SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF PHENOTHIAZINE DERIVATIVES CONTAINING THE ADAMANTYL RADICAL

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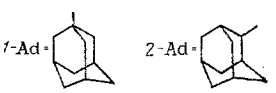
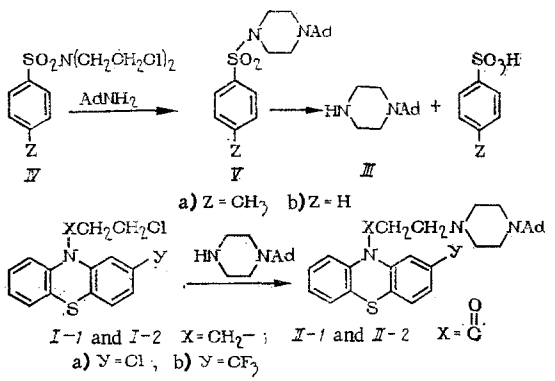
The introduction of a bulky and highly lipophilic radical into the molecule of a physiologically active substance leads, in a number of cases, to a considerable change in the magnitude and character of its biological activity. This has been shown for compounds which have hypoglycemic [1, 2], curare-like [3, 4, 5], hormonal [6], and other forms of pharmacological activities [7]. In this connection it was of interest to ascertain how the introduction of adamantyl radicals affects the activity of compounds of the phenothiazine series, whose 10-dialkylaminoalkyl derivatives have neuroleptic properties [8], while the 10-dialkylaminoacyl derivatives display activity with respect to the cardiovascular system [9].

For pharmacological study we chose the derivatives I and II, which contain an N-adamantylpiperazinyl fragment in the side chain, in connection with the fact that the corresponding N-methylpiperazinyl alkyl and acyl derivatives had the types of pharmacological activity indicated above (see [10, 11]).

As substituents in the 2-position of the phenothiazine ring we used the chloro- or trifluoromethyl groups; both 1- and 2-adamantyl derivatives were prepared (the designations type I-1 and I-2 are used here and throughout to show the presence of 1- or 2-adamantyl radicals in compounds).



N-(Adamantyl)piperazines (III-1 and III-2) and the adamantyl derivatives of phenothiazine I-1, I-2, II-1, and II-2 were prepared by the following scheme:



By the action of the benzenesulfonamide derivative IVa on 1-aminoadamantane the sulfonamide V-1a was obtained; heating 1- or 2-aminoadamantanes with N-toluenesulfonyldi(β-chloroethyl)amine (IVb) in an organic solvent in the presence of a hydrogen chloride acceptor led to the sulfonamides V-1b or V-2b (Table 1). The sulfonamides V obtained were hydrolyzed to the N-(adamantyl)piperazines III-1 and III-2,

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TABLE 1. N^1-Adamantyl-N^2-(Arylsulfonyl)piperazines

Compound	Base							Hydrochloride			
	yield (%)	mp (in deg)*	found (%) N	found (%) S	empirical formula	calc. (%) N	calc. (%) S	mp (in deg)*	Cl^- found (%)	empirical formula	Cl^- calc. (%)
V-1a	87,5	205—7	7,58	8,34	$C_{20}H_{28}N_2O_2S$	7,77	8,89	284—6	8,95	$C_{20}H_{28}N_2O_2S \cdot HCl$	8,92
V-1б	80,7	215—7	7,55	8,54	$C_{21}H_{30}N_2O_2S$	7,48	8,58	276—8	8,49	$C_{21}H_{30}N_2O_2S \cdot HCl$	8,49
V-2б	91,5	189—190	7,32	8,42	$C_{21}H_{30}N_2O_2S$	7,48	8,58	272—5	8,59	$C_2H_{31}ClN_2O_2S$	8,49

*The bases were recrystallized from ethanol; the hydrochlorides, from water.

TABLE 2. Adamantyl Derivatives of 10-Substituted Phenothiazines

Compound	Base							Hydrochloride			
	yield (%)	mp (deg)*	found (%) C	found (%) H	empirical formula	calc. (%) C	calc. (%) H	mp (deg)*	Cl^-, found (%)	empirical formula	Cl^-, calc. (%)
I-1a	67,6	117—9	70,32	7,32	$C_{29}H_{36}ClN_3S$	70,48	7,34	248—250	12,16	$C_{29}H_{36}ClN_3 \cdot 2HCl$	12,50
I-1б	69,6	125—6	68,31	6,32	$C_{30}H_{36}F_3N_3S$	68,29	6,88	248—51	12,19	$C_{30}H_{36}F_3N_3 \cdot 2HCl$	11,80
I-2a	71,5	139—141	70,48	7,34	$C_{29}H_{36}ClN_3S$	70,48	7,34	273—6	12,51	$C_{29}H_{36}ClN_3S \cdot 2HCl$	12,50
I-2б	47,7	60—2	68,40	6,94	$C_{30}H_{36}F_3N_3S$	68,29	6,88	299—301	11,76	$C_{30}H_{36}F_3N_3S \cdot 2HCl$	11,80
II-1a	49,4	150—2	68,77	6,77	$C_{29}H_{34}ClN_3OS$	68,54	6,69	233—236	12,71	$C_{29}H_{34}ClN_3OS \cdot 2HCl$	12,23
II-1б	62,3	73—5	66,66	6,33	$C_{30}H_{34}F_3N_3OS$	66,77	6,33	198—200	11,47	$C_{30}H_{34}F_3N_3OS \cdot 2HCl$	11,57
II-2a	74,2	78—80	68,24	7,28	$C_{29}H_{34}ClN_3OS$	68,54	6,69	240—5	12,04	$C_{29}H_{34}ClN_3OS \cdot 2HCl$	12,23
II-2б	89,2	76—8	67,20	6,04	$C_{30}H_{34}F_3N_3OS$	26,77	6,33	209—210	11,55	$C_{30}H_{34}F_3N_3OS \cdot 2HCl$	11,57

*The bases were recrystallized from aqueous ethanol; the hydrochlorides, from water.

fusion of which with 10-(γ-chloroprophyl)-2--phenothiazine (Y is Cl or CF_3) gave 10'-{γ-N'-(adamantyl)-piperazinyl-N^2]-propyl}-2-Y-phenothiazines (I-1a,b or I-2a,b). By boiling III-1 or III-2 in amyl alcohol in the absence of a hydrogen chloride acceptor with 10-(β-chloropropionyl)-2-Y-phenothiazine we synthesized the 10'-{β-[N'-(adamantyl)piperazinyl-N^2]-propionyl}-2'-Y-phenothiazines (II-1a,b and II-2a, b; see Table 2).

In the pharmacological study of the compounds synthesized, in the laboratory of pharmacology of the cardiovascular system of the Institute of Pharmacology of the Academy of Medicinal Sciences of the USSR (Professors N. V. Kaverina and G. G. Chichikanov) it was found that the acyl derivatives of phenothiazine II-1 and II-2 have a vasodilating action. In experiments on cats narcotized with urethane and chloralose in a dose of 1.5 to 3 mg/kg (introduced intravenously), the blood circulation increased by 50 to 100%, and absorption of oxygen by the blood was reduced. Phenothiazine compounds not containing adamantyl radicals have similar properties [9]. In testing the compounds prepared for psychotropic activity in the psychopharmacology laboratory of the same institute (Yu. I. Vikhlyaev and O. V. Ul'yanova), in their ability to remove phenamine-caused sterotypy and cause hypothermy in experiments on mice, these preparations are inferior to the phenothiazine derivatives used at present.

EXPERIMENTAL*

N^1-(1-Adamantyl)-N^2-(benzenesulfonyl)piperazine (V-1a). To a mixture of IVa, 10 ml of amyl alcohol and 1.3 g of anhydrous sodium carbonate was added a solution of 2 g of 1-aminoadamantane in 10 ml of amyl alcohol with heating and stirring, and the mixture was boiled for 24 h. Acetone (100 ml) was added to the cooled mixture; it was filtered; and the precipitate of V-1a was washed with water, acetone, and ether. Compounds V-1b and V-2b were prepared similarly. Physical constants and analytical data are given in Table 1.

N-(1-Adamantyl)piperazine (III-1). A mixture of 2 g V-1b and 60 ml of 20% hydrochloric acid was boiled for about 10 h, until the precipitate completely dissolved. The mixture was cooled, the precipitate which fell was filtered off and dissolved in ether. The dried ether solution was filtered, the solvent was stripped off, and III-1 was obtained as a residue; yield 1 g (84.5%), mp 83-85° (sublimes). Found, %: C 76.15; H 10.88; N 12.72. $C_{14}H_{24}N_2$. Calculated, %: C 76.29; H 10.99; N 12.72. Hydrochloride: mp 290-292°. Found, %: Cl^- 23.74. $C_{14}H_{24}N_2 \cdot HCl$. Calculated, %: Cl^- 24.11.

Compound III-2 was prepared similarly, yield 90%, mp 71-73° (sublimes). Found, %: C 75.98; H 10.98; N 12.73. $C_{14}H_{24}N_2$. Calculated, %: C 76.29; H 10.99; N 12.72. Hydrochloride: mp 312-316°. Found: Cl^- 23.98. $C_{14}H_{24}N_2 \cdot 2HCl$. Calculated, %: Cl^- 24.11.

10-{γ-[N^1-(1-Adamantyl)piperazinyl-N^2]-propyl}-2-chlorophenothiazine (I-1a). A mixture of 0.003 mole of III-1 and 0.003 mole of 10-(γ-chloropropyl)-2-chlorophenothiazine was heated for 2 h at 170°. The melt was triturated with 20 ml of acetone, and 50 ml of ether plus ether saturated with hydrogen chloride was added to pH 1.0; the precipitate which fell was filtered off, it was dissolved in water with heating, 0.5 g of activated charcoal was added, the solution was filtered and made alkaline with ammonia, and the I-1a was extracted with ether; yield, 1.1 g. The remaining type I compounds and their hydrochlorides were prepared similarly. Their physical constants and analytical data are given in Table 2.

10^1-{β-[-N^1- 2-Adamantyl)piperazinyl-N^2]-propionyl}-2^1-trifluoromethylphenothiazine (II-2b). To a mixture of 5.72 g of 10-(β-chloropropionyl)-2^1-trifluoromethylphenothiazine and 4 g of III-2 was added 5 ml of amyl alcohol, and the mixture was boiled under reflux for 5 h. After cooling, 100 ml of absolute ether was added, and ether saturated with hydrogen chloride was added to pH 1.0; the precipitate was filtered off, it was dissolved in water with heating, 0.5 g of activated charcoal was added, the solution was filtered, the filtrate was made alkaline with sodium bicarbonate, and the II-2b was extracted with ether. The remaining type II compounds were prepared similarly (see Table 2).

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*Uncorrected melting points are given.

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