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ADAMANTANE DERIVATIVES.

V. SYNTHESIS AND RADIOPROTECTIVE PROPERTIES OF N-ADAMANTYL

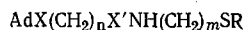
DERIVATIVES OF AMINOTHIOLS

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The synthesis of new compounds containing the structure of mercaptoethylamine is a promising direction in the search for new synthetic radioprotective agents. It is known that the introduction at the nitrogen atom of mercaptoethylamine of aminoalkyl [1] and adamantyl [2] substituents contributes a strengthening of the anti-radiation action.

The synthesis has been carried out and the radioprotective properties have been studied for the adamantyl substituted compounds of general formula (1).



I

Ad = adamantyl-1; X = NH, CH₂; X' = CH₂, CO;

R = H, PO₃H₂, C(=NH)NH₂·HBr; n = 0, 1; m = 2, 3

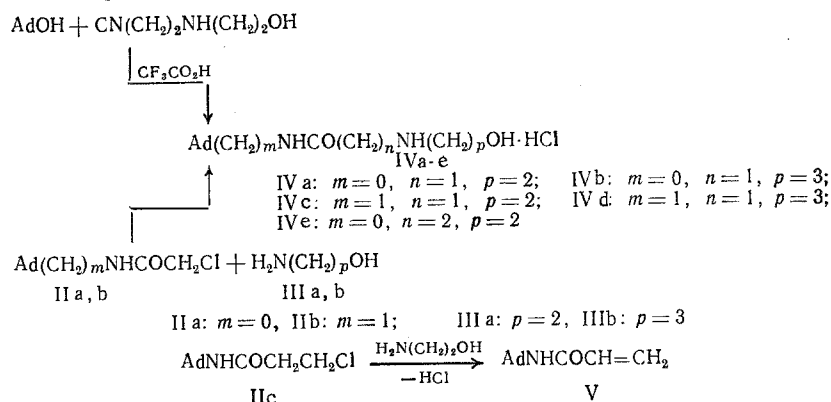
The initial N-(adamantyl-1)-chloroacetamide (IIa), N-(adamantyl-1-methyl)chloroacetamide (IIb), and N-(adamantyl-1)-3-chloropropionamide (IIc) were obtained by the known method of [3]. The aminoalkyl chlorides (IIa, b) were converted by reaction with aminoethanol (IIIa) and 3-aminopropanol (IIIb) into N-(adamantyl-1)-2-(2-hydroxyethylamino)acetamide (IVa), N-(adamantyl-1)-2-(3-hydroxypropylamino)acetamide (IVb), N-(adamantyl-1-methyl)-2-(2-hydroxyethylamino)acetamide (IVc), and N-(adamantyl-1-methyl)-2-(3-hydroxypropylamino)acetamide (IVd) isolated as the hydrochlorides. It was shown with the aid of PMR spectra that dialkylation took place at a small excess of alcohol (III) [for example, at III/II = (1-2.5):1] which was detected by the increase in the number of protons of the adamantane nucleus in relation to the number of protons of the alkylene groups. At a 3-5-fold quantity of hydroxyalkylamine (III) practically pure monoalkylation products (IV) were obtained. Reaction was carried out in boiling isopropyl alcohol for 4-8 h.

On interacting (IIc) with hydroxyamine (IIIa) no alkylation product was obtained but the N-(adamantyl-1)-acrylamide (V), i.e., under these conditions in the presence of base (IIIa) dehydrohalogenation occurred as is characteristic of β-halogen derivatives. The IR and PMR spectra of the isolated product (V) were identical with the literature data of [4].

The hydrochloride of N-(adamantyl-1)-3-(2-hydroxyethylamino)propionamide (IVe) was synthesized by the Ritter reaction from adamantan-1-ol and 3-(2-hydroxyethylamino)propionitrile in the presence of trifluoroacetic acid [5].

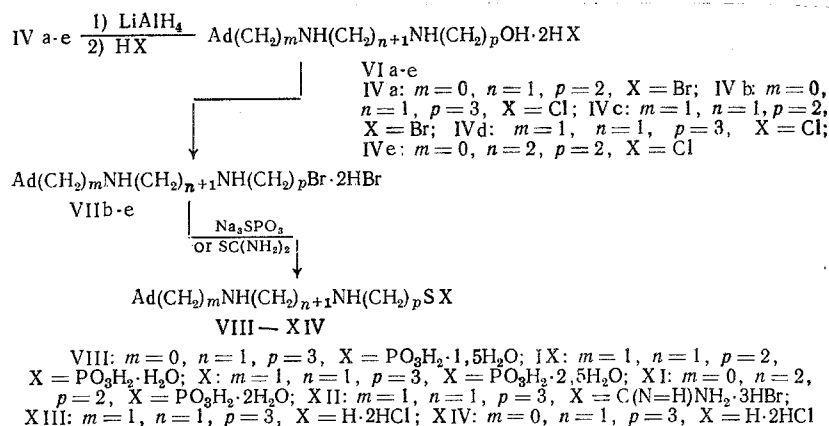
There were absorption bands in the IR spectra of amides (IVa-e) in the region of 3360-3460 cm⁻¹ characteristic of hydroxyl groups, at 3280-3100 cm⁻¹ characteristic of NH groups, and at 1655-1680 and 1555-1580 cm⁻¹ assigned to amide I and amide II.

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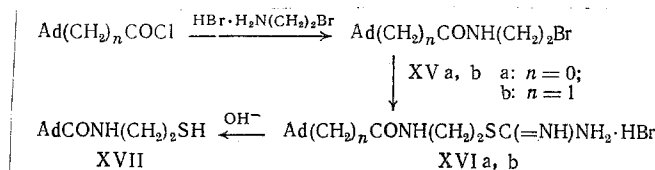


The hydroxyalkylaminoamides (IVa-e) were reduced with lithium aluminum hydride in tetrahydrofuran to the corresponding diamines (VIa-e). The purity of products was checked by IR spectra for the absence of amide absorption bands in the 1550-1680 cm^{-1} region.

The hydroxy group in diamines (VIb-e) was replaced by bromine by the action of phosphorus tribromide in benzene in the presence of catalytic quantities of dimethylformamide (DMF) or by boiling with 48% hydrobromic acid. The diamines (VIb, e) and (VIId, c), respectively, were isolated. By interacting bromo derivatives (VIb-e) with trisodium thiophosphate or (VIId) with thiourea the thiophosphoric acids (VIII-XI) and the isothiuronium salt (XII) were obtained. Thiophosphoric acids (VIII) and (X) were hydrolyzed with dilute hydrochloric acid to the dihydrochlorides of N-(adamantyl-1-methyl)-N'-(3-mercaptopropyl)ethylene diamine (XIII) and N-(adamantyl-1)-N'-(3-mercaptopropyl)ethylene diamine (XIV).



N-(2-Bromoethyl)-2-(adamantyl-1)-acetamide (XVb) was obtained by acylating the hydrobromide of 2-bromoethylamine with adamantan-1-acetic acid chloride. By the action of thiourea in boiling isopropyl alcohol (XVb) was converted into S-[2-(adamantan-1-acetamido)ethyl]isothiuronium bromide (XVIb). Similarly starting from the acid chloride of adamantan-1-carboxylic acid, N-(2-bromoethyl)adamantan-1-carboxamide (XVa) and S-[2-(adamantan-1-carboxamido)ethyl]isothiuronium bromide (XVIa) were obtained. The latter was converted by alkaline hydrolysis into N-(2-mercaptoethyl)adamantan-1-carboxamide (XVII) [6]. Data of elemental analysis, yields, and melting points of compounds obtained for the first time are given in Tables 1-3.



EXPERIMENTAL CHEMISTRY*

IR spectra were recorded on UR-20 (East Germany) and Perkin-Elmer model 180 (Switzerland) instruments in KBr disks, PMR spectra were taken on a Varian HA-100 instrument, internal standard was HMDS.

*The authors are grateful to N. V. Smirnov and Yu. T. Orlov for carrying out the elemental analysis of the studied compounds.

TABLE 1. Hydroxy Derivatives of Adamantane (IVa-e) and (VIa-e)

Com- pound	Yield, %	mp, °C	Found, %				Empirical formula	Calculated, %				R_f
			C	H	N	Cl		C	H	N	Cl	
IVa	62	208-210	58,26	8,77	...	12,42	$C_{14}H_{24}N_2O_2 \cdot HCl$	58,22	8,72	...	12,27	0,60
IVb	86	167-168	59,40	8,94	...	11,55	$C_{15}H_{28}N_2O_2 \cdot HCl$	59,46	8,98	...	11,70	0,51
IVc	73	178-179	59,48	9,25	9,29	11,29	$C_{15}H_{28}N_2O_2 \cdot HCl$	59,49	8,98	9,24	11,70	0,65
IVd	77	169-170	60,44	9,50	8,43	...	$C_{15}H_{28}N_2O_2 \cdot HCl$	60,65	9,22	8,84	...	0,48
IVe	60	147-149	59,44	8,96	9,24	11,67	$C_{15}H_{28}N_2O_2 \cdot HCl$	59,49	8,98	9,24	11,70	0,35
VIa	79	250-251	41,82	7,05	6,87	...	$C_{14}H_{20}N_2O \cdot 2HBr$	42,20	7,05	6,88
VIb	92	210-211	55,35	9,24	...	21,44	$C_{15}H_{28}N_2O \cdot 2HCl$	55,38	9,29	...	21,79	...
VIc	30	293-294	43,45	7,30	6,75	...	$C_{15}H_{28}N_2O \cdot 2HBr$	43,49	7,30	6,76
VId	86	260-264	56,54	9,50	8,36	20,81	$C_{16}H_{30}N_2O \cdot 2HCl$	56,03	9,51	8,25	20,89	...
VIe	51	263-264	55,37	9,32	...	21,44	$C_{15}H_{28}N_2O \cdot 2HCl$	55,38	9,29	...	21,76	...

TABLE 2. Bromo Derivatives of Adamantane (VIIb-e) and (XVb)

Com- pound	Yield, %	mp, °C	Found, %				Empirical formula	Calculated, %				R_f
			C	H	N	Br		C	H	N	Br	
VIIb	85	235-238	37,86	6,18	5,55	...	$C_{15}H_{28}BrN_2 \cdot 2HBr$	37,76	6,12	5,87
VIIc	94	288-289	39,25	6,50	5,59	32,43	$C_{16}H_{30}BrN_2 \cdot 2HBr$	39,13	6,36	5,70	32,54	0,83
VIIe	76	269 (with decomp.)	37,74	6,30	5,99	33,64	$C_{16}H_{30}BrN_2 \cdot 2HBr$	37,76	5,57	5,57	33,49	...
XV	67	121-122	56,20	56,20	7,40	4,63	$C_{14}H_{22}BrNO$	56,01	7,39	4,66	...	0,15

TABLE 3. Amino-thiol Derivatives of Adamantane (VIII-XIV)

Com- pound	Yield, %	mp, °C	Found, %				Empirical formula	Calculated, %				R_f
			C	H	N	S		C	H	N	S	
VIII	72	240 (with decomp.)	47,72	8,70	...	8,35	$C_{15}H_{28}N_2O_2PS \cdot 1,5H_2O$	47,98	8,59	...	8,53	0,69
IX	59	238 (with decomp.)	49,38	8,61	7,58	...	$C_{15}H_{28}N_2O_2PS \cdot H_2O$	49,16	8,52	7,64	...	0,85
X	67	220 (with decomp.)	50,23	8,45	8,45	...	$C_{16}H_{34}N_2O_2PS \cdot 2,5H_2O$	50,61	8,74	7,34	...	0,23
XI	96	245-246	46,88	8,60	7,57	8,53	$C_{15}H_{28}N_2O_2PS \cdot 2H_2O$	46,86	8,65	7,29	8,34	0,60
XII	75	231-232	35,96	6,28	9,98	...	$C_{17}H_{32}N_4S \cdot 3HBr$	35,99	6,22	9,88	...	0,58
XIII	90	274-276	54,00	9,01	7,89	9,21	$C_{16}H_{30}N_2S \cdot 2HCl$	54,07	9,08	7,88	...	0,58
XIV	40	249-251	52,53	8,77	8,34	9,35	$C_{15}H_{28}N_2S \cdot 2HCl$	52,77	8,66	8,21	9,36	0,50
XVb	64	129-130	47,62	7,04	11,15	8,58	$C_{15}H_{28}N_2S \cdot HBr$	47,79	6,95	11,15	8,66	...

Silufol UV-254 plates were used for TLC, R_f values for compounds (IVa-e) were determined in methyl alcohol, for (VIIId, XI, XII, XV) in the system isopropyl alcohol-ammonia (5:1), for (VIII, IX, XIV) in the system methyl alcohol-chloroform-ammonia (2:1:1), and for (X, XIII) in the system ethyl alcohol-ammonia-water (7:1:2).

N-(Adamantyl-1)-2-(2-hydroxyethylamino)acetamide Hydrochloride (IVa). Monoethanolamine (40 g: 0.65 mole) was poured into a solution of (IIa) (30 g: 0.132 mole) in isopropyl alcohol (400 ml) and the mixture boiled for 4 h. The alcohol was distilled off, water (700 ml) was added to the residue, the solution was filtered, and extracted with benzene (3×500 ml). The extract was dried with anhydrous sodium sulfate, evaporated to 1/10 volume, and was treated with an ether solution of hydrogen chloride to acid reaction to methyl orange. The precipitated solid was filtered off, washed with ether, and (IVa) (23.4 g) was obtained. PMR spectrum ($CF_3 \cdot CO_2H$), δ , ppm: 1.32 s (6H, Ad), 1.64 s (6H, Ad), 1.70 s (3H, Ad), 3.15 m (2H, NCH_2CH_2OH), 3.77 m (4H, CH_2OH), $NHCOCH_2$, 6.45 (1H, AdNH), 7.40 (2H, $CH_2NH_2CH_2$).

The PMR spectrum of (IVb) was obtained similarly (CF_3CO_2H), δ , ppm: 1.31 s (6H, Ad), 1.65 s (9H, Ad), 2.05 m (2H, $CH_2CH_2CH_2$), 2.98 m (2H, NCH_2CH_2), 3.61 m (2H, CH_2OH), 4.12 m (2H, $COCH_2N$), 6.50 (1H, CONH), 7.40 (2H, NH_2) (IVc-e).

N-(Adamantyl-1-methyl)-N'-(2-hydroxyethyl)ethylene Diamine Dihydrobromide (VIc). Lithium aluminum hydride (19.0 g: 0.5 mole) was added gradually in a stream of nitrogen to a suspension of (IVc) (28.8 g: 0.108 mole) in tetrahydrofuran (800 ml). The mixture was boiled for 3 h, left overnight, decomposed with cooling with water (19 ml), 15% potassium hydroxide solution (19 ml), and with water (57 ml). The solid was filtered off, the filtrate dried over anhydrous sodium sulfate, and evaporated to 1/5 volume. An ether solution of hydrogen bromide was added to the residue to acid reaction to methyl orange. The precipitated solid was filtered

off and recrystallized from methyl alcohol. Compound (VIc) (13.4 g) was obtained. PMR spectrum ($\text{CF}_3\text{CO}_2\text{H}$), δ , ppm: 1.28 bs (6H), 1.33 bs (6H), 1.60 bs (3H, Ad), 2.48 m (3H_2 , Ad CH_2N , OH), 3.13 m (2H, $\text{NHCH}_2\text{CH}_2\text{OH}$), 3.49 m (4H, N $\text{HCH}_2\text{-CH}_2\text{NH}$), 3.84 m (2H, CH_2OH), 6.9 (2H, Ad CH_2NH_2), 7.7 (2H, NH_2).

N-(Adamantyl-1)-N'-(2-hydroxyethyl)ethylene Diamine Dihydrobromide (VIa), N-(Adamantyl-1)-N'-(3-hydroxypropyl)ethylene Diamine Dihydrochloride (VIb), N-(Adamantyl-1-methyl)-N'-(3-hydroxypropyl)ethylene Diamine Dihydrochloride (VIId), and N-(Adamantyl-1)-N'-(2-hydroxyethyl)propylene Diamine Dihydrochloride (VIe). These were obtained similarly. PMR spectrum of (VIb) in CF_3COOH , δ , ppm: 1.35 bs (6H, Ad), 1.61 bs (6H, Ad), 1.79 and 1.85 (sum of two signals, 3H from Ad and 2H from $\text{CH}_2\text{CH}_2\text{CH}_2$), 3.10 m (2H, NHCH_2 , CH_2CH_2), 3.66 t (2H, CH_2OH), 3.36 m (4H, $\text{NCH}_2\text{CH}_2\text{N}$), 7.0 (2H, Ad NH), 7.6 (2H, $\text{CH}_2\text{NH}_2\text{CH}_2$).

N-(Adamantyl-1)-N'-(2-bromoethyl)propylene Diamine Dihydrobromide (VIIe). Phosphorus tribromide (1.48 g; 0.005 mole) and DMF (0.2 ml) were added dropwise in a stream of nitrogen to a suspension of (VIe) (2.6 g; 0.008 mole) in benzene (50 ml) and the mixture was boiled for 4 h. The solid was filtered off, washed with benzene, and recrystallized from ethyl alcohol. Compound (VIIe) (2.2 g) was obtained.

N-(Adamantyl-1)-N'-(3-bromopropyl)ethylene Diamine Dihydrobromide (VIIb). This compound was obtained similarly. N-(Adamantyl-1)-N'-(2-bromoethyl)ethylene diamine (VIIa) was not obtained under these conditions.

N-(Adamantyl-1-methyl)-N'-(3-bromopropyl)ethylene Diamine Dihydrobromide (VIId). A mixture of (VIId) (2.9 g) and 48% hydrobromic acid (20 ml) was boiled for 4 h periodically distilling off water, then cooled, and filtered. The solid was washed with alcohol and with ether. Compound (VIId) (4.0 g) was obtained.

N-(Adamantyl-1-methyl)-N'-(2-bromoethyl)ethylene Diamine Dihydrobromide (VIIa). This compound was obtained similarly and was used without purification for the synthesis of the derived thiophosphoric acid (IX).

S-[N-[N-(Adamantyl-1-methyl)-2-aminoethyl]-3-aminopropyl] thiophosphoric Acid (X). Sodium thiophosphate dodecahydrate (4.2 g; 0.01 mole) was added in portions to a solution of (VIId) (5.0 g; 0.01 mole) in a 20% aqueous solution of DMF (100 ml). The reaction was continued until the absence of thiophosphate anion from the reaction mixture according to the qualitative reaction for this ion. The precipitated solid was filtered off, washed with water, and with acetone, and was dried in vacuum. Compound (X) (2.72 g) was obtained.

S-[N-[N-(Adamantyl-1)-2-aminoethyl]-3-aminopropyl] thiophosphoric Acid (VIII), S-[N-[N-(Adamantyl-1-methyl)-2-aminoethyl]aminoethyl] thiophosphoric Acid (IX) and S-[N-[N-(Adamantyl-1)-3-aminopropyl]-aminoethyl]thiophosphoric Acid (XI). These compounds were obtained in a similar manner.

S-[N-[N-(Adamantyl-1-methyl)-2-aminoethyl]-3-aminopropyl] isothiuronium Dihydrobromide (XII). A mixture of (VIId) (2.0 g; 0.0047 mole) and thiourea (0.358 g; 0.0046 mole) in *n*-butyl alcohol (20 ml) was boiled for 3 h. After cooling, the precipitated solid was filtered off, washed with acetone, and recrystallized from methyl alcohol. In this way compound (XII) (2.0 g) was obtained.

N-(Adamantyl-1-methyl)-N'-(3-mercaptopropyl)ethylene Diamine Dihydrochloride (XIII). A 15% hydrochloric acid solution (40 ml) was added to (X) (4.3 g) and the mixture was kept on a boiling water bath for 30 min in a stream of argon. The solid precipitated after cooling was filtered off, washed with water, and dried over phosphorus pentoxide. Compound (XIII) (3.46 g) was obtained.

Mercaptan (XIX). Mercaptan (XIX) was obtained similarly.

S-[2-[2-(Adamantyl-1)-acetamido]ethyl] isothiuronium Bromide (XVb). A mixture of (XVb) (5.0 g; 0.0166 mole) and thiourea (1.26 g; 0.0166 mole) in isopropyl alcohol (50 ml) was boiled for 10 h, cooled, the precipitated solid was filtered off, and compound (XVb) (4.0 g) was obtained.

N-(2-Bromoethyl)-2-(adamantyl-1)-acetamide (XVb). A mixture of adamantan-1-acetic acid chloride (6.0 g; 0.0292 mole), 2-bromoethylamine hydrobromide (5.6 g; 0.0282 mole), and xylene (30 ml) was boiled for 2 h. The precipitated solid was filtered off, recrystallized from toluene, and (XVb) (5.66 g) was obtained.

The synthesis of S-[2-(adamantyl-1-methylamino)ethyl]thiosulfuric acid (XVIII) and N-(2-mercaptopropyl)-adamantyl-1-methylamine hydrochloride (XIX) has been described by us previously in [7]. S-[2-(Adamantyl-1-amino)ethyl]thiophosphoric acid (XX) was obtained by the known procedure of [2].

EXPERIMENTAL BIOLOGY

The radioprotective effectiveness of compounds was studied in F_1 ($\text{CBA} \times \text{C}_{57}\text{Bl}$) hybrid mice of weight 19-23 g. Preparations were administered to animals as aqueous solutions or suspensions with carboxymethyl-

TABLE 4. Radioprotective Activity and Toxicity of Adamantane Derivatives

Compound	Mode of administration	LD ₅₀ , mmole/kg	Radioprotective action		
			dose, mmole/kg	number of animals	
				total	% surviving
VIII	Intraperitoneally	0,38	0,20	10	10
IX	"	0,37	0,10	10	10
			0,12	15	0
X	Parenterally	1,38	0,36	15	0
			0,21	15	46
XI	Intraperitoneally	0,49	0,052	15	6
			0,72	10	30
XII	Parenterally	1,67	0,18	10	10
			0,11	15	0
XIII	Intraperitoneally	0,21	0,065	15	13
			0,57	10	22
XIV	"	0,16	0,14	10	20
			0,10	10	0
XVIa	"	0,32	0,025	10	0
			0,12	15	0
XVIIb	"	0,50	0,03	15	0
			0,22	15	20
XVIII	"	0,67	0,053	15	14
			0,30	20	0
XIX	"	3,22	1,30	15	20
			0,325	15	20
XX	Intraperitoneally	2,90	1,30	60	0
			0,36	20	5
XX	"	0,52	0,25	30	60
			0,12	30	30
XX	Parenterally	0,66	0,30	20	65
			—	—	—
Control		—	—	50	0

cellulose and Tween-80 in a volume of 0.2 ml intraperitoneally at 15 min and parenterally at 15-30 min before irradiation.

Irradiation was carried out on gamma equipment EGO-2 at a dose of 950 R at a rate of 150-250 R/min. The effectiveness of compounds was judged by the survival of animals on the 30th day after irradiation.

The toxicity of substances was determined in white random-bred male mice of weight 19-26 g. The LD₅₀ was calculated by the method of V. I. Suslikov and coauthors [8]. The results of experiments are given in Table 4.

On comparing the toxicity of compounds (VII-XIV) with the N²-unsubstituted analogs (I) [1] attention is drawn by the fact that the introduction of an adamantyl substituent led to a sudden 5-10-fold increase in toxicity.

The adamantyl derivatives (XVIa) and (XVII) possessed weak radioprotective properties which are seemingly linked with their slow hydrolysis under conditions in vivo since cysteamine at a concentration of 1 mmole · kg⁻¹ possessed marked antiradiation effectiveness [9]. At the same time their toxic action was displayed at an early time which indicated their rapid absorption into the organism.

Of the considered compounds (VIII-XIV) only compound (X) was somewhat soluble (5%) in water and it alone possessed moderate activity. Compound (XX) which was described previously and was taken as the standard was very soluble in water and possessed marked radioprotective effectiveness on both modes of administration. Attention is drawn by the similarity of the toxicity values on intraperitoneal and on parenteral administration which makes it possible to suggest that this compound is rapidly absorbed from the gastrointestinal tract. Evidently for the display of antiradiation activity in the given class of compounds solubility in water is obligatory.

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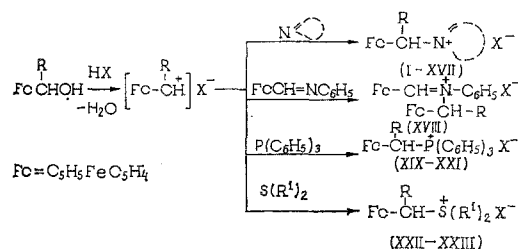
SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF ONIUM COMPOUNDS CONTAINING α -FERROCENYL RADICAL

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Among quaternary ammonium salts, effective preparations have been discovered with a broad spectrum of antimicrobial activity [1-3]. Quaternary salts containing one or two higher aliphatic radicals are fairly effective bactericides, and the introduction of a double or triple bond [4], or a cyclopropane ring [5] into the aliphatic chain appreciably increases their activity. We took into account the unsaturated character of the ferrocenyl group and the fact that some compounds in the ferrocene series have interesting biological activity [6], and in the present work, for the first time carried out the synthesis and evaluation of the antimicrobial action of a series of α -ferrocenylalkylated onium compounds, in particular, ammonium (I-XVIII, XXIV), phosphonium (XIX-XXI), and sulfonium (XXII, XXIII) salts.

The synthesis of the 23 compounds of this series (Table 1) was carried out by the reaction of α -hydroxyferrocenyl derivatives with nucleophilic substrates in a methylene chloride aqueous solution of an HX acid ($X = BF_4, ClO_4$) two-phase system, with vigorous stirring, and at room temperature. Under these conditions there is an α -ferrocenylalkylation of several heterocyclic compounds with a tertiary nitrogen atom and ferrocenyl-aniline (a Schiff base) at the nitrogen atom, triphenylphosphine at the phosphorus atom, and sulfides at the sulfur atom. Thus, previously unknown α -ferrocenylalkyl onium compounds I-XXIII are obtained in high yields.



Synthesized compounds I-XXIII are colored crystalline compounds, which are soluble in polar solvents (water, ethanol, nitromethane) and insoluble in ether and benzene; on heating they melt with decomposition. Their structure is confirmed by the data of elemental analysis (see Table 1), IR spectra, in which absorption bands are present, characteristic of the ferrocenyl ring in the 1405, 1105, 1000, and 830 cm^{-1} region [7], and of the aromatic ring in the 1600-1500 cm^{-1} region [8]. The electronic absorption spectra of the compounds are characterized by two absorption maxima in the UV region at 240-260 and 320-340 nm, and also by a broad absorption maximum in the visible part of the spectrum at 420-450 nm.

The structure of compounds I-XXIII is also confirmed by the fact that during alkaline hydrolysis in water, these compounds decompose into the initial α -hydroxyferrocenyl derivatives and the corresponding bases, which were isolated and identified (bases in the form of known iodomethylates) according to their melting points.

