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Synthesis and Properties of Carbocyclic Schiff Bases

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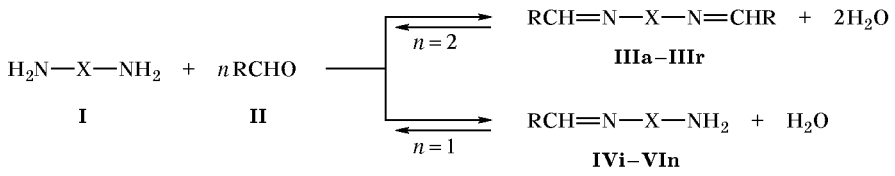
Abstract—New Schiff bases containing both adamantyl and phenyl fragments in a single molecule were synthesized by condensation of appropriate diamines with aromatic aldehydes. The condensation products were brought into reduction and nucleophilic addition reactions.

Schiff bases are potential biologically active compounds, some of which are used as pharmaceuticals. We previously reported on reactions of aldehydes with various aliphatic and aromatic amines [1, 2]. In continuation of these studies, in the present work we synthesized new Schiff bases on the basis of carbocyclic diamines and aromatic aldehydes (Scheme 1). The condensation of 1,4-bis(aminomethyl)cyclohexane with benzaldenyde at a molar reactant ratio of 1:2 in the absence of a solvent (25°C, 1 h) gave product **IIIa** in a moderate yield (42%). By varying the temperature conditions (from 50 to 110°C) we have found that the target product is formed in 90% yield at 50°C. However, the reaction mixture also contained polymerization products. When the reactant molar ratio was changed to 1:4 and the reaction time was increased to 90 min, the yield of product **IIIa** was lower, presumably because of greater contributions of the reverse reaction and polymerization processes. In order to shift the equilibrium toward the target

Scheme 1.



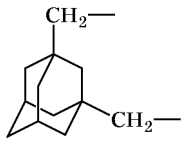
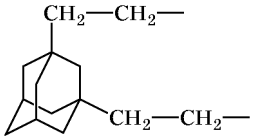
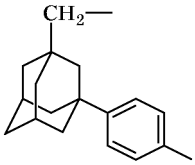
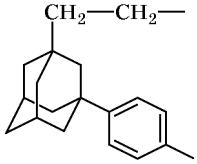
X = —CH_2—C_6H_4—CH_2—, R = Ph (**a**), *m*-FC_6H_4 (**b**), *p*-$O_2NC_6H_4$ (**c**), *p*-$Me_2NC_6H_4$ (**d**); X =  , R = Ph (**e**), *m*-C_6H_4F (**f**), *p*-$O_2NC_6H_4$ (**g**), *p*-$Me_2NC_6H_4$ (**h**); X =  , R = Ph (**i**), *m*-FC_6H_4 (**j**), *m*-$O_2NC_6H_4$ (**k**), *p*-$O_2NC_6H_4$ (**l**), *m*-$PhOC_6H_4$ (**m**), *p*-$Me_2NC_6H_4$ (**n**), *o*-ClC_6H_4 (**o**); X =  , R = *p*-$Me_2NC_6H_4$ (**q**); X =  , R = *p*-$Me_2NC_6H_4$ (**r**).

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Table 1. Yields, melting points, and elemental analyses of compounds **III** and **IV**

Comp. no.	Yield, %	mp, °C, or bp, °C (*p*, mm)	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
IIIa	98	178–180 (4)	84.12	7.85	8.53	$C_{22}H_{26}N_2$	83.02	8.18	8.81
IIIb	96	140–142	73.98	7.18	8.05	$C_{22}H_{24}F_2N_2$	74.58	6.89	7.91
IIIc	98	166–168	66.09	5.35	13.21	$C_{22}H_{24}N_4O_4$	64.71	5.80	13.73
IIId	66	173–175	77.85	8.61	14.03	$C_{26}H_{36}N_4$	77.23	8.91	13.86
IIIe[a]	96	36	84.91	8.15	6.87	$C_{26}H_{39}N_2$	84.32	8.11	7.58
IIIf	97	118–120	73.98	7.18	8.05	$C_{26}H_{28}F_2N_2$	74.58	6.89	7.91
IIIg	97	142–144	67.54	6.18	13.04	$C_{26}H_{28}N_4O_4$	67.83	6.09	12.17
IIIh	69	140–142	79.77	8.34	12.91	$C_{30}H_{40}N_4$	78.95	8.77	12.28
IIIi[b]	97	32	84.98	8.31	7.31	$C_{28}H_{34}N_2$	84.42	8.54	7.03
IIIj	97	118–120	78.27	6.95	6.63	$C_{28}H_{32}F_2N_2$	77.42	5.88	6.42
IIIk	94	144–145	68.25	6.12	10.01	$C_{28}H_{32}N_4O_4$	68.85	6.56	11.47
IIIl	97	133–135	68.12	6.93	11.35	$C_{28}H_{32}N_4O_4$	68.85	6.56	11.47
IIIm	92	86–88	82.92	7.46	5.06	$C_{40}H_{42}N_2O_2$	82.33	7.13	5.98
IIIn	97	146–147	79.11	7.88	6.35	$C_{30}H_{38}N_2O_2$	78.6	8.29	6.11
IIIo	68	131–132	79.71	8.82	11.63	$C_{32}H_{44}N_4$	79.34	9.09	11.57
IIIp	90	104–105	72.17	6.35	6.04	$C_{28}H_{32}Cl_2N_4$	71.95	6.85	5.99
IIIq	91	196–198	82.10	6.18	10.98	$C_{35}H_{42}N_4$	82.60	6.29	11.02
IIIr	98	176–178	81.70	7.73	10.07	$C_{36}H_{44}N_4$	81.20	8.27	10.52
IVi	51	128–130 (2)	80.79	10.19	9.02	$C_{21}H_{30}N_2$	81.55	9.39	9.06
IVj	57	135–136	76.25	8.91	8.12	$C_{21}H_{29}FN_2$	76.83	8.84	8.54
IVk	77	111–113	71.15	8.97	11.19	$C_{21}H_{29}N_3O_2$	70.98	8.17	11.83
IVl	67	136–138	69.96	7.79	11.51	$C_{21}H_{29}N_3O_2$	70.98	8.17	11.83
IVm	65	285–286	79.89	8.12	6.53	$C_{27}H_{34}N_2O$	80.59	8.46	6.97
IVn	79	114–116	78.04	10.03	4.25	$C_{22}H_{33}N_2O$	77.65	9.41	4.71

[a] bp 215–218°C (4 mm).
[b] bp 225–227°C (4 mm).

product and increase its yield, the condensation was carried out with simultaneous removal of water in the temperature range from 125 to 150°C (atmospheric pressure). In this case the yield of diimine **IIIa** was 88%. When the condensation was performed under reduced pressure (40–60 mm) at 60°C, the yield of **IIIa** reached 98% and no polymerization occurred. The reaction was complete in 30 min.

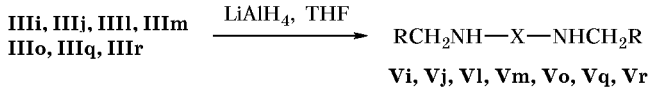
It is known that condensation of amines with aldehydes is favored by polar medium [3]. Using ethanol as solvent, product **IIIm** was formed in more than 85% yield at 40–60°C. We did not obtain better results with other alcohols. We succeeded in synthesizing adamantyl-containing Schiff bases **IVi**–**IVn** having a free amino group by carrying out the reaction at a strictly equimolar reactant ratio. The yield of products **IVi**–**IVn** was 50–60%.

Schiff bases **III** and **IV** were identified by IR and ^{1}H NMR spectroscopy and elemental analysis; their purity was checked by gas–liquid chromatography. Compounds **IIIa**–**IIIr** showed in the IR spectra an absorption band at 1630–1660 cm^{-1}, typical of stretching vibrations of double C=N bond. The absence of absorption in the regions of 1720 and 3400 cm^{-1} indicate complete transformation of the carbonyl and amino groups, respectively. The ^{1}H NMR spectra of **IIIa**–**IIIr** contained a multiplet signal from aromatic protons at δ 6.93–7.58 ppm, a singlet at δ 8.09–8.33 ppm from the CH proton, and signals at δ 1.43 ppm from protons of the adamantane fragment. The amino group in monocondensation products **IVi**–**IVn** gives rise to characteristic IR absorption in the region 3400–3450 cm^{-1} and signals at δ 5.06–5.2 ppm in the ^{1}H NMR spectra. Also,

a positive test for primary amino group was obtained. Table 1 contains yields, melting or boiling points, and elemental analyses of Schiff bases **IIIa**–**IIIr** and **IVi**–**IVn**.

Some bis-condensation products **III** were reduced with lithium aluminum hydride in tetrahydrofuran to obtain the corresponding diamines **V** (Scheme 2). The reduction of Schiff base **IIIl** was accompanied by transformation of the aromatic nitro group into amino. Using sodium tetrahydridoborate as a more selective reducing agent, we succeeded in conserving the nitro group in the substrate [2]. The yields, melting or boiling points, and elemental analyses of compounds **V** are given in Table 2.

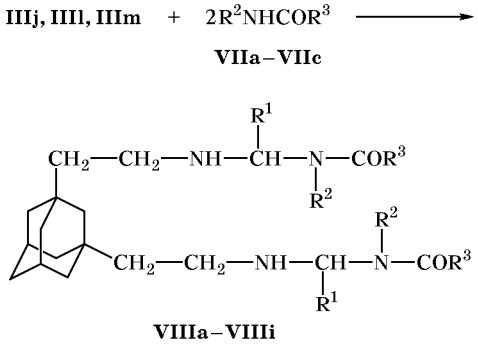
Scheme 2.



Diamines **V** are readily converted into the corresponding dihydrochlorides **VI** by treatment with hydrogen chloride in anhydrous solvents at 0 to 5°C (Scheme 3).

Scheme 3.

Scheme 4.



VII, R^2 = H, R^3 = Me (**a**); R^2 = H; R^3 = Ph (**b**); R^2 = R^3 = Ph (**c**); **VIII**, R^1 = *m*-C_6H_4F, R^2 = H, R^3 = Ph (**a**); R^1 = *m*-C_6H_4F, R^2 = R^3 = Ph (**b**); R^1 = *m*-C_6H_4F, R^2 = H, R^3 = Me (**c**); R^1 = *p*-$C_6H_4NO_2$, R^2 = H, R^3 = Ph (**d**); R^1 = *p*-$C_6H_4NO_2$, R^2 = R^3 = Ph (**e**); R^1 = *p*-$C_6H_4NO_2$, R^2 = H, R^3 = Me (**f**); R^1 = *m*-$PhOC_6H_4$, R^2 = H, R^3 = Ph (**g**); R^1 = *m*-$PhOC_6H_4$, R^2 = R^3 = Ph (**h**); R^1 = *m*-$PhOC_6H_4$, R^2 = H, R^3 = Me (**i**).

The dipolar character of the double C=N bond in Schiff bases makes them highly reactive toward nucleophiles [4, 5]. Such nucleophilic reagents as acetamide (**VIIa**), benzamide (**VIIb**), and benzanilide (**VIIc**) with Schiff bases **III** form addition products at both C=N bonds (Scheme 4).

The reactions were carried out at a molar reactant ratio of 1:2 in toluene under reflux. Products **VIIIa**–**VIIIi** were obtained in 50–90% yield.

According to the results of computational prediction, the ArCH=N– moiety determines a probable spectrum of pharmacological activity of the Schiff bases prepared in this work. Their biological activity should strongly depend on the nature and position of substituent in the aromatic ring. Schiff bases **III** are likely to exhibit antibacterial (antiseptic and tuberculostatic) and fungicide activity, and compounds **V**, **VI**, and **VIII** should possess antitumor, neuroleptic, cardiotonic, analgetic, and fungicide properties. All the synthesized compounds were registered at the All-Russian Scientific Center for Biologically Active Substances (Kupavna).

EXPERIMENTAL

The IR spectra were recorded on a Specord M-82 instrument from samples dispersed in mineral oil or prepared as thin film. The ^{1}H NMR spectra were obtained on a Tesla BS-487 spectrometer at 100 MHz using HMDS as internal reference. GLC was performed on a Tsvet-100 chromatograph equipped with a flame-ionization detector and a 1-m column packed with 5% of DS-550 on Chromaton (0.25–0.45 mm); injector temperature 470°C; oven temperature programming from 100 to 250°C at 40 deg/min; carrier gas flow rate 30 ml/min; sample volume 1 μl.

1,4-Bis(benzylideneaminomethyl)cyclohexane (IIIa). A reactor was charged with 1.5 g (14.2 mmol) of benzaldehyde, and 1 g (7.1 mmol) of 1,4-bis-(aminomethyl)cyclohexane was added with stirring. The mixture was heated for 30 min at 60°C under reduced pressure (40–60 mm) with simultaneous removal of water. The product was purified by vacuum distillation. Yield 2.2 g (98%), bp 178–180°C (4 mm).

1,3-Bis[2-(*m*-phenoxybenzylideneamino)ethyl]-adamantane (IIIm). A mixture of 1 g (4.5 mmol) of 1,3-bis(2-aminoethyl)adamantane and 1.78 g (9 mmol) of *m*-phenoxybenzaldehyde in 10 ml of ethanol was heated for 1.5–2 h at 60°C. After cooling, crystalline product **IIIm** was filtered off. Yield 2.4 g (92%), colorless crystals, mp 86–88°C.

Table 2. Yields, melting points, and elemental analyses of compounds **V**, **VI**, and **VIII**

Comp. no.	Yield, %	mp, °C, or bp, °C (*p*, mm)	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
Vi	72	185–186	84.24	9.38	6.38	$C_{28}H_{38}N_2$	83.58	9.45	6.97
Vj	73	220–222	76.32	7.93	6.85	$C_{28}H_{36}F_2N_2$	76.71	8.22	6.39
Vl	60	95–96	67.36	6.67	10.61	$C_{28}H_{36}N_4O_4$	68.29	7.32	11.38
Vm	81	207–210 (4)	80.86	7.42	4.83	$C_{40}H_{46}N_2O_2$	81.91	7.85	4.76
Vo	65	112–115 (4)	78.45	9.51	12.04	$C_{32}H_{48}N_4$	78.69	9.84	11.47
Vq	90	253–255	80.63	8.50	11.12	$C_{35}H_{46}N_4$	80.46	8.81	10.73
Vr	70	242–244	80.94	8.85	10.21	$C_{35}H_{48}N_4$	80.59	8.96	10.45
VIj[a]	85	239–242	65.04	8.12	5.21	$C_{28}H_{38}Cl_2F_2N_2$	65.75	7.44	5.48
VIl[b]	80	162–164	60.23	6.98	10.01	$C_{28}H_{38}Cl_2N_4O_4$	59.47	6.73	9.90
VIm[c]	92	219–221	72.44	8.50	4.57	$C_{40}H_{48}Cl_2N_2O_2$	72.84	7.28	4.25
VIo[d]	83	77–179	68.24	7.95	9.70	$C_{32}H_{50}Cl_2N_4$	68.45	8.91	9.98
VIIIa	60	125–127	74.26	6.44	8.89	$C_{42}H_{46}F_2N_4O_2$	74.56	6.80	8.28
VIIIb	62	196–197	78.56	6.92	6.94	$C_{54}H_{54}F_2N_4O_2$	78.26	6.52	6.76
VIIIc	79	63–65	70.14	7.82	9.97	$C_{32}H_{42}F_2N_4O_2$	69.57	7.61	10.14
VIIId	70	132–133	69.04	6.88	11.92	$C_{42}H_{46}N_6O_6$	69.04	6.30	11.51
VIIIe	84	151–153	73.39	6.53	10.05	$C_{54}H_{54}N_6O_6$	73.43	6.12	9.52
VIIIf	90	171–172	62.22	8.31	12.11	$C_{32}H_{42}N_6O_6$	63.36	6.93	13.86
VIIIg	59	114–116	78.65	6.24	6.40	$C_{54}H_{56}N_4O_4$	78.64	6.79	6.79
VIIIh	58	189–190	80.95	6.76	5.44	$C_{66}H_{64}N_4O_4$	81.15	6.56	5.74
VIIIi	67	67–68	75.45	7.86	8.84	$C_{44}H_{52}N_4O_4$	75.43	7.43	8.00

[a] Found Cl, %: 12.74; calculated Cl, %: 13.89.
[b] Found Cl, %: 11.80; calculated Cl, %: 12.57.
[c] Found Cl, %: 9.70; calculated Cl, %: 10.77.
[d] Found Cl, %: 11.92; calculated Cl, %: 12.66.

Schiff bases **IIIb**–**IIIl** and **IIIn**–**IIIr** were synthesized in a similar way.

1-(2-Aminoethyl)-3-[2-(*p*-nitrobenzylideneamino)ethyl]adamantane (IVl). *p*-Nitrobenzaldehyde, 0.68 g (4.5 mmol), was slowly added under stirring to 1 g (4.5 mmol) of 1,3-bis(2-aminoethyl)adamantane, and the mixture was heated for 1.5–2 h at 60°C. The product was purified by recrystallization from dimethylformamide. Yield 1.07 g (67%), colorless crystals with mp 136–138°C. Compounds **IVi**–**VIk**, **IVm**, and **IVn** were obtained in a similar way.

1,3-Bis[2-(benzylamino)ethyl]adamantane (Vi). A solution of 0.44 g (1.1 mmol) of Schiff base **IIIi** in 10 ml of THF was slowly added to a mixture of 0.5 g (1.1 mmol) of $LiAlH_4$ and 30 ml of THF. The mixture was heated for 5 h at 66°C and cooled, and 2 ml of water was added. The precipitate was filtered off, the filtrate was evaporated, and the residue was recrystallized from acetone. Yield 0.26 g (72%), colorless crystals, mp 185–186°C.

Diamines **Vj**, **Vl**, **Vm**, **Vo**, **Vq**, and **Vr** were synthesized in a similar way. Liquid products were purified by vacuum distillation.

1,3-Bis[2-(*m*-phenoxybenzylamino)ethyl]adamantane dihydrochloride (VIm). A reactor was charged with 1.2 g (2 mmol) of compound **Vm** and 15 ml of diethyl ether, and the mixture was saturated with hydrogen chloride on cooling with ice. The progress of the reaction was monitored following the gain in weight (a solid separated from the solution). Yield 1.2 g (92%), colorless crystals mp 219–221°C. Diamine dihydrochlorides **VIj**, **VIl**, and **VIm** were synthesized in a similar way (Table 2).

1,3-Bis[2-(α-benzamido-*p*-nitrobenzylamino)ethyl]adamantane (VIIId). A solution of 0.5 g (1 mmol) of Schiff base **IIIl** in 30 ml of toluene was added to 0.48 g (2 mmol) of benzamide, and the mixture was refluxed for 3 h. The solvent was distilled off, and the residue was recrystallized from benzene.

Yield 0.45 g (70%), slightly colored crystals, mp 132–133°C. Compounds **VIIIa**–**VIIIc** and **VIIIf**–**VIIIi** were synthesized in a similar way (Table 2).

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