ISSN 1070-3632, Russian Journal of General Chemistry, 2012, Vol. 82, No. 4, pp. 693–696. © Pleiades Publishing, Ltd., 2012.
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Synthesis of (*E*)-2-Methoxy-6-(*R*-imino)methylphenols and 2-Methoxy-6-(*R*-amino)methylphenols

E. A. Dikusar

Institute of Physical Organic Chemistry, National Academy of Sciences of Belarus,
ul. Surganova 13, Minsk, 220072 Belarus
e-mail: dikusar@ifoch.bas-net.by

Received February 14, 2011

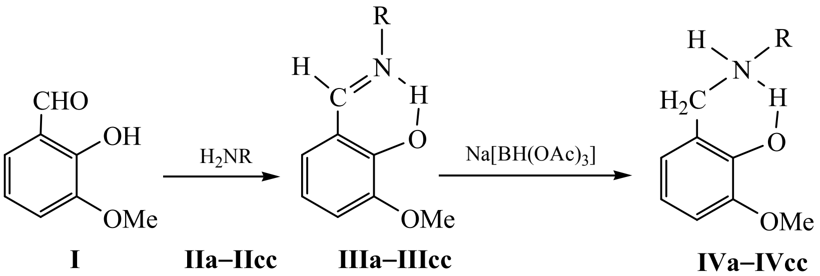
Abstract—(*E*)-2-Methoxy-6-(*R*-imino)methylphenols were synthesized by the condensation of 2-hydroxy-3-methoxybenzaldehyde with primary amines. By reduction of the iminophenols with sodium triacetoxyborohydride 2-methoxy-6-(*R*-amino)methylphenols were obtained.

DOI: 10.1134/S1070363212040159

The necessity to control the newly emerging resistant pathogen strains stimulates permanently a research on the synthesis of new biocidal agents to update their range [1]. Using the ester and azomethine bonds as the mounting elements (linkers) for covalent attachment of different functional and pharmacophore groups to the aldehydes of the vanillin series may serve as an example of such molecular design [2]. Previously we reported on the synthesis of Schiff bases, the derivatives of 4-hydroxy-3-methoxy(ethoxy)benzaldehydes with high biological activity [3, 4].

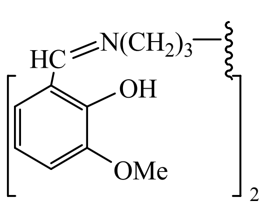
In this paper we describe the preparative method of the synthesis of hydroxy-containing Schiff bases **III** obtained by condensation of 2-hydroxy-3-methoxybenzaldehyde (*ortho*-vanillin) **I** with aliphatic, cycloaliphatic, and aromatic amines **II** in anhydrous methanol at the boiling point of the solvent. The yield of compounds **III** was 80–87%.

We have studied reduction of hydroxyazomethines **III** with sodium triacetoxyborohydride $Na[BH(OAc)_3]$ in ether at a temperature of 20–25°C. Reduction of azomethines **III** to the corresponding hydroxyamines **IV** is completed in 10–12 h. The yield of the hydroxyamines **IV** was almost quantitative, 92 to 94%. At the reduction, which was carried out in specially chosen mode of moderate temperature and acid exposure [5], there was no side reaction of reduction or hydrolysis of the side ester groups in the compounds **IVd–IVg, IVy, IVz**.

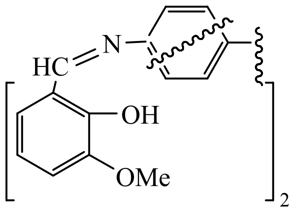


I **IIa–IIcc** **IIIa–IIIcc** **IVa–IVcc**

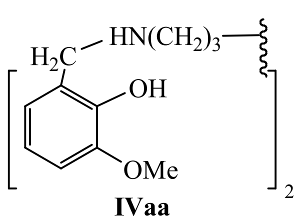
II–IV, R = *n*-$C_{18}H_{37}$ (**a**), cyclo-C_6H_{11} (**b**), CH(1-Ad)Me (**c**), CH_2CO_2Me (**d**), *L*-$CH(CHMe_2)CO_2Me$ (**e**), *L*-$CH(CHCH_2Me_2)CO_2Me$ (**f**), *L*-CH(CHMeEt)CO_2Me (**g**), C_6H_5 (**h**), 4-MeC_6H_4 (**i**), 2-biphenyl (**j**), 4-biphenyl (**k**), 1-naphthyl (**l**), 2-naphthyl (**m**), 2,6-$Cl_2C_6H_3$ (**n**), 3-BrC_6H_4 (**o**), 4-BrC_6H_4 (**p**), 4-IC_6H_4 (**q**), 1-bromo-2-naphthyl (**r**), 2-hydroxyphenyl (**s**), 4-phenoxyphenyl (**t**), 4-MeC(O)C_6H_4 (**u**), 4-EtC(O)C_6H_4 (**v**), 3-$HO_2CC_6H_4$ (**w**), 4-$HO_2CC_6H_4$ (**x**), 4-$EtO_2CC_6H_4$ (**y**), 4-$BuO_2CC_6H_4$ (**z**).



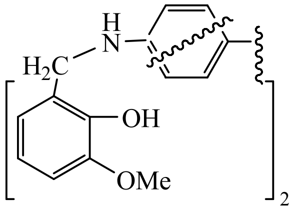
IIIaa



IIIbb, IIIcc



IVaa



IVbb, IVcc

(**IIIaa, IVaa**) 1,6-hexamethylenediamine derivatives, (**IIIbb, IIIcc** and **IVbb, IVcc)** derivatives of 1,3- and 1,4-phenylenediamine.

The resulting compounds **III** and **IV** are crystalline or amorphous glassy substances, soluble in ether, benzene, chloroform, dimethylformamide, dimethyl sulfoxide, and insoluble in water. The structure of compounds **III** and **IV** was proved by elemental analysis and determination of molecular weight (see the table).

The IR spectra of compounds **III** and **IV** contain the following characteristic absorption bands (ν, cm^{-1}): CH_{arom} 3080±5, 3060±5, 3010±5, CH_{akyl} 2950±5, 2920±5, 2850±5; C=O (**IIId–IIIg, IIIu–IIIz, IVd–IVg, IVu–IVz**) 1685±25, $C=C_{arom}$ 1585±5, 1470±5 1445±5; C–O 1275±5, 1255±5, 1085±5, and 970±5; $C–H_{arom}$ 885±5, 745±5, 715±5; in the spectra of azomethins **III**, C=N 1630±15; in the spectra of the amines **IV**, NH 3410±5.

In the ^{1}H NMR spectra of compounds **III** and **IV** there are the following characteristic signals of protons, confirming their structure (δ, ppm): 3.9±0.2 s (3H, MeO), 6.8–7.1 m (3H, C_6H_3), 13.5±0.2 s (1H, OH); azomethines **III**, 8.6±0.1 s (1H, HC=N), which is characteristic of the azomethines of (*E*)-configuration [6], amines **IV**, 4.3±0.1 s (2H, CH_2) and 6.2±0.4 br.s (1H, NH). In contrast to the derivatives of 4-hydroxy-3-methoxybenzaldehyde whose phenol protons resonate in the region of 5.4±0.4 br.s (1H, OH) [3, 4], the signals of phenol protons in the spectra of compounds **III** and **IV** are shifted downfield significantly due to the formation of intramolecular hydrogen bonds [7].

In the IR and ^{1}H NMR spectra of the synthesized (*E*)-2-methoxy-6-(*R*-imino)methylphenols **III** and 2-methoxy-6-(*R*-amino)methylphenols **IV** the characteristic

Yields, melting points and elemental analysis data

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %			*M*	
			C	H	N		C	H	N	found	calculated
IIIa	84	43–44	77.68	11.48	3.16	$C_{26}H_{45}NO_2$	77.37	11.24	3.47	387.4	403.64
IIIb	82	–	72.51	8.32	5.63	$C_{14}H_{19}NO_2$	72.07	8.21	6.00	221.8	233.3
IIIc	87	92–93	77.04	8.66	4.05	$C_{20}H_{27}NO_2$	76.64	8.68	4.47	303.9	313.4
IIId	80	–	59.56	6.01	5.86	$C_{11}H_{13}NO_4$	59.19	5.87	6.27	209.7	223.2
IIIe	82	–	63.67	7.34	4.99	$C_{14}H_{19}NO_4$	63.38	7.22	5.28	257.0	265.3
IIIf	81	–	64.92	7.65	4.67	$C_{15}H_{21}NO_4$	64.50	7.58	5.01	270.4	279.3
IIIg	81	–	64.80	7.68	4.92	$C_{15}H_{21}NO_4$	64.50	7.58	5.01	272.3	279.3
IIIh	86	84–85	74.35	5.89	5.88	$C_{14}H_{13}NO_2$	73.99	5.77	6.16	221.1	227.3
IIIi	87	102–103	75.02	6.43	5.54	$C_{15}H_{15}NO_2$	74.67	6.27	5.81	235.4	241.3
IIIj	85	83–84	79.58	5.44	4.17	$C_{20}H_{17}NO_2$	79.19	5.65	4.62	294.7	303.4
IIIk	87	114–115	79.72	5.75	4.42	$C_{20}H_{17}NO_2$	79.19	5.65	4.62	291.5	303.4
IIIl	86	95–96	78.23	5.58	4.73	$C_{18}H_{15}NO_2$	77.96	5.45	5.05	270.3	277.3
IIIm	85	101–102	78.35	5.40	4.86	$C_{18}H_{15}NO_2$	77.96	5.45	5.05	272.5	277.3
IIIn[a]	80	–	57.19	3.89	4.35	$C_{14}H_{11}Cl_2NO_2$	56.78	3.74	4.73	285.6	296.2
IIIo[b]	82	93–94	55.28	4.10	4.25	$C_{14}H_{12}BrNO_2$	54.92	3.95	4.58	294.6	306.1
IIIp[c]	83	122–123	55.20	4.14	4.31	$C_{14}H_{12}BrNO_2$	54.92	3.95	4.58	290.7	306.1
IIIq[d]	83	133–134	47.92	3.69	3.66	$C_{14}H_{12}JNO_2$	47.61	3.42	3.97	345.4	353.2

(Contd.)

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %			*M*	
			C	H	N		C	H	N	found	calculated
IIIr[e]	84	152–153	61.07	4.12	3.58	$C_{18}H_{14}BrNO_2$	60.69	3.96	3.97	342.8	356.2
IIIs	85	203–204	69.48	5.47	5.40	$C_{14}H_{13}NO_3$	69.12	5.39	5.76	232.5	243.3
IIIt	84	103–104	75.46	5.47	3.93	$C_{20}H_{17}NO_3$	75.22	5.37	4.39	308.9	319.4
IIIu	85	128–129	71.57	5.84	4.80	$C_{16}H_{15}NO_3$	71.36	5.61	5.20	260.4	269.3
IIIv	85	141–142	72.31	6.19	4.72	$C_{17}H_{17}NO_3$	72.07	6.05	4.94	268.5	283.3
IIIw	80	211–212	66.89	5.04	4.67	$C_{15}H_{13}NO_4$	66.41	4.83	5.16	292.7	271.3
IIIx	81	254–255	66.93	4.97	4.74	$C_{15}H_{13}NO_4$	66.41	4.83	5.16	290.1	271.3
IIIy	86	93–94	68.54	5.77	4.60	$C_{17}H_{17}NO_4$	68.21	5.72	4.68	289.6	299.3
IIIz	86	92–93	70.14	6.68	3.87	$C_{19}H_{21}NO_4$	69.71	6.47	4.28	318.0	327.4
IIIaa	83	77–78	69.20	7.45	7.05	$C_{22}H_{28}N_2O_4$	68.73	7.34	7.29	365.2	384.5
IIIbb	80	131–132	70.63	5.37	7.08	$C_{22}H_{20}N_2O_4$	70.20	5.36	7.44	357.3	376.4
IIIcc	82	232–233	70.65	5.51	7.12	$C_{22}H_{20}N_2O_4$	70.20	5.36	7.44	365.6	376.4
IVa	94	27–28	77.25	11.85	3.16	$C_{26}H_{47}NO_2$	76.98	11.68	3.45	387.1	405.7
IVb	93	42–43	71.86	9.19	5.64	$C_{14}H_{21}NO_2$	71.46	8.99	5.95	223.6	235.3
IVc	93	127–128	76.45	9.38	4.16	$C_{20}H_{29}NO_2$	76.15	9.27	4.44	306.8	315.5
IVd	93	45–46	58.74	6.79	5.76	$C_{11}H_{15}NO_4$	58.66	6.71	6.22	216.0	225.2
IVe	92	–	63.28	8.17	4.92	$C_{14}H_{21}NO_4$	62.90	7.92	5.24	257.3	267.3
IVf	94	–	64.45	8.29	4.71	$C_{15}H_{23}NO_4$	64.03	8.24	4.98	270.6	281.4
IVg	93	–	64.36	8.19	4.62	$C_{15}H_{23}NO_4$	64.03	8.24	4.98	274.3	281.4
IVh	94	–	73.72	6.64	5.78	$C_{14}H_{15}NO_2$	73.34	6.59	6.11	221.5	229.3
IVi	94	–	74.46	7.18	5.33	$C_{15}H_{17}NO_2$	74.05	7.04	5.76	236.6	243.3
IVj	93	–	78.90	6.35	4.21	$C_{20}H_{19}NO_2$	78.66	6.27	4.59	292.5	305.4
IVk	94	128–129	79.02	6.34	4.16	$C_{20}H_{19}NO_2$	78.66	6.27	4.59	297.0	305.4
IVl	92	157–158	77.74	6.25	4.60	$C_{18}H_{17}NO_2$	77.40	6.13	5.01	268.4	279.3
IVm	93	155–156	77.83	6.08	4.72	$C_{18}H_{17}NO_2$	77.40	6.13	5.01	265.6	279.3
IVn[f]	94	–	56.68	4.57	4.28	$C_{14}H_{13}Cl_2NO_2$	56.39	4.39	4.70	289.4	298.2
IVo[g]	94	103–104	54.90	4.76	4.23	$C_{14}H_{14}BrNO_2$	54.56	4.58	4.55	297.5	308.2
IVp[h]	93	100–101	54.77	4.65	4.20	$C_{14}H_{14}BrNO_2$	54.56	4.58	4.55	299.1	308.2
IVq[i]	94	104–105	47.69	4.14	3.61	$C_{14}H_{14}JNO_2$	47.34	3.97	3.94	342.8	355.2
IVr[j]	94	–	60.58	4.11	3.52	$C_{18}H_{16}BrNO_2$	60.35	4.50	3.91	350.2	358.2
IVs	92	114–115	68.88	5.97	5.26	$C_{14}H_{15}NO_3$	68.56	6.16	5.71	238.0	245.3
IVt	92	–	75.08	6.13	4.02	$C_{20}H_{19}NO_3$	74.75	5.96	4.36	309.3	321.4
IVu	94	185–186	71.10	6.34	4.75	$C_{16}H_{17}NO_3$	70.83	6.32	5.16	260.7	271.3
IVv	94	147–148	71.81	6.78	4.62	$C_{17}H_{19}NO_3$	71.56	6.71	4.91	276.4	285.3
IVw	94	159–160	66.25	5.84	4.76	$C_{15}H_{15}NO_4$	65.92	5.53	5.13	288.7	273.3
IVx	92	179–180	66.37	5.72	4.80	$C_{15}H_{15}NO_4$	65.92	5.53	5.13	286.5	273.3
IVy	93	123–124	68.17	6.51	4.22	$C_{17}H_{19}NO_4$	67.76	6.36	4.65	291.1	301.3
IVz	94	118–119	69.68	7.23	3.94	$C_{19}H_{23}NO_4$	69.28	7.04	4.25	322.6	329.4
IVaa	92	143–144	68.45	8.51	6.88	$C_{22}H_{32}N_2O_4$	68.01	8.30	7.21	365.3	388.5
IVbb	92	–	69.32	6.54	6.81	$C_{22}H_{24}N_2O_4$	69.46	6.36	7.36	368.4	380.4
IVcc	93	152–153	69.83	6.48	6.96	$C_{22}H_{24}N_2O_4$	69.46	6.36	7.36	–	380.4

[a] Found Cl, %: 23.60. Calculated Cl, %: 23.94. [b] Found Br, %: 25.59. Calculated Br, %: 26.10. [c] Found Br, %: 25.66. Calculated Br, %: 26.10. [d] Found I, %: 35.41. Calculated I, %: 35.93. [e] Found Br, %: 22.14. Calculated Br, %: 22.43. [f] Found Cl, %: 23.51. Calculated Cl, %: 23.78. [g] Found Br, %: 25.50. Calculated Br, %: 25.93. [h] Found Br, %: 25.68. Calculated Br, %: 25.93. [i] Found I, %: 35.42. Calculated I, %: 35.73. [j] Found Br, %: 22.06. Calculated Br, %: 22.31.

absorption bands and the proton signals confirming the presence of the structural fragments R are observed.

EXPERIMENTAL

IR spectra of the compounds were recorded on a FTIR Protégé-Nicolet 460 spectrophotometer from a thin layer or KBr pellets, ^{1}H NMR spectra were taken on a Tesla BS-587A spectrometer (100 MHz) from 5% solutions in deuterochloroform, the chemical shifts were determined with respect to the internal TMS. Molecular mass was determined by cryoscopy in benzene.

For the study was used 2-hydroxy-3-methoxybenzaldehyde **I** of "pure" grade, 99% of the main product, mp 41–42°C.

(*E*)-2-Methoxy-6-(R-imino)methylphenols (IIIa-IIIz). A solution of 5 mmol of 2-hydroxy-3-methoxybenzaldehyde **I** and 5 mmol of the corresponding monoamine **IIa-IIz** in 40 ml of anhydrous methanol was refluxed for 30–45 min. The solution was cooled to 0–5°C, the precipitated crystals of an azomethine were filtered off on a porous glass filter, washed with cold methanol, and air-dried for 6–8 h. Glassy azomethines were separated by decantation, the final purification was performed by column chromatography on neutral alumina, 40–100 μm, II degree activity by Brockmann, eluent dichloromethane.

Bisazomethines (IIIaa–IIIcc). A solution of 10 mmol of 2-hydroxy-3-methoxybenzaldehyde **I** and 5 mmol of a diamine **II** in 50 ml of anhydrous methanol was refluxed for 45 min. Target products were isolated similarly to the azomethines **IIIa–IIIz**.

2-Methoxy-6-(R-amino)methylphenols (IVa–IVz). A solution of 5 mmol of azomethine **IIIa–IIIz**, 10 mmol of $NaBH_4$, and 30 mmol of glacial acetic acid in 50 ml of anhydrous ether was left for 18–20 h at 20–25°C. The solution was washed with water and 5% $NaHCO_3$ solution, the solvent was removed in a vacuum. The residue was purified by recrystallization from a benzene–hexane mixture or by column chromatography on silica gel (100–160 μm, eluent benzene).

Diamines (IVaa–IVcc). A solution of 5 mmol of a bisazomethine **IIIaa–IIIcc**, 20 mmol of $NaBH_4$, and 60 mmol of glacial acetic acid in 100 ml of anhydrous ether was left for 18–20 h at 20–25°C. Target products were purified by recrystallization from a benzene–hexane mixture.

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