N-ADAMANTYL DERIVATIVES OF AROMATIC AMINES. PART II.[1] SYNTHESIS AND NEUROTROPIC ACTIVITY OF N-(5-R- OR 6-R-ADAMANT-2-YL)ARYLAMINES

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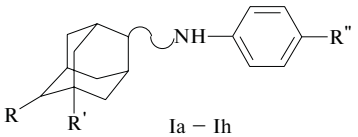
The group of N-(adamant-2-yl)arylamines contains the drug bromantan – a highly active psycho- and immunostimulant [1 – 5]. As is known, the main metabolites of adamantane derivatives contain a hydroxy group at the nodal position of the adamantane nucleus [6].

The aim of this study was to synthesize and characterize a series of previously unreported 2,5- and 2,6-disubstituted adamantanes (Ia – Ih):



Ia – Ih

Here, R, R′, and R″ are the substituents indicated in Table 1. Initial compounds in the synthesis of drugs Ia – Ih were 5-hydroxyadamant-2-one (II), 5-chloroadamant-2-one (III), 2,6-dioxoadamantane (IV), and 5-acetylaminoadamant-2-one (V). Hydroxyketone II and diketone IV were obtained through oxidation of adamantanone with a mixture of nitric and sulfuric acids [7]. Chloroketone III was synthesized with a high yield from hydroxyketone II under the action of thionyl chloride [7]. 5-Acetylaminoadamant-2-one (V) was obtained from II through the Ritter reaction [4].

The interaction of initial compounds II – V with unsubstituted aniline and *para*-chloro, bromo, and fluoro-anilines was studied under Leuckart reaction conditions. The reactions of ketones II, III, and V with anilines were conducted at 130 – 160°C in the presence of concentrated formic acid, at a ketone – amine ratio of 1 : 2. The resulting formyl derivatives were subjected to acid hydrolysis. The synthesis of compound Ia proceeded more smoothly when aniline was replaced by its formyl derivative. The bases Ia – Ih, as well as their hydrochlorides, appear as white crystalline substances. The yields, reaction durations, TLC characteristics, and melting points of compounds Ia – Ih and their hydrochlorides are presented in Table 1.

As is known, 2,5-disubstituted adamantanes can exist as *syn* and *anti* (*cis* and *trans*) stereomers [8]. The TLC data indicated that compounds Ia – Id and Ih are mixtures of both stereomers (see the R_f values in Table 1); at the same time, TLC did not reveal stereomers in compounds Ie – Ig. After repeated recrystallizations from various solvents, we succeeded in isolating individual *anti* stereomers of compounds Ia and Id, which was confirmed by ^{1}H NMR data.

The synthesized compounds were studied by spectroscopic methods. The IR spectra of bases Ia, Ib, Id, and Ih display the absorption bands of hydroxy groups at the nodal atom of adamantane in the region of 3300 – 3350 cm^{-1}. The spectra of all compounds contain intense bands at 2940 – 2840 cm^{-1} corresponding to the stretching vibrations of –CH– groups in the adamantane ring. The characteristic bands at 1450 – 1500 cm^{-1} are due to the bending vibrations of –NH– groups. The absorption at 840 – 810 cm^{-1} observed in the spectra of Ib – Ie, Ig, and Ih reflects the 1,4-substitution in the benzene ring. The intense band at 715 cm^{-1} in the spectrum of compound Id belongs to stretching vibrations of the C–Br bonds, while the vibrations of C–F bonds are manifested at 1100 cm^{-1}.

The proposed structures of the synthesized compounds were also confirmed by analysis of the ^{1}H and ^{13}C NMR data. The spectra of 2,5-disubstituted adamantane derivatives revealed clear differences in the ^{13}C NMR chemical shifts of *syn* and *anti* isomers present in the mixtures. This was possible because of strongly different j-*syn* and j-*anti* effects of the bridging substituents [8]. The signals from C_4–C_9 carbons in the ^{13}C NMR spectra of *anti* isomers are observed at at a lower field (5.10 – 5.90 ppm), while the signals from C_8–C_{10} carbons occur at a higher field (6.50 – 6.70 ppm) as

[1] For Part I, see [1].].

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TABLE 1. Yields and Physicochemical Characteristics of the Synthesized N-(5-R′- or 6-R-Adamant-2-yl)arylamines (Ia – Ih)

Compound	R	R′	R″	Reaction time, h	Yield, %	Hydrochloride: m.p., °C	R_f	Base	
								M.p., °C	Empirical formula
Ia	H	OH	H	12	59.0	237 – 238	0.64 0.70	187 – 189	$C_{16}H_{21}NO$
Ib	H	OH	F	15	75.0	221 – 223	0.30 0.40	98 – 107	$C_{16}H_{20}FNO$
Ic	H	Cl	F	10	80.0	221 – 222	0.52 0.64	83 – 85	$C_{16}H_{19}ClFNO$
Id	H	OH	Br	11	76.1	257 – 259	0.36 0.46	136 – 141	$C_{16}H_{20}BrNO$
Ie	*p*-BrC_6H_4NH–	H	Br	15	60.0	221 – 224	0.85	190 – 191	$C_{22}H_{24}Br_2N_2$
If	C_6H_5–NH–	H	H	15	60.5	321 – 324	0.32	45 – 47	$C_{22}H_{26}N_2$
Ig	H	–$NHCOCH_3$	Br	10	62.0	231 – 233	0.73	–	$C_{18}H_{21}BrNO$
Ih	H	OH	Cl	12	65.0	210 – 212	0.42 0.47	122 – 124	$C_{16}H_{20}ClNO$

compared to the corresponding signals for *syn* isomers. An example is offered by the ^{13}C NMR characteristics of compound Ib presented in Table 2.

Another characteristic feature of the ^1H NMR spectra of 2,5-disubstituted adamantane derivatives is the difference in the ^1H NMR chemical shifts of protons in position 2 of the adamantane ring of *syn* and *anti* isomers. The greater low-field shift of the signal of H2 proton in the spectrum of *anti* isomer allows the ratio of stereomers in a mixture to be estimated from the ratio of integral intensities of the two signals. The parameters of the ^1H NMR spectra of compounds Ia – Id and Ih are listed in Table 3.

The synthesized compounds have been pharmacologically characterized previously [4, 5, 9]. It was demonstrated that introduction of the second substituent in either nodal or bridging positions of the adamantane ring leads to a decrease in the psychostimulant activity.

EXPERIMENTAL CHEMICAL PART

The ^1H and ^{13}C NMR spectra of the synthesized compounds were measured on a Bruker AC-250 spectrometer computer-controlled by a standard Bruker microprogram package using $CDCl_3$ as the solvent and TMS as the internal standard. The spectra were recorded under conditions of complete spin – spin proton decoupling, without suppression of the ^{13}C – ^1H interaction, and interpreted using data on the selective double resonance.

The IR absorption spectra were measured on a Perkin-Elmer spectrophotometer using samples pelletized with KBr. The R_f values were determined by TLC on Silufol UV-254 plates eluted in a hexane – ethyl acetate – ethanol – concentrated ammonia solution (5 : 3 : 2 : 1) system; the spots were detected under UV illumination. The data of elemental analysis of the synthesized compounds agree with the results of analytical calculations using empirical formulas.

N-(5-Hydroxyadamant-2-yl)aniline (Ia). A mixture of 3 g (0.018 mole) of 5-hydroxyadamantan-2-one, 4.35 g (0.036 mole) of formanilide, and 1.1 g (0.024 mole) of formic acid was boiled for 12 h at 150 – 160°C and cooled. Then, 10 ml of a 15% hydrochloric acid solution was added and the mixture was boiled for 1 h, cooled, and alkalized with sodium bicarbonate. Finally, the product was extracted with chloroform (5 × 25 ml) and the chloroform evaporated to dryness to obtain 2.6 g (59%) of compound Ia; m.p., 188 – 189°C (recrystallization from ethanol), see Table 1.

N-(5-Hydroxyadamant-2-yl)-*p*-fluoroaniline (Ib). To a mixture of 4 g (0.036 mole) of *p*-fluoroaniline and 1.72 g (0.036 mole) of 99% formic acid heated to 100°C was gradu-

TABLE 2. Parameters of the ^{13}C NMR Spectra of N-(5-Hydroxyadamant-2-yl)-*p*-fluoroaniline (Ib)

Isomer	Isomer content	Chemical shift d, ppm (TMS)										
		$C_{1,3}$	C_2	$C_{4,9}$	C_5	C_6	C_7	$C_{8,10}$	Aromatic substituent*			
									$C_{1'}$	$C_{2',6'}$	$C_{3',5'}$	$C_{4'}$
syn	10	31.52	66.47	37.99	66.05	44.85	29.10	35.56	131.39	125.75	116.56	161.77
anti	90	30.61	67.24	43.88	65.75	44.85	29.10	28.88	131.39	125.75	116.56	161.77

* Signals from carbons of the aromatic ring were assigned based on the additivity rule.

TABLE 3. Parameters of the ^{1}H NMR Spectra of 2,5-Disubstituted Adamantanes

Compound	Isomer	Isomer content, %	Chemical shift: d, ppm (CDCl3)				
			Adamantane ring (m, 13H)	H_2 (m, 1H)	Aromatic ring		Other protons*
					$H_{2',6'}$ (m, 2H)	$H_{3',5'}$ (m, 2H)	
Ia	*anti*	100	1.30 : 2.50	3.45	6.51	7.02	6.65 (m, $H_{4'}$), 3.00 (s, NH, OH)
Ib	*syn*	10	1.35 : 2.70	3.32	7.18	7.61	3.60 (s, NH, OH)
	anti	90	1.35 : 2.70	3.45	7.18	7.61	3.60 (s, NH, OH)
Ic**	*syn*	27	1.36 : 2.76	3.29	6.97	7.35	10.30 (s, NH)
	anti	73	1.36 : 2.76	3.40	6.97	7.35	10.30 (s, NH)
Id	*anti*	100	1.25 : 2.40	3.47	6.46	7.23	3.90 (s, NH, OH)
Ih	*syn*	17	1.28 : 2.35	3.34	6.49	7.08	3.70 (s, NH, OH)
	anti	83	1.28 : 2.35	3.46	6.49	7.08	3.70 (s, NH, OH)

* Protons of NH and OH groups yield a common averaged signal.
** Compound studied in the form of a salt.

ally added 3 g (0.018 mole) of 5-hydroxyadamantan-2-one. The reaction mixture was boiled for 15 h at 150 – 160°C, cooled, and then treated as described above for compound Ia to obtain 2.8 g (75%) of compound Ib.

N-(5-Chloroadamant-2-yl)-*p*-fluoroaniline (Ic). To a mixture of 2.2 g (0.02 mole) of *p*-fluoroaniline and 1.0 g (0.021 mole) of 99% formic acid heated to 100°C was gradually added 2 g (0.011 mole) of 5-hydroxyadamantan-2-one, and the reaction mass was boiled for 10 h at 150 – 160°C. Then, 10 ml of a 15% hydrochloric acid solution was added and the mixture was boiled for 2 h and cooled. The precipitate was separated by filtration, washed with ethyl ether (2 × 30 ml), and suspended in water. The suspension was alkalized with sodium bicarbonate and extracted (5 × 25 ml) with ethyl ether. The ether extract of compound Ic was dried with magnesium sulfate. After separating the drying agent by filtration, the solvent was evaporated to dryness to yield 2.4 g (80%) of compound Ic representing a mixture of stereomers (see Table 1).

Analogous procedures were used to obtain compounds Id (yield, 76%) and Ih (yield, 80%) by reactions of 5-hydroxyadamant-2-one with *p*-bromoaniline and *p*-chloroaniline, respectively (Table 1).

N-(Acetylaminoadamant-2-yl)-*p*-bromophenylamine hydrochloride (Ig · HCl). A mixture of 6.9 g (0.095 mole) of *p*-bromoaniline, 4.15 g (0.023 mole) of 5-acetylaminoadamant-2-one, and 3 ml of 99% formic acid was treated for 10 h at 140°C and cooled. Then, 15 ml of a 15% hydrochloric acid solution was added and the mixture was boiled for 1 h and cooled. The precipitate was separated by filtration, washed with water, and dried to obtain 4.5 g of compound Ig in the form of hydrochloride; m.p., 231 – 233°C.

2,6-Di(*p*-bromophenylamino)adamantane (Ie · 2HCl). A mixture 3.28 g (0.02 mole) of 2,6-dioxoadamantane, 20 g (1.18 mole) of *p*-bromoaniline, and 15 ml of 99% formic acid was treated for 6 h at 110°C. Then, the formic acid was distilled off and the reaction mass was heated for another 10 h and cooled. Then, 10 ml of concentrated HCl and 20 ml of water were added and the mixture was boiled for 2 h and cooled. The precipitate was separated by filtration and washed sequentially with water (2 × 20 ml), toluene (2 × 20 ml), and water again (3 × 20 ml). The resulting technical product was purified by crystallization from ethanol to obtain 6.58 g of dihydrochloride Ie; m.p., 221 – 224°C.

An analogous procedure were used to obtain compounds If by reaction of diketone IV with aniline.

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