ISSN 1070-3632, Russian Journal of General Chemistry, 2009, Vol. 79, No. 11, pp. 2402–2405. © Pleiades Publishing, Ltd., 2009.
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Synthesis of Aryl-*N*,*N*′-bis(quinolin-8-yl)methanediamines

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Received April 16, 2009

Abstract—Condensation of substituted benzaldehydes with 8-aminoquinoline in methanol gave the corresponding aryl-*N*,*N*′-bis(quinolin-8-yl)methanediamines.

DOI: 10.1134/S107036320911019X

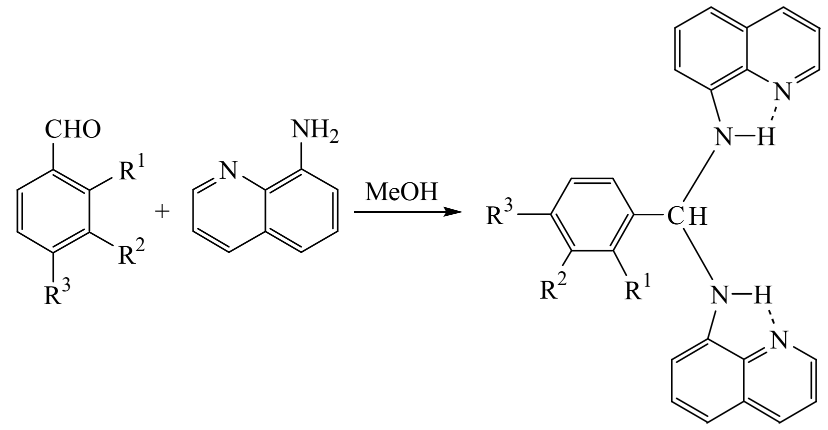
1,1-Diamines (aminals) are relatively unstable compounds, and they readily undergo hydrolysis [1]. Nevertheless, some 1,1-diamines exhibit strong biological activity [2–4].

The goal of the present work was to develop a preparative procedure for the synthesis of aryl-*N*,*N*′-bis(quinolin-8-yl)methanediamines by condensation of substituted benzaldehydes **I** with 8-aminoquinoline (**II**). The reactions were carried out by heating the reactants (**I**-to-**II** ratio 1:2) in boiling anhydrous methanol over a period of 1.5–2 h. As a result, we isolated the corresponding aryl-*N*,*N*′-bis(quinolin-8-yl)-methanediamines **III**–**XL** having hydroxy, alkoxy, and acyloxy groups in 92–98% yield. Mild reaction conditions ensured conservation of labile ester groups (no hydrolysis or aminolysis was observed). When the reaction was performed with equimolar amounts of the reactants with a view to obtain the corresponding Schiff bases, in most cases the products were mixtures of compounds aminals **III**–**XL** and initial benzaldehydes **I**. We succeeded in isolating only Schiff base **XLI** (yield 50%) in the reaction of 8-aminoquinoline (**II**) with 4-hydroxy-3-methoxybenzaldehyde (vanillin) at a ratio of 1:1; presumably, the formation of **XLI** was favored by its poor solubility in a mixture of methanol with diethyl ether. Analogous results were obtained previously for structurally related compounds [5]. The predominant formation of aminals **III**–**XL** rather than Schiff bases (as in reactions of substituted benzaldehydes **I** with 1-aminonaphthalene [6]) is likely to be determined by stabilizing effect of intramolecular hydrogen bond [7].

Compounds **III**–**XL** are colorless or slightly colored crystalline or glassy substances. Their structure was confirmed by elemental analyses, IR, UV, and ^{1}H NMR spectra, and the determination of molecular weights by cryoscopy (see table). The IR spectra of **III**–**XL** contained absorption bands due to vibrations of the NH bonds (3472±5, 3373±5 cm^{-1}, C–H bonds in the aromatic rings (3080±3, 3060±5, 3037±3, 3003±1, 820±2, 791±2, 750±3 cm^{-1}); aliphatic C–H bonds (2965±5, 2935±5, 2900±5, 2835±3 cm^{-1}), aromatic C–C bonds (1604±4, 1595±5, 1575±3, 1508±3, 1474±3, 1419±5, 1376±3, 1335±2 cm^{-1}), and C–O bonds (1260±10, 1142±5, 1111±4, 1084±3, 1032±3 cm^{-1}). In the IR spectra of esters **VIII**–**XXV** and **XXVII**–**XL**, stretching vibrations of the ester carbonyl group gave rise to absorption at 1755±15 cm^{-1}. The presence of a nitro group in molecule **XXII** is confirmed by appearance of the characteristic absorption bands at 1539 and 1352 cm^{-1}. Aminals **III**–**XL** displayed the following absorption maxima in the electronic spectra, λ_{max}, nm (ε): 198 (61000), 251 (33000), 350 (8000).

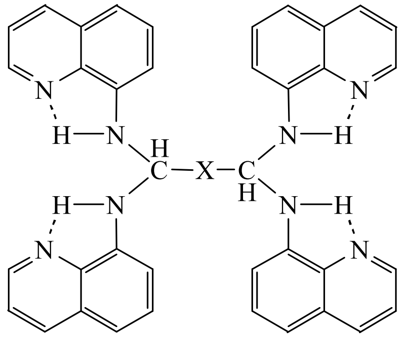
In the ^{1}H NMR spectra of **III**–**XL**, protons in the NH groups resonated as a broadened singlet at δ 4.50–6.50 ppm, and aromatic protons and C**H**(NH)$_2$ gave rise to a multiplet in the region 6.75–8.95 ppm. Protons in the methoxy group appeared in the ^{1}H NMR spectra of **V**–**XXV**, **XXVII**, **XXXVI**, and **XXXIX** as a singlet at δ 3.87–3.97 ppm, and compounds **XXVI**–**XXXVII** and **XL** characteristically showed in the spectra a triplet in the region δ 1.20–1.60 ppm and a quartet at 3.90–4.30 ppm due to methyl and methylene protons, respectively, in the ethoxy group. Signals from the methyl protons in the acetyl group of acetates **VIII** and **XXVIII** were located at δ 2.32 ppm.

The IR spectrum of (*E*)-*N*-(4-hydroxy-3-methoxybenzylidene)quinolin-8-amine (**XLI**) contained an absorption band at 1620 cm^{-1} due to stretching



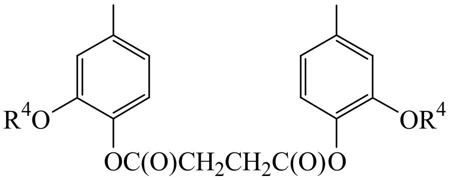
I **II** **III–XXXVII**

$R^1 = R^2 = R^3$ = H (**III**); $R^1 = R^3$ = HO, R^2 = H (**IV**), $R^1 = R^2$ = H, R^3 = MeO (**V**); R^1 = H, R^2 = MeO, R^3 = HO (**VI**), MeO (**VII**), $MeCO_2$ (**VIII**), $EtCO_2$ (**IX**), $PrCO_2$ (**X**), Me_2CHCO_2 (**XI**), $BuCO_2$ (**XII**), $Me_2CHCH_2CO_2$ (**XIII**), $Me(CH_2)_6CO_2$ (**XIV**), $Me(CH_2)_8CO_2$ (**XV**), $Me(CH_2)_{16}CO_2$ (**XVI**), $H_2C{=}CMeCO_2$ (**XVII**), $C_6H_5MeCHCH_2CO_2$ (**XVIII**), $C_6H_5CO_2$ (**XIX**), 2,4-$Cl_2C_6H_3CO_2$ (**XX**), 4-$BrC_6H_4CO_2$ (**XXI**), 3-$O_2NC_6H_4CO_2$ (**XXII**), 1-$AdCO_2$ (**XXIII**), $MeOCO_2$ (**XXIV**); $EtOCO_2$ (**XXV**); R^2 = EtO, R^3 = HO (**XXVI**), MeO (**XXVII**), $MeCO_2$ (**XXVIII**), $EtCO_2$ (**XXIX**), $PrCO_2$ (**XXX**), Me_2CHCO_2 (**XXXI**), $BuCO_2$ (**XXXII**), $Me_2CHCH_2CO_2$ (**XXXIII**), 4-$MeC_6H_4CO_2$ (**XXXIV**), 1-$AdCO_2$ (**XXXV**), $MeOCO_2$ (**XXXVI**); $EtOCO_2$ (**XXXVII**).



XXXVIII–XL

X = 4,4'-$C_6H_4C_6H_4$ (**XXXVIII**),



(**XXXIX, XL**); R^4 = Me (**XXXIX**), Et (**XL**).

vibrations of the azomethine C=N bond, and the CH=N proton resonated at δ 8.47 ppm in the ^1H NMR spectrum. In the UV spectrum of **XLI**, we observed absorption maxima at λ 198 (ε 48000), 254 (25000), and 345 mm (10000).

EXPERIMENTAL

The IR spectra were recorded in KBr on a Nicolet Protégé-460 spectrometer with Fourier transform. The UV spectra were measured on a Specord UV-Vis spectrophotometer from 1×10^{-4} M solutions in methanol. The ^1H NMR spectra were obtained on a Tesla BS-587A instrument (100 MHz) from 5% solutions in chloroform-*d* or DMSO-d_6 using tetramethylsilane as internal reference. The elemental compositions were determined with an accuracy of ±0.1% on an Elementar Vario EL-III C,H,N,O,S-analyzer. The molecular weights (*M*) were measured by cryoscopy in benzene.

Yields, melting points, elemental analyses, and molecular weights of compounds **III**–**XLI**

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %			*M*	
			C	H	N		C	H	N	found	calculated
III	93	–	80.12	5.48	14.47	$C_{25}H_{20}N_4$	79.76	5.35	14.88	361.7	376.5
IV	92	68–69	73.82	5.10	13.28	$C_{25}H_{20}N_4O_2$	73.51	4.94	13.72	387.6	408.5
V	94	–	77.03	5.62	13.32	$C_{26}H_{22}N_4O$	76.83	5.46	13.78	388.1	406.5
VI	94	–	74.10	5.35	12.93	$C_{26}H_{22}N_4O_2$	73.92	5.25	13.26	401.8	422.5
VII	97	–	74.75	5.73	12.52	$C_{27}H_{24}N_4O_2$	74.29	5.54	12.84	419.6	436.5
VIII	98	99–100	72.68	5.34	11.65	$C_{28}H_{24}N_4O_3$	72.40	5.21	12.06	448.0	464.5
IX	96	143–144	73.09	5.65	11.32	$C_{29}H_{26}N_4O_3$	72.79	5.48	11.71	462.3	478.5
X	97	123–124	73.58	5.87	11.02	$C_{30}H_{28}N_4O_3$	73.15	5.73	11.37	473.4	492.6
XI	98	128–129	73.60	5.83	10.99	$C_{30}H_{28}N_4O_3$	73.15	5.73	11.37	476.6	492.6
XII	95	120–121	73.94	6.13	10.63	$C_{31}H_{30}N_4O_3$	73.50	5.97	11.06	488.2	506.6
XIII	92	–	74.01	6.10	10.88	$C_{31}H_{30}N_4O_3$	73.50	5.97	11.06	484.7	506.6
XIV	93	72–73	74.79	6.80	9.96	$C_{34}H_{36}N_4O_3$	74.43	6.61	10.21	532.7	548.7
XV	94	71–72	75.40	7.18	9.28	$C_{36}H_{40}N_4O_3$	74.97	6.99	9.71	553.8	576.7
XVI	96	50–51	77.08	8.22	7.73	$C_{44}H_{56}N_4O_3$	76.71	8.19	8.13	652.5	688.9
XVII	93	155–156	73.92	5.47	11.03	$C_{30}H_{26}N_4O_3$	73.45	5.34	11.42	472.9	490.6
XVIII	95	67–68	76.41	5.89	9.45	$C_{36}H_{32}N_4O_3$	76.04	5.67	9.85	546.2	568.7
XIX	98	121–122	75.66	5.16	10.24	$C_{33}H_{26}N_4O_3$	75.27	4.98	10.64	502.3	526.6
XX[a]	96	81–82	66.84	4.16	9.07	$C_{33}H_{24}Cl_2N_4O_3$	66.56	4.06	9.41	580.4	595.5
XXI[b]	97	102–103	65.84	4.23	8.96	$C_{33}H_{25}BrN_4O_3$	65.46	4.16	9.25	581.6	605.5
XXII	95	92–93	69.57	4.52	12.03	$C_{33}H_{25}N_5O_5$	69.34	4.41	12.25	566.2	571.6
XXIII	98	191–192	76.48	6.34	9.17	$C_{37}H_{36}N_4O_3$	76.00	6.21	9.58	552.9	584.7
XXIV	92	122–123	70.32	5.20	11.28	$C_{28}H_{24}N_4O_4$	69.99	5.03	11.66	453.4	480.5
XXV	94	126–127	70.88	5.67	10.98	$C_{29}H_{26}N_4O_4$	70.43	5.30	11.33	472.5	494.5
XXVI	93	121–122	74.67	5.72	12.35	$C_{27}H_{24}N_4O_2$	74.29	5.54	12.84	425.4	436.5
XXVII	93	–	74.99	6.02	11.97	$C_{28}H_{26}N_4O_2$	74.65	5.82	12.44	431.0	450.5
XXVIII	92	95–96	73.10	5.48	11.32	$C_{29}H_{26}N_4O_3$	72.79	5.48	11.71	453.7	478.5
XXIX	94	142–143	73.43	5.80	11.02	$C_{30}H_{28}N_4O_3$	73.15	5.73	11.37	470.2	492.6
XXX	93	128–129	73.58	6.18	10.86	$C_{31}H_{30}N_4O_3$	73.50	5.97	11.06	482.4	506.6
XXXI	93	140–141	73.87	6.12	10.82	$C_{31}H_{30}N_4O_3$	73.50	5.97	11.06	480.3	506.6
XXXII	94	106–107	74.19	6.29	10.33	$C_{32}H_{32}N_4O_3$	73.82	6.20	10.76	505.8	520.6
XXXIII	93	–	74.12	6.35	10.34	$C_{32}H_{32}N_4O_3$	73.82	6.20	10.76	512.2	520.6

Table. (Contd.)

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %			*M*	
			C	H	N		C	H	N	found	calculated
XXXIV	98	121–122	76.00	5.68	9.75	$C_{35}H_{30}N_4O_3$	75.79	5.45	10.10	538.7	554.6
XXXV	95	197–198	76.64	6.72	9.04	$C_{38}H_{38}N_4O_3$	76.23	6.40	9.36	582.4	598.7
XXXVI	94	138–139	70.25	5.21	11.23	$C_{29}H_{26}N_4O_4$	70.43	5.30	11.33	478.3	494.5
XXXVII	94	137–138	71.12	5.29	10.84	$C_{30}H_{28}N_4O_4$	70.85	5.55	11.02	486.5	508.6
XXXVIII	96	118–119	80.38	5.19	14.65	$C_{50}H_{38}N_8$	79.98	5.10	14.92	731.3	750.9
XXXIX	95	81–82	72.85	5.24	11.76	$C_{56}H_{46}N_8O_6$	72.56	5.00	12.09	901.6	927.0
XL	95	73–74	73.25	5.38	11.25	$C_{58}H_{50}N_8O_6$	72.94	5.28	11.73	938.8	955.1
XLI	50	184–185	73.45	5.19	9.84	$C_{17}H_{14}N_2O_2$	73.37	5.07	10.07	265.4	278.3

[a] Found Cl, %: 11.67. Calculated Cl, %: 11.91. [b] Found Br, %: 12.87. Calculated Br, %: 13.20.

Initial vanillin and vanillal esters were synthesized according to the procedures reported in [8–11]; 8-aminoqionoline (**II**) was commercial product of analytical grade, purity 99%, mp 59–60°C.

Aryl-*N*,*N*′-bis(quinolin-8-yl)methanediamines III–XL (*general procedure*). A solution of 5 mmol of substituted benzaldehyde **I** and 10 mmol of 8-aminoqionoline (**II**) in 50 ml of anhydrous methanol was heated for 1.5–2 h under reflux. In the synthesis of bis-aminals **XXXVI**–**XL**, 5 mmol of the corresponding dialdehyde and 20 mmol of 8-aminoqionoline (**II**) were taken. The hot solution was filtered through a filter paper, and the filtrate was cooled and left to stand for 10–15 h at 5°C. Crystalline products were separated by filtration through a glass porous filter, washed with a small amount of methanol, and dried in air. Liquid glassy products were separated by decanting and dissolved in anhydrous diethyl ether, the solution was filtered through a filter paper, and the solvent was removed under reduced pressure.

(*E*)-2-Methoxy-4-{[(quinolin-8-yl)imino]methyl}-phenol (XLI). A solution of 5 mmol of 4-hydroxy-3-methoxybenzaldehyde (vanillin) and 5 mmol of 8-aminoqionoline (**II**) in 50 ml of anhydrous methanol–diethyl ether (1 : 1) was heated for 30 min under reflux. The hot solution was filtered through a folded filter paper, and the filtrate was cooled and left to stand for 10–15 h at 5°C. The precipitate was filtered off through a glass frit, washed with a small amount of diethyl ether, and dried in air.

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