SYNTHESIS AND RADIOPROTECTIVE ACTIVITY OF SOME DERIVATIVES OF *N*-(3-ARYLADAMANT-1-YLMETHYL)MERCAPTOACETAMIDINE

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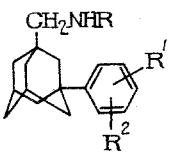
The synthesis of potential radioprotectors in a series of (3-aryladamant-1-ylalkyl)mercaptoacetamidine derivatives (I) was recently reported [5]. Compounds containing a methyl, methoxyl, and methylthiol group and also a fluorine atom in the benzene ring were prepared by a multistage synthesis. It was of interest to synthesize and study the radioprotective activity of similar compounds with different groups, in particular those with a hydroxyl group in the aromatic ring.

We previously [2] obtained several 1-aminomethyl-3-aryladamantanes (IIa-c) — starting compounds for the synthesis of I — by reaction of benzene derivatives with 1-aminomethyl-3-hydroxyadamantane in the presence of concentrated sulfuric acid. This method could not be used to synthesize II with a hydroxyl group in the benzene ring, since sulfonation of the benzene ring occurred at the same time during reaction.

The preparation of 1-(hydroxyaryl)adamantane derivatives starting from unsubstituted adamantane by heating 1-bromoadamantane for many hours with a large excess of phenols has been described in [3, 4].

By heating equimolar quantities of 1-aminomethyl-3-bromoadamantane hydrobromide with phenol, *o*-cresol, and 3,4-xylenol, we obtained 3-(4-hydroxyphenyl)-, 3-(3-hydroxy-4-methyl)-, and 3-(2-hydroxyl-4,5-dimethyl)-1-aminomethyladamantanes IId, IIe, and IIf, respectively, which were isolated as their hydrobromides. The presence of a phenolic hydroxyl group in IId was confirmed by the preparation of its *p*-acetyl derivative (III). The structure of compounds IId-f and III was confirmed from their PMR spectra. The signals from the 14 protons of the adamantane ring occur in the spectrum at high field (δ 1.38-2.14 ppm). In the case of IId the presence of the OH group at the 4-position of the benzene ring was clearly established from the pattern of the signals appearing in the spectrum as two pairs of magnetically equivalent protons. The positions of the substituents in IIe-f were established by correlation with the spectra of the model compounds *o*-cresol and 3,4-xylenol (Table 1).

Reaction of amines IIa-f with chloroacetonitrile in the presence of sodium methoxide gave the hydrobromides of the respective *N*-(3-aryladamant-1-ylmethyl)chloroacetamidines IVa-f, which were converted without further purification to the required products. The synthesis of *N*-[3-(4-bromophenyl)adamant-1-ylmethyl]- (Va), *N*-[3-(4-tolyl)adamant-1-ylmethyl]- (Vb), *N*-[3-(4-hydroxyphenyl)adamant-1-ylmethyl]-(Vd), *N*-[3-(3-hydroxy-4-methyl)adamant-1-ylmethyl]-(Ve), and *N*-[3-(2-hydroxy-4,5-dimethyl)adamant-1-ylmethyl]- (Vf) -acetamidinethiosulfuric acids was achieved by reaction of chloroacetamidines IVa, b, d-f with sodium thiosulfate.



II: R=H·HBr; III: R=H, R^1=CH_3COO; R^2=H; IV: R=C(=NH)CH_2Cl; V: R=C(=NH)CH_2SSO_3H; VI: R=C(=NH)CH_2SPO_3HNa; VII: R=C(=NH)CH_2SH. a) R^1=4-Br, R^2=H; b) R^1=4-CH_3, R^2=N; c) R^1=3-CH_3. R^2=4-CH_3; d) R^1=4-OH, R^2=H; e) R^1=3-OH, R^2=4-CH_3; f) R^1=2-OH, R^2=4,5-$(CH_3)_2$.

Chloroacetamidines IVa, c, d were treated with sodium phosphorothioate to give *N*-[3-(4-bromophenyl)adamant-1-ylmethyl]- (VIa), *N*-[3-(3,4-dimethyl)adamant-1-ylmethyl]- (VIc), and *N*-[3-(4-hydroxyphenyl)adamant-1-ylmethyl]- (VId) -

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TABLE 1. PMR Spectroscopic Data for Compounds IId-f and III*

Compound	δ, ppm, J, Hz (DMSO)					
	ArH	$ArCH_3$	CH_2N	NH_3^+	OH	adamantane and other protons
IId	7,15AB(2H, H^2, H^6) 6,69AB(2H,H^3,H^5) $J_{5,6}$9,0 Hz	—	2,57 s	7,62 br.s	9,14 s	1,14—1,52
IIe	6,68s(1H, H^5) 6,94s(1H,H^6) 7,03s(1H,H^2) $J_{2,6}$ 2 Hz $J_{5,6}$ 8,5 Гц	2,10 s	2,58	7,64 br.s	9,02 s	2,13—1,51
IIf	6,82s(1H, H^6) 6,54s(1H, H^3)	2,07 s 2,08 s	2,57 s	7,70 br.s	8,90 s	2,12—1,38
III	7,40AB(2H,H^2,H^6) 6,98AB(2H, H^3, H^5) $J_{5,6}$9,0 Hz	—	2,60 s	—	—	1,83—1,53 2,25s(3H, CH_3)
o-cresol	6,76dd(1H,H^3) $J_{3,4}$ 8,0Hz,$J_{3,4}$8,0Hz,$J_{3,5}$ 1,0 Hz 6,97td(1H,H^4) $J_{4,5}$ 7,5Hz,$J_{4,6}$ 1,5 Hz 6,67dd(1H, H^5), 7,03dd(1H,H^6)	2,11 s	—	—	9,19 s	—
3,4-xylenol	6,88(1H,H^5) 6,46(1H,H^6) 6,54(1H,H^2) $J_{2,6}$2,5 Hz $J_{5,6}$8,0 Hz	2,11s(3-CH_3) 2,08s(4-CH_3)	—	—	8,95 s	—

*Data for *o*-cresol and 3,4-xylenol are given in Table 1 for comparison.

acetamidinothiophosphoric acids as their monosodium salts. The latter compound could not be isolated in a pure state, and by heating with hydrochloric acid it was converted to *N*-[3-(4-hydroxyphenyl)adamant-1-ylmethyl]mercaptoacetamidine (VIId).

The radioprotective activity of the compounds synthesized was studied in experiments with mice.

EXPERIMENTAL (CHEMICAL)

The PMR spectra were recorded on a WM-250 instrument (Brüker) in DMSO-d_6 solution, with TMS as the internal standard. The course of the reactions and purity of the products were monitored by means of TLC on Silufol UV-254 nm plates (ethyl acetate—hexane—ethanol—ammonia system). The results of elemental analysis of all the compounds synthesized corresponded to the calculated values. The yields, melting points, and empirical formulae are given in Table 2.

3-(2-Hydroxy-4,5-dimethylphenyl)-1-aminomethyladamantane Hydrobromide (IIf). A mixture of 8 g (0.025 mole) of 3-bromo-1-aminomethyladamantane hydrobromide and 3.1 g (0.025 mole) of 3,4-xylenol was heated for 8 h in a bath at 145-150°C. The reaction mixture was cooled, diluted with water, acidified with hydrobromic acid, and evaporated to dryness. After crystallization from a mixture of ethanol and ether, 5.8 g of hydrobromide IIf was obtained.

3-(4-Hydroxyphenyl)-1-aminomethyladamantane (IId) and 3-(3-hydroxy-4-methylphenyl)-1-aminomethyladamantane (IIe) were synthesized in a similar manner.

3-(4-Acetoxyphenyl)-1-aminomethyladamantane Hydrobromide (III). To a suspension of 0.34 g (0.001 mole) of hydrobromide IId in 4 ml of acetic acid saturated with HBr was added 3 ml of acetyl chloride. The mixture was agitated for 2 h, the volatile components were evaporated off under vacuum, and 0.25 g of hydrobromide III was obtained. IR spectrum, ν_{max}, cm^{-1}: 1755 (C=O).

***N*-[3-(2-Hydroxy-4,5-dimethylphenyl)adamant-1-ylmethyl]chloroacetamidine Hydrobromide (IVf).** To a solution of NaOMe (obtained from 0.04 g of Na in 50 ml of methanol) was added 2 g (0.026 mole) of chloroacetonitrile, and the mixture was agitated for 1 h and supplemented with 4.65 g (0.013 mole) of hydrobromide IIf. The mixture was acidified with

TABLE 2. Characteristics of Compounds IId-f, III, Va, b, d-f, VIa, c, and VIId

Compound	Yield, %	mp, °C (ethanol–ether)	Empirical formula
IIa-HBr	83	240—3	$C_{17}H_{23}NO \cdot HBr$
IIIe-HBr	44	243—6	$C_{18}H_{25}NO \cdot HBr$
IIf-HBr	64	251—4	$C_{19}H_{27}NO \cdot HBr$
III-HBr	66	209—12	$C_{19}H_{25}NO_2 \cdot HBr$
Va	63,5	180—183	$C_{19}H_{25}BrN_2S_2O_3$
Vb	95	177—180*	$C_{20}H_{28}N_2O_3S_2$
Vd	60	198—201	$C_{19}H_{26}N_2O_4S_2 \cdot H_2O$
Ve	68	173—7	$C_{20}H_{28}N_2O_4S_2 \cdot 3H_2O$
Vf	80	190—2	$C_{21}H_3N_2O_4S_2$
VIa	60	115—118 (decomp.)	$C_{19}H_{25}BrN_2S_2PO_3Na \cdot 3H_2O$
VIc	96	118—120 (decomp.)	$C_{21}H_{30}N_2PO_3S_2Na \cdot 5H_2O$
VIId-HCl	92	213—6 (decomp.)	$C_{19}H_{27}N_2OS \cdot HCl \cdot 1{,}5H_2O$

*According to [5], mp is 184-186°C.

TABLE 3. Toxicity and Radioprotective Activity of Compounds Synthesized*

Compound	SL_{50}, mg/kg	ED, mg/kg	Survival rate, %
Va	23	7,2	0
Vb	8	4	20
Vd	74	25	40
Ve	>300	100	0
Vf	15	5	10
VIa	20	7	30
VIc	65	20	50
		30	65
VId·HCl	>300	50	13

*Survival rate in the control was 0-5%.

an alcoholic solution of HCl up to pH 4 and then agitated for 2 h at room temperature. After cooling to 10°C, the precipitate that had formed was filtered off and washed with ether, yielding 5.5 g of hydrobromide IVf. The hydrobromides of the other chloroacetamidines IV were synthesized in a similar manner.

***N*-[3-(2-Hydroxy-4,5-dimethylphenyl)adamant-1-ylmethyl]acetamidinothiosulfuric Acid (Vf).** To a suspension of 2 g (0.045 mole) of hydrobromide IVf in 33 ml of methanol was added a solution of 1.1 g (0.045 mole) of sodium thiosulfate in 12 ml of water, and the mixture was refluxed for 40 min and decolorized with activated carbon. On addition of water to the solution, a precipitate was formed, which was washed with ether to yield 1.6 g of thiosulfuric acid Vf..

N-[3-(4-bromophenyl)adamant-1-ylmethyl]- (Va), *N*-[3-(4-tolyl)adamant-1-ylmethyl]- (Vb), *N*-[3-(4-hydroxyphenyl)adamant-1-ylmethyl]- (Vd), and *N*-[3-(3-hydroxy-4-methylphenyl)adamant-1-ylmethyl]- (Ve) - acetamidinothiosulfuric acids were obtained in a similar manner.

Monosodium Salt of *N*-[3-(3,4-dimethylphenyl)adamant-1-ylmethyl]acetamidinothiophosphoric Acid (VIc). To a solution of 0.65 g (0.0017 mole) of the hydrochloride of amidine IVc in 10 ml of ethanol and 7 ml of water was added a solution of 0.7 g (0.00175 mole) of sodium phosphorothioate dodecahydrate in 7 ml of water, and the mixture was agitated in a stream of nitrogen for 40 min. The precipitate that formed was filtered off, washed with water, and dried, yielding 0.9 g of phosphorothioate VIc. In order to purify the precipitate, it was dissolved in methanol and filtered, and a quantity of water equal to half the volume of methanol was slowly added. The precipitate was filtered off and dried with acetone and ether. Phosphorothioate VIa was obtained in a similar manner.

***N*-[3-(4-Hydroxyphenyl)adamant-1-ylmethyl]mercaptoacetamidine Hydrochloride (VIId).** To a solution of 2.5 g (0.006 mole) of amidine IVd in 23 ml of methanol was added a solution of 2.3 g (0.006 mole) of sodium phosphorothioate dodecahydrate in 20 ml of water. The mixture was agitated for 15 min, and the precipitate that formed was filtered off and washed with water, ethanol, and ether. This residue (0.8 g) was then boiled for 15 min with 12 ml of a 10% solution of hydrochloric acid in a stream of argon. The mixture was cooled, and the precipitate was filtered off, washed with water, and dried, yielding 0.7 g of hydrochloride VIId.

EXPERIMENTAL (BIOLOGICAL)

The acute toxicities of the compounds synthesized were determined using the standard method, and the results were treated according to a literature method [1]. The radioprotective activity was investigated in (CBA $\times$ $C_{57}Bl_6$)F_1 strain female mice. The animals were irradiated on a IGUR unit with capacity 66 and 168 Gy/min, receiving doses of 8 and 8.2 Gy. The compounds were administered ip in aqueous solution 15 min before irradiation. The animals were monitored for 30 days.

It follows from Table 3 that most of the compounds have relatively high toxicity. Thiosulfate Vd and phosphorothioate VIc exhibited the highest radioprotective activities.

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