SYNTHESIS AND BIOLOGICAL ACTIVITY OF ADAMANTANE DERIVATIVES.

IV. VIRAL INHIBITING ACTIVITY OF SOME ADAMANTYLAMINES

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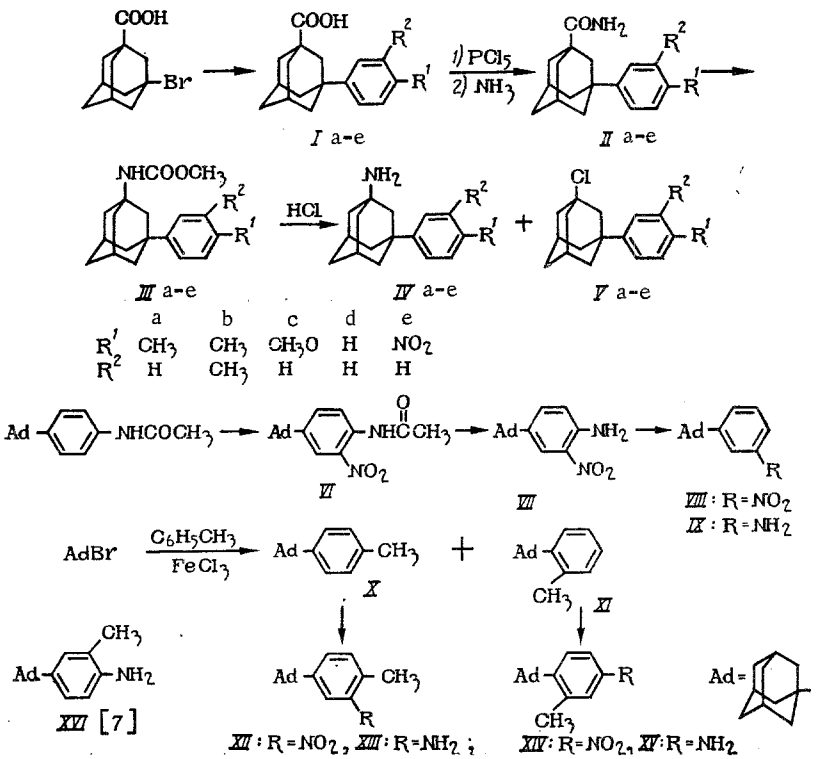
It has been shown that 3-methyl-1-aminoadamantane inhibits the reproduction of the influenza virus to a lesser extent than 1-aminoadamantane. This is due to spatial hindrance caused by the methyl group [1]. However, 1-amino-3,5-dimethyl-7-ethyladamantane [2] and 1,3-diamino-5,7-dimethyl- and 1,3-di-(N-methoxycarbonyl)amino-5,7-dimethyladamantane [3, 4] have been claimed to be active antiviral compounds. It was therefore of interest to determine how the activity of 1-aminoadamantane was modified by the inductive and steric effects of aryl substituents in the 3-position, and that of 1-(4'-aminophenyl)adamantane, by the introduction of a methyl group into the phenyl nucleus. With this in view, the amines obtained by the following routes were tested (Ic was obtained by Stepanov et al. [5], IId-Vd by Stepanov et al. [6], and Ie-Ve, by Stetter et al. [7]):



On heating 1-bromoadamantane-3-carboxylic acid with an excess of toluene in the presence of zinc chloride, the acid Ia is formed, and when o-xylene is used, acid Ib is produced. Reaction of acids Ia-c with phosphorus pentachloride gives the acid chlorides, which were converted without further purification into the amides IIa-c by treatment with aqueous ammonia. The Hoffman reaction with the latter afforded the urethanes IIIa-c, which on acid hydrolysis

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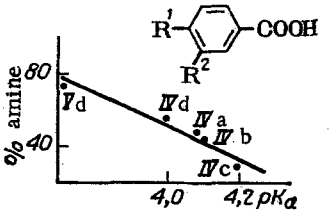

Fig. 1. Dependence of yield of amine on the pK_a of the corresponding benzoic acids.

afforded a mixture of the corresponding amines IVa-c and the chloro derivatives Va-c. The yields of the amines and the chloro compounds were determined with an accuracy of ±5% from three independent determinations.

It has previously been shown that acid hydrolysis of substituted adamantane-1-acetamides or the -1-urethanes gives the amines or the chloro compounds only, depending on the nature of the substituent in the 3-position. An exception is phenyl, which on acid hydrolysis gives both products [6, 8].

Our results show that acid hydrolysis of the urethanes IIIa-e proceeds with concurrent rupture of both the adamantane–nitrogen bond and the nitrogen–carbonyl bond. Introduction into the benzene ring of the electron-donating methoxy group (IIIc) increases the positive charge on the first ring carbon atom of adamantane by transmission of its inductive effect, thereby increasing the yield of the chloro compound. Introduction of a nitro group (IIIe) increases the yield of the amine. The percentage amine content in the hydrolysis products of urethanes Ia-e is determined by the pK_a values of the benzoic acids having the same substituents (see Fig. 1; pK_a).

It is pointed out that determination of the percentage content of the amines or chloro compounds in the hydrolysis products of the 3-substituted adamantane-1-urethanes is a better measure of the inductive effects of these substituents on the functional group than determination of the acidity of similarly substituted adamantane-1-carboxylic acids, or of the basicity of the corresponding amines.

Nitration of p-adamantylacetanilide [8] affords VI, which on hydrolysis followed by diazotization and reduction of the diazonium group gives the nitro derivative VIII. Reaction of 1-bromoadamantane with toluene in the presence of ferric chloride affords 1-(4'-methylphenyl)- (X) and 1-(2'-methylphenyl)adamantane (XI) in a ratio of 2:1. Nitration of these products leads to compounds XII and XIV. The amines IX, XIII, and XV were obtained by reduction of the corresponding nitro derivatives with hydrogen over Raney nickel.

The antiviral activity of the amines was determined under the conditions described previously. Activity was evaluated as in [9].

Table 1 gives the results of single tests. It will be seen that the 3-aryl-substituted adamantanes IVa-e are mainly active against the influenza virus. The highest activity is displayed by the compound having an unsubstituted phenyl group (IVd). Introduction of the electron-accepting nitro group reduces the activity (IVe), and substitution by electron-donating groups (IVa-c) gives inactive compounds. It is suggested that in these compounds the activity is determined not so much by the inductive effects of the substituents on the amino group as by steric factors.

Moving the amino group in the m-position to the adamantyl moiety (IX) results in a change in the spectrum of activity as compared with p-adamantylaniline (XVIII).

Introduction of the methyl group into the phenyl nucleus results in a sharp drop in activity towards the influenza virus (XIII, XV, and XVI, as compared with XVIII), but the amine XIII inhibits the ECHO-6 virus more strongly than the amine XVIII, and unlike the latter it is active against the variolovaccine virus. Amine XIII is more active than its isomer XVI. It is probable that in the case of the adamantylanilines also, introduction of a methyl group modifies activity in consequence of steric effects.

EXPERIMENTAL

1-(4'-Methylphenyl)adamantane-3-carboxylic acid (Ia). A mixture of 2.6 g of 1-bromoadamantane-3-carboxylic acid, 15 ml of toluene, and 1.5 g of anhydrous zinc chloride was

TABLE 1. Antiviral Activity of Amino Derivatives of Aminazine

Compound	Influenza A_2	Adenovirus type 3	ECHO-6	Arbovirus	Variolovaccine
IVa	—	—	—	—	—
IVb	+	—	—	—	—
IVc	—	—	+	—	—
IVd	++++	+	—	N. T.	—
IVe	++++	—	—	—	—
IX	—	++	—	—	±
XIII	+	—	++++	—	++
XV	—	+	+	N. T.	—
XVI	—	N. T.	—	+	±
XVII	++++	N. T.	—	N. T.	++
XVIII	++++	—	++	++++	—

Note: N.T.) not tested; —) no activity; ±, +, ++ ...) increasing antiviral activity.

boiled for 1 h. The organic layer was washed with water, the solvent was removed, and the residue was crystallized from benzene. Yield 1.8 g (71%), mp 175-176°. Found, %: C 79.54, 79.91, H 8.13, 8.03. $C_{18}H_{22}O_2$. Calculated, %: C 79.59, H 8.20.

1-(3',4'-Dimethylphenyl)adamantane-3-carboxylic acid (Ib). Obtained in a similar manner to Ia from 10 g of 1-bromoadamantane-3-carboxylic acid, 20 ml of o-xylene, and 1.5 g of zinc chloride. Yield 9 g (82.3%), mp 215-216° (alcohol). IR spectrum (ν, cm^{-1}): 1700 (CO), 825 (1,2,4-substituted benzene ring). Found, %: C 80.05, 80.16, H 8.64, 8.57. $C_{19}H_{24}O_2$. Calculated, %: C 79.95, H 8.83.

Amides IIa-c. A mixture of equimolar amounts of the acids (Ia-c) with phosphorus pentachloride in a 5-10-fold quantity of carbon tetrachloride was boiled for 1 h. The solvent was distilled off, and the residue was treated three times with 15 ml of carbon tetrachloride followed by distillation of the latter. The residue was dissolved in anhydrous dioxan, and the solution was added with stirring to a tenfold excess of 25% aqueous ammonia. After keeping overnight, the precipitate was filtered off. Data on the compounds obtained are given in Table 2.

Urethanes (IIIa-c). A solution of the amide in anhydrous methanol was added to an equimolar amount of sodium methoxide dissolved in methanol. The resulting solution was cooled to 0°, and an equimolar amount of bromine was added. Stirring was continued for 1 h at 0° and 4 h at 55°, followed by dilution with water. After keeping overnight, the precipitate which separated was filtered off and washed with water. Data on the compounds obtained are given in Table 2.

Acid Hydrolysis of the Urethanes. A mixture of the urethane with a tenfold excess of conc. hydrochloric acid was boiled for 10 h. After cooling, the chloro compounds Va-c which separated were filtered off and washed with water. The combined filtrates were evaporated to dryness, the residue was dissolved in the minimum amount of anhydrous methanol, and the amine hydrochlorides IVa-c were precipitated by adding anhydrous ether. Data on the hydrolysis products of the urethanes are given in Table 3.

1-(3'-Nitro-4'-acetamidophenyl)adamantane (VI). p-Adamantylacetanilide (2 g) was added over 1 h with stirring and cooling to a mixture of 0.4 ml of 82% nitric acid and 2.1 ml of conc. sulfuric acid. The mixture was stirred for a further 3 h, and poured at room temp. onto 50 g of ice followed by isolation of the precipitate. Yield 1.6 g (80%), mp 208-210° (methanol-benzene). Found, %: N 8.61, 9.01. $C_{18}H_{22}N_2O_2$. Calculated, %: N 8.80.

1-(3'-Nitro-4'-aminophenyl)adamantane (VII). A mixture of 15 g of the amine VI, 2.5 g of sodium hydroxide, 4 ml of water, and 10 ml of alcohol was boiled for 7 h. After cooling, the precipitate which separated was isolated and crystallized from alcohol. Yield 12.7 g (90%), mp 218-219°. Found, %: N 10.26, 10.59. $C_{16}H_{20}N_2O_2$. Calculated, %: N 10.28.

TABLE 2. Properties of the Amines (IIa-c) and the Urethanes (IIIa-c)

Compound	Yield (%)	Melting point (deg)*	Found. N (%)	Molecular formula	Calculated N (%)
IIa	99,5	127—8	5,29, 5,54	$C_{18}H_{23}NO$	5,20
IIb	98,8	161—2	5,03, 5,13	$C_{19}H_{25}NO$	4,94
IIc	93,0	139—140	4,96, 5,01	$C_{18}H_{23}NO_2$	4,91
IIIa	88,5	102—3	4,91, 4,87	$C_{19}H_{25}NO_2$	4,67
IIIb	94,5	79—80	4,68, 4,53	$C_{20}H_{27}NO_2$	4,47
IIIc	57,0	114—5	4,66, 4,72	$C_{19}H_{25}NO_3$	4,43

*Compound IIIb was recrystallized from hexane, and the remainder from alcohol.

TABLE 3. Properties of Products IVa-c and Va-c Obtained by the Acid Hydrolysis of the Urethanes IIIa-c

Urethane	Product	Yield (%)	Melting point (deg)*	Found. Cl (%)	Molecular formula	Calculated. Cl (%)
IIIa	IVa	37,0	278—9	12,55, 12,59	$C_{17}H_{24}ClN$	12,77
IIIa	Va	62,3	96—7	13,93, 13,85	$C_{17}H_{21}Cl$	13,61
IIIb	IVb	37,7	264—5	11,88, 11,99	$C_{18}H_{26}ClN$	12,16
IIIb	Vb	52,5	75—6	13,14, 13,26	$C_{18}H_{23}Cl$	12,93
IIIc	IVc	26,8	325—6	11,86, 11,97	$C_{17}H_{24}ClNO$	12,09
IIIc	Vc	70,0	73—4	12,53, 12,76	$C_{17}H_{21}ClO$	12,84

*Hydrochlorides IVa-c were crystallized from water, and compounds Va-c from alcohol.

1-(3'-Nitrophenyl)adamantane (VIII). To a solution of 13.4 g of the amine VII in 120 ml of glacial acetic acid was added over 30 min a solution of 6.75 g of sodium nitrate in 45 ml of conc. sulfuric acid, at such a rate that the temperature did not exceed 20°. The mixture was stirred for a further 30 min at room temperature, then added over 30 min with vigorous stirring to a suspension of 21 g of cuprous oxide in 180 ml of anhydrous alcohol. The precipitate was isolated, washed with 200 ml of ether, 0.5 liter of water was added to the filtrate, and the ether layer was separated. The aqueous solution was extracted with ether, and the combined ether extracts were washed with water until neutral, and the solvent distilled off. Yield 10.1 g (80%), mp 85-86° (methanol). Found, %: N 5.56, 5.57. $C_{16}H_{19}NO_2$. Calculated, %: N 5.44.

1-(3'-Aminophenyl)adamantane (IX). A mixture of 9.9 g of VIII, 100 ml of methanol, and 0.2 g of Raney nickel was reduced with hydrogen at 20 atm and 70° for 3 h, then filtered to remove the catalyst, and the solvent distilled off. Yield 7.6 g (84.4%), mp 135-136° (aqueous alcohol). Found, %: N 6.15, 6.41. $C_{16}H_{21}N$. Calculated, %: N 6.16.

1-(4'-Methylphenyl)adamantane (X) and 1-(2'-Methylphenyl)adamantane (XI). To a boiling mixture of 7 g of anhydrous ferric chloride and 200 ml of toluene was added with stirring over 30 min a solution of 1-bromoadamantane in 50 ml of toluene. The mixture was stirred for a further 4 h, 100 ml of water added, and the organic layer separated and washed with water until neutral. The solvent was distilled off and the residue fractionally crystallized from methanol to give 12 g of X (60%), mp 101-102° (literature value 101-102° [8]).

The yield of XI was 5.9 g (29.7%), mp 56-58°. Found, %: C 89.92, 89.67, H 9.86, 9.75. $C_{17}H_{22}$. Calculated, %: C 90.20, H 9.80.

1-(3'-Nitro-4'-methylphenyl)adamantane (XII). Compound X (40 g) was added with stirring over 2 h to a mixture of 33 ml of 56% nitric acid and 47 ml of conc sulfuric acid at such a rate that the temperature did not exceed 40°. The mixture was stirred for a further 2 h at 40°, and poured onto 300 g of ice. Yield 38 g (79.1%), mp 102-103° (acetone). Found, %: N 5.30, 5.32. $C_{17}H_{21}NO_2$. Calculated, %: N 5.15.

1-(3'-Amino-4'-methylphenyl)adamantane (XIII). Obtained in a similar way to IX from 7.9 g of XII, 2 g of Raney nickel, and 180 ml of methanol. Yield 4.9 g (71.8%), mp 140-141° (alcohol). Found, %: N 5.69, 5.97. $C_{17}H_{23}N$. Calculated, %: N 5.82.

1-(2'-Methyl-4'-nitrophenyl)adamantane (XIV). Obtained in a similar way to XII from 3 g of XI, 2 ml of 56% nitric acid and 4 ml of conc. sulfuric acid. Yield 1.2 g (34%), mp 119-121° (methanol). Found, %: N 5.31, 5.34. $C_{17}H_{21}NO_2$. Calculated, %: N 5.15.

1-(2'-Methyl-4'-aminophenyl)adamantane (XV). Obtained in a similar way to IX from 1 g of XIV, 0.1 g of Raney nickel, and 100 ml of methanol. Yield 0.6 g (67.5%), mp 121-122° (methanol). Found, %: N 5.94, 6.02. $C_{17}H_{23}N$. Calculated, %: N 5.82.

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BIOLOGICAL ACTIVITY OF TRANSFORMED STEROIDS.

V*. SYNTHESIS AND COMPARATIVE EXAMINATION OF THE BIOLOGICAL PROPERTIES OF 16α,17α-DIOXOLANES AND OXATHIOLANES OF THE PREGNANE SERIES

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In order to determine the mode of action of steroid hormones at the molecular level, it is of great interest to compare the biological activities of compounds which differ only slightly in their chemical structure such as may be incorporated into geometrical models. Comparison of the biological activity of such analogs from parallel series may on the one hand indicate the similarity or dissimilarity of their physiological mode of action, or on the other hand classify their biological functions in respect to the requirements for differing degrees of specificity of chemical structure in the steroid molecule. Finally, the introduction of small changes in the geometry of the molecule may be depended upon to provide an indication of the "signature" [2], corresponding to interaction with a particular biological receptor.

We have taken as our basic model a series of 20-oxopregnanes condensed in the 16α,17α-positions with heterocycles, since several such compounds are already known to possess biological activity (e.g., algestone acetophenonide and acetonide, triamcinolone acetonide, and synalar).

*For Communication IV, see [1].

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