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SYNTHESIS AND ANTIVIRAL ACTIVITY OF HALOGENATED ADAMANTYLPHENOLS

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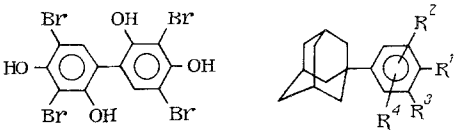
The biologically active derivatives of biphenyl include the antiviral preparation tebrophen (I) [1]. We thought it of interest to prepare its adamantyl analogs, in which one of the benzene rings is replaced by the adamantyl system (II), and to examine their biological activity, since many compounds of the adamantane series also display antiviral activity [2].



I II

R^1=OH; R^2=H, OH; $R^{3,4}$=Br, F

We synthesized 4-(1-adamantyl)phenol (III) [3] and 4-(1-adamantyl)resorcinol (IV) by refluxing 1-bromoadamantane with phenol or resorcinol in benzene until the evolution of hydrogen bromide ceased. We were able to get both the mono and dibromo derivatives by bromination of (III), depending on the reaction conditions. 2,6-Dibromo-4-(1-adamantyl)phenol (V) was formed in 89.3% yield when III was treated with bromine in a mixture of methanol and acetic anhydride. We got the same compound when the reaction was carried out in carbon tetrachloride or glacial acetic acid, though the yield was slightly lower, 83% and 75%, respectively. We used a milder brominating agent, dioxane dibromide in ether, to prepare 2-bromo-4-(1-adamantyl)phenol (VI). In regard to the iodo derivatives, 2-iodo-4-(1-adamantyl)phenol (VII) was readily formed by treatment of III with iodine monochloride in glacial acetic acid. The yield of VII was 93%. We turned to a stronger iodinating agent, iodine in morpholine, to introduce a second iodine atom, but were unable to get the desired compound, isolating only the monoiodo derivative VII in lower yield, 50%.

For the biological tests we also synthesized (using iodine monochloride) 1,3-bis(3-iodo-4-hydroxyphenyl)adamantane (VIII).

Bromination of 4-(1-adamantyl)resorcinol in carbon tetrachloride (under conditions equivalent to those for the bromination of resorcinol itself) gave 2,6-dibromo-4-(1-adamantyl)resorcinol (IX), the adamantyl analog of tebrophen, in 9% yield, together with 1-bromoadamantane and 2,4,6-tribromoresorcinol. We isolated the same bromolysis products of 1-adamantylresorcinol from the bromination of IV in glacial acetic acid. Only by using a mixture of methanol and glacial acetic acid (10:1) as solvent were we able to prepara IX in 91.5% yield. In contrast to bromination, the iodination of 1-adamantylresorcinol with iodine monochloride in glacial acetic acid was not accompanied by iodinolysis and formed 2,6-diiodo-4-(1-adamantyl)resorcinol (X) in 96.5% yield. This rather facile bromolysis of the carbon—carbon bond between the aryl and adamantyl systems is not totally unexpected. The action of

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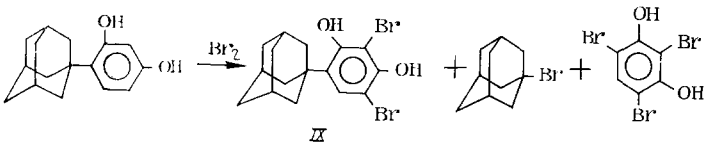

IX

excess bromine in glacial acetic acid or ether on phenols substituted in the o-position by secondary or tertiary alkyl radicals is known [4, 5] to cause bromolysis of the side chain and perbromination of the phenol ring.

The bromolysis of IV in glacial acetic acid or carbon tetrachloride seems to be of the same type and is the result of several factors — the properties of the solvent, the reactivity of the halogen — in conjunction with the particular properties of the adamantyl system, whose sterically bulky structure weakens the carbon—carbon bond with the aromatic ring and promotes its cleavage.

We tested the synthetic halogenated adamantylphenols and adamantylresorcinols against two influenza viruses, A/PR/8/34 (HON1) and A/Bethesda/63 (H2N2).

We assayed the virucidal activity of the compounds by mixing specific volumes of their solutions or suspensions of various concentrations with different amounts (1-100) of 100% embryo infecting doses (EID_{100}) of the virus. The mixtures were kept at 14°C for 1 h and then 0.2 ml was injected into the allantoic cavity of nine-day-old chick embryos. After 48 h incubation in a thermostat at 37°C we measured the titer of the influenza virus in the allantoic fluid using the hemagglutination reaction. The activity was expressed as the amount of neutralized EID_{100} of the influenza virus. To examine their virustatic effect we injected the compounds in the maximum tolerated and lower doses into allantoic sac of of the embryos 1 h before viral challenge. We assayed the virustatic effect by comparing the titers of the hemagglutinins of the influenza virus grown in the embryos treated with the test compounds and in the control embryos, which received only physiological solution. We also examined the activity of the compounds against influenzal pneumonia in mice. The mice received the test compound in the maximum tolerated and lower doses 1 h before intranasal challenge with the influenza virus and on the next four days. We evaluated the chemotherapeutic activity by comparing the survival rate in the test and control groups.

Compounds IX, V, and VII had virucidal activity. Compound IX had the greatest activity, completely neutralizing 1 EID_{100} in a concentration of 100 μg/ml, whereas the other two compounds had the same effect only in a concentration of 1000 μg/ml. The test compounds had no virustatic effect in tests on chick embryos and no therapeutic effect in influenzal pneumonia.

Thus, these tests reveal that several of these newly synthesized halogenated adamantylresorcinols and adamantylphenols have virucidal activity toward influenza virus but that their activity does not exceed that of the antiviral preparations tetrophen and amantadine.

EXPERIMENTAL CHEMISTRY

The IR spectra were recorded on a UR-10 in vaseline oil and the PMR spectra on a JNM-4H-100 in CCl_4 solution, with tetramethylsilane as internal standard. Mass spectra were measured with an MX-1303. Thin-layer chromatography was carried out on Silufol UV-254 plates in chloroform—acetone (9:1).

4-(1-Adamantyl)resorcinol (IV). A mixture of 1-bromoadamantane (30 g, 0.14 mole) [6] and resorcinol (30.8 g, 0.28 mole) in benzene (40 ml) and water (1 ml) was refluxed with stirring in a stream of inert gas until the evolution of hydrogen bromide ceased (4-5 h). The benzene was evaporated under vacuum. The residue was washed with hot water to remove unreacted resorcinol and dried. Crystallization gave IV (27.1 g, 78.5%), mp 235-236°C (from toluene). Found, %: C 78.41; H 8.24. $C_{16}H_{20}O_2$. Calculated, %: C 78.70, H 8.20.

Bromination of 4-(1-Adamantyl)resorcinol. Method A. To a suspension of IV (4.88 g, 0.02 mole) in glacial acetic acid (25 ml) was added at room temperature with stirring a solution of bromine (6.4 g, 0.04 mole) in glacial acetic acid (10 ml). The precipitate dissolved and the temperature of the reaction mixture rose to 30-35°C; evolution of hydrogen bromide could not be detected. After 3 h stirring the reaction mixture was left overnight and then poured into water. The resulting precipitate was filtered off, washed with water, and dried to give a precipitate (10 g, 88% based on the starting compounds), which was a mixture of two compounds. Evaporation of the mother liquor gave 4,6-dibromo-(1-adamantyl)resorcinol (1 g),

mp 148.5-149.5°C (from methanol), R_f 0.82. Found, %: C 47.56, H 4.39, Br 39.48. $C_{16}H_{18}Br_2O_2$. Calculated, %: C 47.56, H 4.39, Br 39.80. IR spectrum (ν, cm^{-1}): 2907, 2933, 1453, 1357, 1155 (1-adamantyl); 3480, 3495 (OH); 1600-1580 (C=C); 870 (C—Br). PMR spectrum (δ, ppm): 5.55 (1H), 7.14 (2H, doublet), 5.78 (3H, singlet), 1.69 and 2.00 (adamantyl ring protons).

Crystallization of the precipitate gave 2,4,6-tribromoresorcinol (5.5 g), mp 111.5-112.5°C (from carbon tetrachloride), R_f 0.575. Found, %: C 20.58, H 1.04, Br 69.05. $C_6H_3Br_3O_2$. Calculated, %: C 20.70, H 0.86, Br 69.30. IR spectrum (ν, cm^{-1}): 3470 (O—H), 3070 (C—H), 1580 and 1460 (C=C), 870 (1,2,3,4,5-substituted aromatic nucleus), 880 (C—Br). PMR spectrum (δ, ppm): 7.58 (2H), 3.46 (1H, 3H). Literature [6]: mp 111-112°C. The mother liquor after crystallization was evaporated and the residue gave 1-bromoadamantane (3.05 g), mp 116-117°C (from methanol), R_f 0.92. IR spectrum (ν, cm^{-1}): 2907, 2933, 2957, 1453, 1357, 1155, 799. Literature [7]: mp 115-116°C.

Method B. To a suspension of IV (9.75 g, 0.04 mole) in carbon tetrachloride (50 ml) was slowly added bromine (12.2 g, 0.12 mole) at room temperature with vigorous stirring. The reaction mixture was stirred until the evolution of hydrogen bromide ceased (about 8-10 h). The solvent was evaporated to one third of the original volume and the precipitate was filtered off and dried. Recrystallization gave 2,4,5-tribromo resorcinol (8.95 g), mp 111.5-112.5°C (from carbon tetrachloride), R_f 0.575. The mother liquor after evaporation under vacuum gave 1-bromoadamantane (5.35 g), mp 115-116°C (from methanol), R_f 0.92.

2,6-Dibromo-4-(1-adamantyl)resorcinol (IX). Bromine (3.2 g, 0.02 mole) was slowly added at room temperature with stirring to a solution of IV (2.44 g, 0.01 mole) in a mixture of glacial acetic acid (1.1 ml, 0.02 mole) and methyl alcohol (11 ml). The mixture was stirred for 1 h to bring the reaction to completion and then poured into water. The resulting precipitate was filtered off, washed with water, and dried. Crystallization gave IX (3.8 g, 91.5%), mp 148.5-149.5°C (from methanol), R_f 0.82.

2,6-Diiodo-4-(1-adamantyl)resorcinol (X). To a suspension of IV (2.44 g, 0.01 mole) in glacial acetic acid (120 ml) was added a solution of iodine monochloride (3.24 g, 0.02 mole) in glacial acetic acid (20 ml). The reaction mixture was stirred for another 2 h and then poured into water (700 ml) and extracted with ether. The ethereal solution was washed successively with water, sodium bisulfite solution, water, sodium carbonate solution, and water, and dried over calcium chloride. The solvent was evaporated. Recrystallization gave X (4.8 g, 96.5%), mp 184-185°C [from dioxane—water (2:1)]. Found, %: C 38.76, H 3.65, I 51.19. $C_{16}H_{18}I_2O_2$. Calculated, %: C 38.73, H 3.65, I 51.16. IR spectrum (ν, cm^{-1}): 1155, 1357, 1460, 2860, 2910, 2933 (1-adamantyl), 3465, 3465 (OH), 420-465 (C—I).

2-Iodo-4-(1-adamantyl)phenol (VII). This was prepared like compound X. The yield was 93%, mp 110-112°C [from dioxane—water (2:1)]. Found, %: C 54.01, H 5.45, I 35.98. $C_{16}H_{19}IO$. Calculated, %: C 54.25, H 5.41, I 35.83. IR spectrum (ν, cm^{-1}): 1155, 1350, 1453, 2850, 2906, 2933 (1-adamantyl), 3485 (OH), 420-470 (C—I).

2,6-Dibromo-4-(1-adamantyl)phenol (V). This was prepared from III under the conditions specified for the preparation of IX. The yield was 89%, mp 123-124°C (from petroleum ether). Found, %: C 49.60, H 4.70, Br 41.23. $C_{16}H_{18}Br_2O$. Calculated, %: C 49.74, H 4.66, Br 41.45.

2-Bromo-4-(1-adamantyl)phenol (VI). To a solution of III (6.6 g, 0.028 mole) in ether (30 ml) was added a solution of dioxane dibromide (8.25 g, 0.033 mole) in ether (30 ml). The reaction mixture was left overnight. The ethereal solution was washed with sodium sulfite solution and with water and dried. The solvent was evaporated. Recrystallization gave VI (4.8 g, 54%), mp 98-100°C (from petroleum ether). Found, %: C 62.45, H 6.32, Br 26.02. $C_{16}H_{19}BrO$. Calculated, %: C 62.55, H 6.23, Br 26.01. IR spectrum (ν, cm^{-1}): 1150, 1353, 1450, 2860, 2910, 2933 (1-adamantyl), 3460 (OH), 420-480 (C—Br).

1,3-Bis(3-iodo-4-hydroxyphenyl)adamantane (VIII). To a suspension of 1,3-bis(4-hydroxyphenyl)adamantane (3.2 g, 0.01 mole) [8] in acetic acid (20 ml) was added a solution of iodine monochloride (8.1 g, 0.05 mole) in acetic acid (20 ml) over a period of 1.5 h. The mixture was left overnight. The precipitate was filtered off, washed with water, and dried. Recrystallization gave VIII (3.2 g, 73.5%), mp 147-150°C [from dioxane—water (2:1)]. Found, %: C 46.58, H 4.21, I 43.97. $C_{22}H_{23}I_2O_2$. Calculated, %: C 46.09, H 4.04, I 44.28. IR spectrum (ν, cm^{-1}): 1155, 1350, 14509,* 2850, 2910 (1-adamantyl), 3180 (OH), 430 (C—I).

*As in Russian original.

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RADIOPROTECTANT PROPERTIES OF SOME BENZIMIDAZOLE DERIVATIVES

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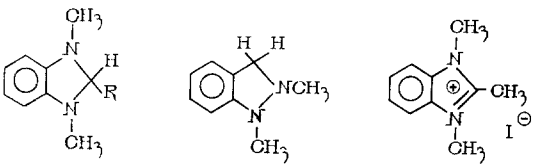
Many molecules which contain the imidazole moiety are biologically active, including major metabolites and well-known drugs. In particular, it is noted in the literature [1] that imidazole and benzimidazole display radioprotectant properties.

The benzimidazole derivatives which we have tested as potential radioprotectants may be divided into two types. The first type comprises strong reducing agents, namely the hydride donors [2,3] 1,3-dimethylbenzimidazoline [2,4,5] (I) and 1,3-dimethyl-2-phenylbenzimidazoline [6, 7] (II). In addition to these compounds, 1,2-dimethylindazoline [3, 8] (III), a hydride donor which is isomeric with I, and 1,2,3-trimethylbenzimidazolium iodide [6, 9] (IV) have been tested. The azolines I-III are analogs of the biochemical reducing agents NADH and NADPH, which are probably involved in free radical reactions [10]. It would therefore be expected that the azolines would participate in redox processes in the body, and might display free radical inhibitory properties. The benzimidazolium salt IV was tested as a model of products formed in the oxidation of azolines I-III.



I, II *III* *IV*

I: R=H
II: R=Ph

The second type of benzimidazole derivatives consists of the sulfur-containing compounds 1-methyl-2-methylthiobenzimidazole hydrochloride (V), 1-methyl-2(γ-aminopropylthio)benzimidazole oxalate (VI), 1,5,6-trimethyl-2-methylthiobenzimidazole hydrochloride (VII), 1-methyl-2-methylthio-5,6-dimethoxybenzimidazole hydrochloride (VIII), and 2-(γ-dimethylaminopropylthio)-5,6-dimethoxybenzimidazole (IX). Benzimidazole (X) [11] was tested at the same time.

Experiments were carried out on white mice weighing 18-22 g. The toxicities of the compounds were first determined in nonirradiated animals using the method of Lichfield and Willcoxon. The radioprotectant properties were determined in mice subjected to a single irradiation by x rays in an RUM-17 apparatus, at a dose rate of 96 R/min (total dose 700 rd). The compounds were administered intraperitoneally 10 min before the animals were irradiated.

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