ADAMANTYLPYRIDINES AND THEIR BIOLOGICAL ACTIVITIES

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A wide range of pharmacological activities, including anti-anginal and hypertensive [13, 14], vasodilator [15, 16], antioxidant, and psychotropic activities [3-6, 12] are found in compounds belonging to the class of substituted pyridines.

Adamantane derivatives such as the psychotropic and antidepressant compounds gludantan [6] and adapramine [2], and immunotropic compounds of the adamantyl-phenothiazine and -aniline series also possess a variety of pharmacological properties. Adamantane derivatives are also known to exhibit positive inotropic action resulting from blockage of the calcium channels [17].

The wide spectrum of biological activities exhibited by these classes of compounds provides a perspective for investigations in the synthesis and study of the pharmacological activities in the adamantylpyridine series.

With the goal of studying the effects of introducing the pyridine group on the pharmacological spectrum of adamantane derivatives, the directed syntheses of several adamantylpyridines were undertaken. Using the Leuckart reaction, adamantan-2-one and aminopyridines were condensed to yield 3-(adamant-2-ylamino)pyridine (I) and 4-(adamant-2-ylamino)pyridine (II) [8].

For comparative pharmacological studies on the effects of esterification of primary, secondary and tertiary alcohol derivatives of adamantane, adamantyl esters of nicotinic and 5-bromonicotinic acids (III-VI) were synthesized. N-acylation of 1- and 2-aminoadamantanes with the acid chloride of 5-bromonicotinic acid yielded the amides VII-IX. Condensation of the ethyl ester of 5-aminonicotinic acid with the acid chloride of 1-adamantancarboxylic acid yielded amide X.

In carrying out the acylation of 4-amino-3-hydroxy-2-ethyl-6-methylpyridine with 1-adamantane-carboxychloride in toluene in the presence of triethylamine at 35-40°C, a mixture of N- and O-acylated compounds was obtained (XI-XII). Under more stringent conditions such as reflux the reaction yielded a single product 4-adamantoylamino-3-adamantoyloxy-6-methyl-2-ethylpyridine (XII). Under mild conditions such as conducting the reaction at 0°C with an equimolar quantity of the acid chloride only the N-acyl compound was obtained (XI).

In the alkylation of 1-(N-methylamino)adamantane with 4-bromomethyl-3-hydroxy-2-ethyl-6-methylpyridine (XIII) under reflux in toluene in the presence of an HBr acceptor the compound XIV was obtained. The starting material XIII was obtained from the action of hydrobromic acid on 4-acetoxylmethyl-2-ethyl-6-methyl-3-acetoxypyridine.

The psychotropic properties of the substituted adamantylpyridines were studied. We examined the effects in mice of the compounds on spontaneous activity, prevention of development of triftazine catalepsy, and on physical working efficiency (swimming with weights of up to 10% of body weight). The acute toxicities of the compounds were determined. A significant positive effect on spontaneous motor activity was shown by compounds I, III, and V.

Statistically significant increases in the duration of swimming by weighted mice was shown by compounds V, VII, and VIII. It is interesting to note that an increase in the working efficiency was brought about, as a rule, by compounds containing a bromine atom in the pyridine ring.

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TABLE 1. Pharmacological Activity of the Studied Compounds

Compound	Dose mg/kg	Motor activity: point of recording of indication (time) of maximal action (h)	Motor activity: number of movements of the animals in the chamber at this point in time (% of control)	Physical working efficiency of the animals: number of animals in the control	Physical working efficiency of the animals: average duration of swimming in the control group (M ± m)**	Physical working efficiency of the animals: number of animals in the expt.	Physical working efficiency of the animals: average duration of swimming in the exptl. group (M ± m)	Physical working efficiency of the animals: % of control	Development of catalepsy in the animals: number of animals in the control	Development of catalepsy in the animals: number of animals in the expt.	Development of catalepsy in the animals: % of control	LD_{50} mg/kg
I	5	5	434	20	202±15	20	230±16	114				2820 (2300—3400)
	10	5	202	20	202±15	20	220±17	109	5	5	100	
	50	5	365	20	202±15	20	210±13	104				
IV*	5	4	111	29	272±36	30	286±31	125				3000
	10	4	316	29	272±36	30	305±39	112	5	5	100	
	50	4	283	29	272±36	30	270±37	99				
V	5	5	252	20	298±37	20	357—60	120				282
	10	5	165	20	298±37	19	391±55	131	5	5	100	182—296
	50	5	380	20	298±37	20	420±34***	141				
VII	5	5	141	18	219±30	20	346±86	158				
	10	5	230	18	219±30	20	231±40	106				
	50	5	126	28	219±30	29	430±56***	196	15	15	94	>3000
VIII	5	4	111									
		5	223	18	219±30	20	203—17	93				>3000
	10	4	79									
		5	117	18	219±30	19	249±58	114	15	15	81	
	50	4	27									
		5	268	28	288±42	20	475±117***	165				
IX	5	5	142	20	254±42	20	274±34	108				>3000
	10	5	217	20	254±42	20	196—21	77	10	10	91	
	50	5	167	20	254±42	20	318—116	125				
X	5	5	190	20	298±37	20	290±35	97				435
	10	5	119	20	298±37	20	342±70	115	10	10	79	162—826
	50	5	280	20	298±37	20	309±28	104				
XII	1	5	132	1	—	—	—	125				
	10	5	261	10	—	—	—	74	10	10	40	>3000

*Number of animals in the control = 2.

**Average duration of swimming in the control group (general population, number of animals 146) was 172 ± 18 sec.

***The difference of the indication in the control and experimental groups was statistically significant.

The compounds under study, with the exclusion of I, IV, and V, possessed central dopaminoimetic activity, as shown by their ability to prevent the development of triftazine catalepsy. An increase in the anticataleptic activity apparently could be brought about by substitution of a bromine atom for the ethoxycarbonyl group on the pyridine ring (compound X). Among the compounds synthesized, compound XII (amido-ester) exhibited the greatest psychostimulatory effect. In the strength of its anti-cataleptic activity it exceeded mindantan and fenamine. The compounds with the exceptions of V and X possessed for the most part low toxicity (see Table 1).

The results obtained confirm the value of searching for new psychotropic drugs among the adamantylpyridines.

EXPERIMENTAL (CHEMISTRY)

IR spectra were obtained on a Perkin-Elmer Model 580 spectrometer in KBr pellets. Thin layer chromatography was carried out using Silufol UV-254 plates in a hexane/ethylacetate/ethanol/ammonia 5:3:1:1 solvent system (visualization with iodine vapors and with UV light). The values obtained from elemental analyses corresponded with the theoretical calculated values.

3-(Adamant-2-ylamino)pyridine (I). A mixture of 3.68 g (0.08 mole) 98% HCOOH and 7.68 g (0.072 mole) 3-aminopyridine were heated to 100°C, then 6 g (0.04 mole) 2-adamantone was added in portions and the mixture held at a bath temperature of 150-160°C for 11 h, cooled, 15 ml 18% HCl added, and the mixture refluxed for 2.5 h. After addition of 30 ml water, the pH was adjusted to 8-9 with $NaHCO_3$, and the mixture extracted with ether (3×40 ml). The organic extract was dried with 2 g $MgSO_4$ and 0.5 g activated carbon, filtered after 6 h and the solvent removed

to yield 10.5 g (81.3%) I. mp 104-150°C (aqueous ethanol). R_f 0.71, $C_{15}H_{20}N_2$. Hydrochloride I; mp 245-246°C. $C_{15}H_{21}ClN_2$.

4-(Adamant-2-ylamino)pyridine (II). Obtained as in [9].

Adamant-2-yl Ester of 5-Bromonicotinic Acid (III). A mixture of 0.6 g (0.004 mole) adamantan-2-ol and 1 g (0.0045 mole) of 5-bromonicotinoyl chloride in dry toluene (10 ml) was refluxed for 5 h, then the toluene was evaporated to yield 1.2 g (0.0036 mole) (90%) III. mp 110-111.5°C (from aqueous ethanol). R_f 0.78, $C_{16}H_{18}BrNO_2$.

Adamant-1-yl Ester of 5-Bromonicotinic Acid (IV). A mixture of 1.1 g (0.01 mole) 5-bromonicotinoyl chloride and 1.5 g (0.01 mole) adamantan-1-ol in 15 ml toluene was refluxed for 10 h, cooled, and the precipitate filtered to yield 0.8 g (47.9%) IV. mp 82-83°C (from aqueous ethanol). R_f 0.72. $C_{16}H_{18}BrNO_2$.

Hydrochloride of β-(N-methyl-N-(adamant-1-yl)amino)ethyl ester of 5-bromonicotinic acid (V). A mixture of 1 g (0.0045 mole) 5-bromonicotinoyl chloride and 1.1 gm (0.0045 mole) of the hydrochloride of 1-(N-methyl-N-(β-oxyethyl)amino)adamantane [7] in 10 ml toluene was refluxed for 6 h, cooled and the resulting precipitate filtered and washed with heptane (5x10 ml) to yield (after drying) 2 g (93.5%) V. mp 219-220°C (from ethanol). R_f 0.66. $C_{19}H_{26}BrClN_2O_2$.

5-Nicotinoyloxyadamantan-2-one (VI). A mixture of 3.3 g (0.002 mole) 5-hydroxyadamantan-2-one and 2.83 g (0.002 mole) nicotinoyl chloride in 15 ml toluene was refluxed for 15 h, the solvent removed, the residue dissolved in $CHCl_3$, washed with water (2x30 ml), the organic phase dried with $MgSO_4$ and activated charcoal, filtered, the solvent removed, and the residue crystallized from benzene/petr. ether 1:5 to yield 2.4 g (45%) VI. mp 90-91°C. R_f 0.33. $C_{16}H_{17}NO_3$. In the IR spectrum broad absorption bands for ester and ketone carbonyls were observed at 1720 cm^{-1}, as were the characteristic pyridine bands at 1594, 1480, and 1430 cm^{-1}.

1-(5-Bromonicotinoylamino)adamantane (VII). A mixture of 1.8 g (0.0082 mole) 5-bromonicotinoyl chloride and 1.5 g (0.008 mole) 1-aminoadamantane hydrochloride were refluxed for 10 h in 15 ml dry toluene, cooled, 50 ml dry ether added, filtered, the filtrate washed with $NaHCO_3$ solution (230 ml), then water (2x20 ml), yielding after drying and removal of the solvent 1.4 g (66.03%) VII. mp 148-149°C (from aqueous ethanol). R_f 0.77. $C_{16}H_{18}BrN_2O$.

2-(5-Bromonicotinoylamino)adamantane (VIII). A mixture of 1.8 g (0.0082 mole) 5-bromonicotinoyl chloride and 1.5 g (0.008 mole) of 2-aminoadamantane hydrochloride in 15 ml dry toluene were refluxed for 15 h, 100 ml dry ether added, the solution washed with a solution of $NaHCO_3$ (2x50 ml), then water (2x100 ml), yielding after drying and removal of the solvent 1.5 g (46.9%) VIII. mp 182-183°C (from aqueous ethanol). R_f 0.75. $C_{16}H_{19}BrN_2O$.

1-N-(5-bromonicotinoylmethylamino)adamantane (IX). A mixture of 1.45 g (0.00717 mole) 1-methylaminoadamantane, 1.9 g (0.0086 mole) 5-bromonicotinoyl chloride and 20 ml toluene were refluxed for 30 h. After removal of the solvent the residue was stirred in 30 ml of 5% aqueous ammonia, extracted with ether, the ethereal extract washed with 50 ml of 5% HCl, dried with Na_2SO_4, and the solvent removed to yield 1.1 g (43.8%) IX. mp 140-141°C (from aqueous ethanol). R_f 0.5. $C_{17}H_{21}BrN_2O$.

Ethyl 5-(adamant-1-oylamino)nicotinate (X). 2.8 g (0.017 mole) of 3-amino-5-carboxyethylpyridine was dissolved in 50 ml dry benzene, 2.5 ml (1.72 g, 0.01 mole) triethylamine added, and a solution of 4 g (0.02 mole) 1-adamantanecarboxychloride in 20 ml dry benzene was added dropwise with stirring. The mixture was stirred at 20°C for 3 h, and the resulting precipitate of triethylamine hydrochloride was filtered out and washed with benzene (2x10 ml). The organic phases were combined and dried to yield after removal of the solvent 4 g (72.3%) X. mp 145-147°C (from aqueous ethanol). R_f 0.7 $C_{19}H_{24}N_2O_3$. Hydrochloride, mp 230-231°C (from ethanol), $C_{19}H_{25}ClN_2O_3$.

4-Adamantoylamino-3-adamantoyloxy-6-methyl-2-ethylpyridine hydrochloride (XII). A suspension of 1.52 g (0.01 mole) 4-amino-3-hydroxy-2-ethyl-6-methylpyridine in 50 ml dry toluene and 4 ml Et_3N was stirred at 5-10°C as a solution of 4.2 g (0.021 mole) 1-adamantanecarboxychloride in 20 ml dry toluene was added dropwise. The mixture was stirred a this temperature for 0.5 h, then heated to reflux for 3 h (the reaction was followed by TLC). At the conclusion of the reaction the Et_3N.HCl was removed by filtration and washed with dry toluene. The combined organic phases were evaporated and the residue stirred with water, then filtered. White powder, mp 180-183°C. The yield of XII was 4.45 g (93%). R_f 0.72. IR spectrum, cm^{-1}; 3475 (NH), 1755, 1695 (C=O).

The hydrochloride was obtained by adding ethanolic HCl to an alcohol solution of the crude material until the pH reached 2-3. The hydrochloride precipitate was filtered and washed with acetone. Snow-white crystals, mp 218-220°C (from absolute ethanol). $C_{30}H_{40}N_2O_3$.HCl.

4-Adamantoylamino-3-hydroxy-6-methyl-2-ethylpyridine (XI). A suspension of 0.34 g (0.002 mole) 4-amino-3-hydroxy-6-methyl-2-ethylpyridine in 25 ml toluene containing 0.4 ml dry Et_3N was stirred at 0°C as a solution of 0.39 g (0.002 mole) 1-adamantanecarboxychloride in 10 ml dry toluene was added. The reaction mixture

was kept at 0-5°C for 0.5 h, then allowed to warm to 20-25°C and stirred for an additional 2 h. The $Et_3N \cdot HCl$ precipitate was filtered out and washed with toluene. The toluene solutions were combined and washed with water, then the solvent removed. The resulting product was dissolved in boiling ethanol. A precipitate formed on cooling, amounting to about 0.1 g was established as compound XII, mp 180-183°C. The ethanolic solution was evaporated to yield the white crystalline compound XI, white crystalline powder with R_f 0.12 and mp 139-141°C, yield 0.37 g (52.9%). $C_{19}H_{26}N_2O_2$. IR spectrum, cm^{-1}: 3320-3430 (OH, NH), 1680 (C=O). Hydrochloride, white crystals with mp 210-212°C, $C_{19}H_{26}N_2O_2 \cdot HCl$.

4-Bromomethyl-2-ethyl-6-methyl-3-hydroxypyridine hydrobromide (XIII). A solution of 43.2 g (0.172 mole) 4-acetoxymethyl-2-ethyl-6-methyl-3-acetoxypyridine in 200 ml 48% HBr was refluxed for 4-6 h, the solvent removed under vacuum, the residue stirred with a mixture of i-PrOH and ether, and filtered out to yield 25.92 g (60%) XIII. mp 122-123°C. $C_9H_{13}BrNO$.

2-Methyl-4-(N-methyl-N-adamant-1-yl)aminomethyl-5-hydroxy-6-ethylpyridine (XIV). A mixture of 6 g (0.02 mole) 2-methyl-4-bromomethyl-5-hydroxy-6-ethylpyridine, 3.66 g (0.22 mole) 1-(methylamino)adamantane, 1.6 g powdered NaOH and 30 ml dry toluene were refluxed for 5 h. After cooling the inorganic precipitate was filtered out and washed with toluene (2×20 ml). The combined organic phases were washed with water (3×50 ml), yielding after drying and removal of the solvent 4.2 g (56.2%) of compound XIV as an oil. On adding a solution of ethanolic HCl to compound XIV in ether, the dihydrochloride was obtained. mp 175-177°C (from ethanol). $C_{20}H_{30}N_2O \cdot 2HCl$.

EXPERIMENTAL (BIOLOGY)

The biological activity of the compounds was examined by tests designed to determine psychostimulatory effect. For this we evaluated spontaneous motor activity (SMA), physical working efficiency and also anticataleptic activity (with the goal of observing a central dopaminomimetic affect). SMA of white mice was studied using an acetometer. For 1 hour preceding the recording of SMA a group of 5 animals was administered with the compound intraperitoneally in doses of 5, 10 and 50 mg/kg, or with distilled water (control). Every 60 minutes the number of movements made over a 5 minute period was registered. The length of observation in this test was 5 h.

The influence of the compounds in the dynamic physical working efficiency of the organism was determined using the performance of mice in a swimming trial with weights attached to their tails (amounting to 10% of the body weight); the water temperature was 27°C [11].

The anticataleptic activity of the compounds was studied by determining the degree of prevention of triftazine catalepsy (2.5 mg/kg intraperitoneally) in white unpedigreed male mice. The degree of development of catalepsy was evaluated using the points of Morpurgo [18]. The compounds were administered intraperitoneally in doses of 100 mg/kg 30 minutes prior to the administration of triftazine, the degree of catalepsy development was evaluated 1 h after its administration.

The acute toxicities of the compounds were determined as in [10]. The results of the experiments are presented in Table 1.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME 1-HYDROXY-3-AMINOALKYLADAMANTANES AND THEIR DERIVATIVES

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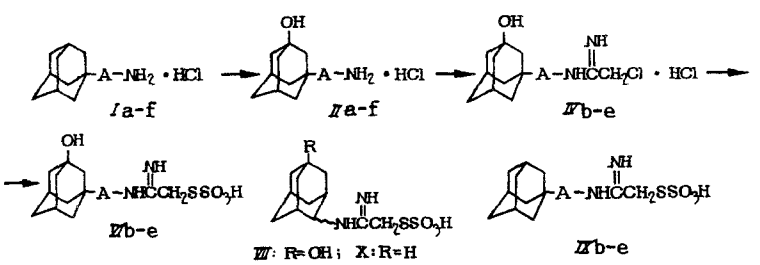
Some adamantanes have been found to possess a wide spectrum of biological activity [2, 4, 7, 8], drugs such as remantadine and adapromine having already found application for the prophylaxis and early treatment of influenza. There have been reports of the radioprotectant effects of N-adamantyl derivatives of 2-acetamidinethiosulfuric and thiophosphoric acids [9, 12].

In order to assess their biological activity, and to establish structure-activity relationships, we have now obtained some adamantanes containing a hydroxy group in the ring, such compounds having different hydrophobic properties, thereby potentially modifying the uptake and distribution of the compounds in the body.



Throughout A: a) bond, b) CH_2O, c) $(CH_2)_2$ d) $(CH_2)_3$ e) $CH(CH_3)$, f) $CH(CH_2CH_3)$

The 3- and 5-hydroxy-derivatives of 1- and 2-aminoadamantane and their derivatives have previously been obtained by treatment with a mixture of nitric and sulfuric acids [6]. It was shown that hydroxylation also occurred smoothly and cleanly when the amino-group in the 1-position was separated from the ring by a hydrocarbon chain A, the aminoalkyladamantane hydrochlorides (Ia-f) affording 71-85% yields of the hydroxylated compounds 3-amino-, 3-aminomethyl-, 3-aminoethyl-, 3-aminopropyl-, 3-(1-aminoethyl)-, and 3-(1-aminopropyl)-1-hydroxyadamantanes (IIa-f). The structures of (IIb-f) were confirmed by PMR spectroscopy. Similarly, 2-aminoadamantane hydrochloride gave 1-hydroxy-4-aminoadamantane (III). Treatment of the amines (IIb-e) with chloroacetonitrile in methanol in the presence of catalytic amounts of sodium methoxide afforded the chloracetamidines (IVb-e). Under the same condi-

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