectively under conditions of intense stirring in the hot aqueous extracts at low alum concentrations (0.25-0.5%) in the presence not only of Devarda's alloy but also of the more inexpensive zinc. In this way the metal is not thrown away with the residues but is used many times over in the reduction stage, since the amount of zinc consumed in one working cycle of the reduction reaction does not exceed 10% of the initial quantity of metal. In this way the overall consumption of metal was significantly reduced (25-50 times). All this sharply reduces the contamination of effluent during production.

The present work is devoted to an investigation of the possibility of separating (I) and (II) by a dissociative extraction method based on the difference in basicity of these substances. Both (I) and (II) are weak bases which interact with water according to:

All-Union Scientific-Research Institute for Medicinal Plants, Moscow region. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 14, No. 5, pp. 65-69, May, 1980. Original article submitted February 1, 1979.

 0091-150X/80/1405-0316$07.50