13. Organic Syntheses, Vol. 1, Wiley (1948).
14. G. Lepore, S. Miglan, D. E. Blagdon, et al., J. Org. Chem., 38, 2590 (1973).
15. N. V. Koshkin, Zh. Obshch. Khim., 5, 1460 (1935).

SYNTHESIS AND BIOLOGICAL ACTIVITY OF ADAMANTANE DERIVATIVES.

III. ANTIVIRAL ACTIVITY OF 1-(4'-AMINOPHENYL)ADAMANTANE DERIVATIVES

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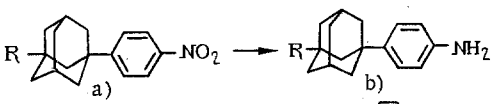
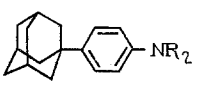
It is known that 1-aminoadamantane is an influenza virus inhibitor. We have found that 1-(4'-aminophenyl)adamantane and some of its derivatives also possess antiviral properties and have a wider activity spectrum.

We tested compounds prepared according to the following scheme.

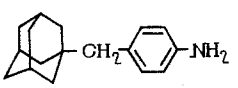


I: R=NHCOCH3
II: R=COOH
III: R=COOCH3
IV: R=CH2OH
V: R=CONH2

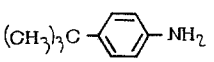
VI: R=CON(CH2CH2)2O
VII: R=NHCOOCH3
VIII: R=NH2
IX: R=OH



X: R=H; XI: R=CH3
XII: R=C2H5



XIII



XIV

Amide Ia was prepared by Ritter's method from the known 1-(4'-nitrophenyl)-3-bromoadamantane [1]. Saponification of this bromide with 5% hydrochloric acid in dimethylformamide gives alcohol IXa. Amides Va and VIa were prepared from 1-(4'-nitrophenyl)adamantane-3-carbonyl chloride [1] and ammonia or morpholine. Amide Va was converted into urethane VIIa by Hofmann's method, and the latter was converted into amine VIIIa by acid hydrolysis. Compounds IIa-IVa are described in [2]. Nitro compounds Ia-IXa were reduced with hydrogen over Raney nickel to give amines Ib-IXb. Amines XI and XII were prepared by alkylating the known 1-(4'-aminophenyl)adamantane (X) [1] with dimethyl or diethyl sulfate in a weakly alkaline medium. Amine XIII is described in [1], and the preparation of amine XIV is described in [3].

The antiviral activity of the compounds obtained were studied against influenza A2 virus, type 3 adenovirus, ECHO-6 virus, Venezuelan equine encephalomyelitis (VEE) virus, and vaccinia virus. The investigations with ECHO-6 and type 3 adenovirus were carried out on passaged cutaneous-muscular fibroblasts from human embryos, those with VEE and vaccinia

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TABLE 1. Results of Antiviral Activity Study

Compound	Maximum tolerable concentration in various cell systems (in μg/ml)	Therapeutic index				
		influenza A2	type 3 adenovirus	ECHO-6	VEE	vaccinia
Ib	60—100	2	4	—	n.i.	—
IIb	200—500	4	8	—	n.i.	—
IIIb	50—100	4	—	—	—	—
IVb	200—250	2	4	—	—	—
Vb	100	—	—	—	n.i.	—
VIb	100	2	—	—	—	1
VIIb	500—100	2	1	2	n.i.	—
VIIIa	10—30	4	—	—	—	1
VIIIb	100	8	—	—	—	—
IXb	10	1	—	n.i.	n.i.	—
Xb	100—500	8	—	2	4	—
XI	5—10	—	—	—	n.i.	—
XII	5—10	4	—	—	n.i	—
XIII	10—25	n.i.	—	n.i.	—	n.i.
XIV	100—200	—	1	1	n.i.	—

Note. n.i.) not investigated.

TABLE 2. 1-(4'-Aminophenyl)adamantane Derivatives

Compound	Yield (%)	Melting point (deg)*	N found (%)	Empirical formula	N calculated (%)
Ib	54,7	182—3	9,90,10,01	$C_{18}H_{24}N_2O$	9.86
IIb	63,9	189—90	5,52,5,40	$C_{17}H_{21}NO_2$	5,16
IIIb	56,6	91—2	5,09,5,14	$C_{18}H_{23}NO_2$	4,93
IVb	56,0	135—6	5,87,5,64	$C_{17}H_{23}NO$	5,45
Vb	90,0	222—3	10,48,10,51	$C_{17}H_{22}N_2O$	10,37
VIb	40,0	133—5	7,94,7,87	$C_{21}H_{28}N_2O_2$	8,23
VIIb	56,6	107—8	9,49,9,44	$C_{18}H_{24}N_2O_2$	9,33
VIIIb	47,8	141—3	11,42,11,48	$C_{16}H_{22}N$	11,56
IX	56,4	214—6	5,44,5,56	$C_{16}H_{21}NO$	5,76

*Compounds Ib, IVb and VIIb-IXb were crystallized from carbon tetrachloride; IIb from chloroform; IIIb from heptane; and Vb and VIb from methanol.

were carried out on fibroblast tissue from chicken embryos, and those with the influenza virus were carried out on fragments of chorionic-allantoic membrane from chicken embryos.

Virus samples with infectivities of 0.1-1.0 TCD_{50} (for ECHO and adenovirus 0.001 TCD_{50}, for VEE); or 0.001 BVU/ml (for vaccinia) were incubated in the presence of 1 ml of a supporting medium containing the preparation in doses which were nontoxic for the cell culture, until cytopathogenic changes appeared in the virus control. Samples were then taken to determine the infective activity of the reproduced virus. The infective activity of the virus was determined by titration in a tissue culture using a well-known method [4]. The minimum effective concentration was taken to be the concentration of a compound which decreased the titer of the reproduced virus by a factor of not less than 10. The activity of the preparations was evaluated in terms of their therapeutic index. For vaccinia, primary sampling was carried out by screening on Petri dishes [5]. The data are given in Table 1.

Most of the derivatives investigated are active to some extent or other against influenza A2 virus. Aminophenyladamantane X has a therapeutic index of 8 in this case. The simultaneous introduction of an aminophenyl group and an amino group (VIIIb) slightly increases the toxicity towards the cell system without decreasing the activity. The introduction of other substituents into the adamantane nucleus decreases the activity. Alkylation of the amino group (XI and XII) weakens the effect on the influenza virus compared with aminophenyladamantane X. It is interesting to note that the replacement of the hydroxyl group in IXb by a hydroxymethyl group (IVb) leads to a considerable decrease in toxicity and a slight increase in activity.

Three compounds showed pronounced activity against type 3 adenovirus. Since aminophenyladamantane X itself is inactive, we can conclude that the activity of compounds Ib, IIb, and IVb is due to the presence of an amide group bonded to the adamantane nucleus.

Amine X and urethane VIIb have an inhibiting effect on ECHO-6 virus. Replacement of the adamantyl residue by t-butyl (XIV) results in a decrease in activity.

Only amine X has a pronounced effect on VEE virus. The group of compounds studied have no effect against vaccinia virus.

EXPERIMENTAL

1-(4'-Nitrophenyl)-3-acetamidoadamantane (Ia). A mixture of 20 g of 1-(4'-nitrophenyl)-3-bromoadamantane and 100 ml acetonitrile was stirred at room temperature and treated with 25 ml concentrated sulfuric acid over 2 h. The mixture was boiled for 2 h, poured into 500 ml water, left overnight, and the precipitate separated, washed with water, dried, and crystallized from ethyl acetate, to give 14.5 g (77%) of Ia, mp 188-189°. Found, %: N 8.74, 8.86. $C_{18}H_{22}N_2O_3$. Calculated, %: N 8.92.

1-(4'-Nitrophenyl)adamantane-3-carboxamide (Va). A mixture of 4.5 g of IIa and 15 ml of thionyl chloride was boiled for 2 h. The excess thionyl chloride was distilled off *in vacuo*, and the residue was treated three times with anhydrous benzene (10 ml each) and the benzene distilled off under the same conditions. The residue was dissolved in 20 ml of anhydrous tetrahydrofuran, and the solution added to 30 ml of 25% aqueous ammonia while stirring. The mixture was left overnight and the precipitate separated to give 3 g (66.7%) of Va, mp 187-188° (from methanol). Found, %: N 9.48, 9.51. $C_{17}H_{20}N_2O_3$. Calculated, %: N 9.33.

1-(4'-Nitrophenyl)adamantane-3-carboxylic Acid Morpholide (VIa). A solution of the acid chloride of IIa (obtained from 4.5 g IIa) in 15 ml tetrahydrofuran was added to a solution of 4.5 g morpholine in 50 ml tetrahydrofuran. The mixture was left overnight, treated with 300 ml water, and the precipitate separated and washed with 5% hydrochloric acid and water to neutrality, to give 3.2 g (57.1%) of VIa, mp 167-168° (from methanol). Found, %: N 7.42, 7.66. $C_{21}H_{26}N_2O_4$. Calculated, %: N 7.57.

1-(4'-Nitrophenyl)-3-methoxycarbonylaminoadamantane (VIIa). A solution of 4.2 g of amide Va in 30 ml methanol was added to a solution of 1.23 g sodium in 30 ml of anhydrous methanol. The mixture was treated at 0° with 1.5 ml of anhydrous bromine over 30 min while stirring, kept at 55° for 4 h, poured into 100 ml water, and the precipitate crystallized from methanol to give 4.1 g (90.7%) of VIIa, mp 156-157°. Found, %: N 8.83, 8.68. $C_{18}H_{22}N_2O_4$. Calculated, %: N 8.47.

1-(4'-Nitrophenyl)-3-aminoadamantane (VIIIa). A mixture of 1.9 g of urethane VIIa and 30 ml of concentrated hydrochloric acid was boiled for 8 h, cooled, filtered, and the filtrate evaporated to dryness *in vacuo*. The residue was crystallized from water to give 1.3 g (73%) of VIIIa.HCl, mp 293-294°. Found, %: N 9.03, 8.63; Cl 11.18, 11.26. $C_{16}H_{21}ClN_2O_2$. Calculated, %: N 9.06; Cl 11.49.

1-(4'-Nitrophenyl)-3-hydroxyadamantane (IXa). A mixture of 6.7 g 1-(4'-nitrophenyl)-3-bromoadamantane, 30 ml dimethylformamide, and 3 ml of 15% hydrochloric acid was boiled for 6 h, poured into 100 ml water, and filtered to give 5.1 g (94.4%) of IXa, mp 148-149° (from carbon tetrachloride). Found, %: N 5.18, 5.26. $C_{16}H_{19}NO_3$. Calculated, %: N 5.13.

Amino Compounds Ib-IXb. The corresponding nitro compounds were dissolved in methanol, reduced with hydrogen over Raney nickel at room temperature and atmospheric pressure for 4-6 h, the catalyst filtered off, the filtrate evaporated, and the residue crystallized. Data on the compounds obtained are given in Table 2. Their hydrochlorides were used for studying their antiviral activity.

1-(4'-Dimethylaminophenyl)adamantane (XI). A mixture of 1 g of amine X, 5 ml dimethyl sulfate and 1 g sodium bicarbonate was stirred at room temperature for 1 h, treated with 20 ml water, left overnight, made alkaline with 20% sodium hydroxide solution, and extracted three times with ether. The combined extracts were dried over potassium hydroxide, filtered, and the amine precipitated with dry hydrogen chloride, to give 0.8 g (71.4%) of XI.HCl, mp 216-217° (from water). Found, %: N 5.28, 5.12; Cl 11.52, 11.77. $C_{18}H_{26}ClN$. Calculated, %: N 4.81; Cl 11.86.

1-(4'-Diethylaminophenyl)adamantane (XII). This was prepared from 1 g of amine X, 5 ml diethyl sulfate and 1 g sodium bicarbonate analogously to amine XI. Yield 0.8 g (67.3%), mp 227-229° (from water). Found, %: 4.18, 4.36; Cl 10.86, 11.06. $C_{20}H_{30}ClN$. Calculated, %: N 4.39; Cl 11.12.

LITERATURE CITED

1. F. N. Stepanov, E. I. Dikolenko, and G. I. Danilenko, Zh. Organ. Khim., 2, 640 (1966).
2. F. N. Stepanov and G. I. Danilenko, Zh. Organ. Khim., 3, 914 (1967).
3. M. Senkowski, Ber. Dtsch. Chem. Ges., 23, 2402 (1890).
4. P. F. Zdrodovskii and M. I. Sokolov (editors), Handbook on Laboratory Diagnosis of Viral and Rickettsial Diseases [in Russian], Moscow (1965).
5. R. Rada and N. Zavada, Neoplasma (Bratisl.), 9, 57 (1962).

RELATIONSHIP BETWEEN THE CATALYTIC ACTIVITY OF COMPOUNDS OF COPPER(II) AND DERIVATIVES OF N-PHENYLANTHRANILIC ACID AND THE PHYSIOLOGICAL ACTIVITY OF LIGANDS

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Derivatives of N-phenylanthranilic acid have been used in recent years in medical practice as antiinflammatory, analgesic, and antipyretic agents. They are favorably distinguished from the steroid preparations previously used for analogous purposes — glucocorticoids — by the low frequency of side reactions [1].

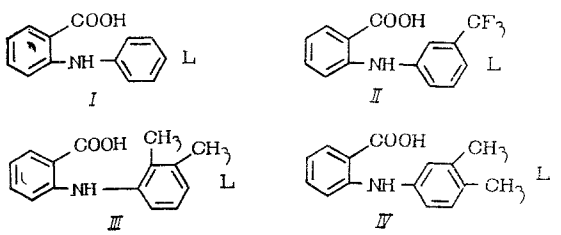
Derivatives of N-phenylanthranilic acid are capable of forming coordination compounds with copper(II) [2, 3].

We studied the catalytic activity of these complex compounds in certain model reactions: the oxidation of ascorbic acid by oxygen and the decomposition of hydrogen peroxide, i.e., reactions of the oxidase and catalase types:

$$2C_6H_8O_6 + O_2 \longrightarrow 2C_6H_6O_6 + 2H_2O \quad (1)$$
$$2H_2O_2 \longrightarrow 2H_2O + O_2 \quad (2)$$

Both these reactions, as is well known, are catalyzed by hydrated copper(II) ions or complex compounds of copper(II) [4, 9].

In the work we used N-phenylanthranilic acid (L_I-L_{VI}).



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