ISSN 1070-3632, Russian Journal of General Chemistry, 2007, Vol. 77, No. 11, pp. 1924–1927. © Pleiades Publishing, Ltd., 2007.
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2-[3-Alkoxy-4-(hydroxy, alkoxy, acyloxy)phenyl]-2,3-dihydro-1*H*-benzimidazoles on the Basis of Vanillin and Vanillal Derivatives

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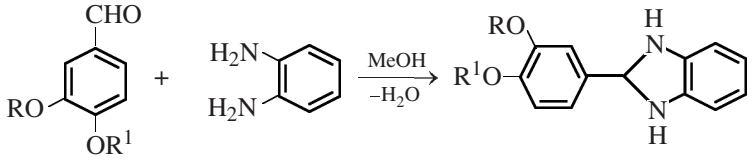
Received April 9, 2007

Abstract — Previously unknown 2-[3-alkoxy-4-(hydroxy, alkoxy, acyloxy)phenyl]-2,3-dihydro-1*H*-benzimidazoles were prepared by the reaction of aldehydes of the vanillin series and their ethers and esters with 1,2-phenylenediamine in absolute methanol.
DOI: 10.1134/S1070363207110138

Natural aldehydophenols, such as vanillin and vanillal (3-methoxy- and 3-ethoxy-4-hydroxybenzaldehydes), as well as their ethers and esters are available building blocks carrying the aromatic structural fragment containing methoxy, ethoxy, and ester groups. They are well suitable for purposeful synthesis of various classes of biologically active compounds [1–3].

The aim of this work is to develop a preparative synthesis of previously unknown 2-[3-alkoxy-4-(hydroxy, alkoxy, acyloxy)phenyl]-2,3-dihydro-1*H*-benzimidazoles containing hydroxy, ether, and ester groups. Target 2,3-dihydro-1*H*-benzimidazoles **IIIa**–**IIIα**, **IVa**–**IVγ** were obtained by condensation of vanillin, vanillal, or their ethers and esters **I** with 1,2-phenylenediamine (**II**) in absolute methanol under reflux in 82–89% yields. The reactions were complete in 0.5 h and occurred under mild conditions without catalysts, which allowed preservation of the labile ester group.



I **II** **IIIa**–**IIIα**, **IVa**–**IVγ**

III, R = Me, R^1 = H (**a**), Me (**b**), MeC(O) (**c**), EtC(O) (**d**), PrC(O) (**e**), $Me_2CHC(O)$ (**f**), $Me(CH_2)_6C(O)$ (**g**), $Me(CH_2)_7C(O)$ (**h**), $Me(CH_2)_8C(O)$ (**i**), $Me(CH_2)_{16}C(O)$ (**j**), $H_2C{=}CMeC(O)$ (**k**), *cyclo*-$C_6H_{11}C(O)$ (**l**), $C_6H_5CH_2C(O)$ (**m**), $C_6H_5(CH_2)_2C(O)$ (**n**), $C_6H_5C(Me)HCH_2C(O)$ (**o**), *Z*-$C_6H_5C(H){=}C(C{\equiv}N)C(O)$ (**p**), $C_6H_5C(O)$ (**q**), 4-$ClC_6H_4C(O)$ (**r**), 2,4-$Cl_2C_6H_3C(O)$ (**s**), 2,4-$Cl_2C_6H_3OCH_2C(O)$ (**t**), 4-$BrC_6H_4C(O)$ (**u**), 3-$O_2NC_6H_4C(O)$ (**v**), 3,5-$(O_2N)_2C_6H_3C(O)$ (**w**), MeO(O)C (**x**), EtO(O)C (**y**), $MeO(O)C(CH_2)_2C(O)$ (**z**), $Cl_2C{=}CClCH_2C(O)$ (α); **IV**, R = Et, R^1 = H (**a**), Me (**b**), MeC(O) (**c**), EtC(O) (**d**), PrC(O) (**e**), $Me_2CHC(O)$ (**f**), $Me_2CHCH_2C(O)$ (**g**), $Me(CH_2)_4C(O)$ (**h**), $Me(CH_2)_5C(O)$ (**i**), $Me(CH_2)_6C(O)$ (**j**), $Me(CH_2)_7C(O)$ (**k**), $Me(CH_2)_8C(O)$ (**l**), $Me(CH_2)_{11}C(O)$ (**m**), $Me(CH_2)_{16}C(O)$ (**n**), *cyclo*-$C_6H_{11}C(O)$ (**o**), $C_6H_5(CH_2)_2C(O)$ (**p**), $C_6H_5C(Me)HCH_2C(O)$ (**q**), *trans*-$C_6H_5C(H){=}C(H)C(O)$ (**r**), *Z*-$C_6H_5C(H){=}C(C{\equiv}N)C(O)$ (**s**), 4-$MeC_6H_4C(O)$ (**t**), 2,4-$Cl_2C_6H_3C(O)$ (**u**), 2,4-$Cl_2C_6H_3OCH_2C(O)$ (**v**), 3-$O_2NC_6H_4C(O)$ (**w**), 4-$O_2NC_6H_4C(O)$ (**x**), 3,5-$(O_2N)_2C_6H_3C(O)$ (**y**), MeO(O)C (**z**), EtO(O)C (α), $MeO(O)C(CH_2)_2C(O)$ (β), $Cl_2C{=}CClCH_2C(O)$ (γ).

2,3-Dihydro-1*H*-benzimidazoles **IIIa**–**IIIα**, **IVa**–**IVγ** are colored (largely yellow) viscous glass-like or crystalline substances soluble in benzene, chloroform, acetone, and lower alcohols, and insoluble in water and hexane. The compounds do not contain admixtures of the starting materials and need no additional purification. The structure of 2,3-dihydro-1*H*-benzimidazoles was proved by the elemental analyses, cryoscopic molecular weights (see table), and IR, UV, and ^{1}H NMR spectra. According to the ^{1}H NMR spectra, their purity is 95 ± 1%.

Yields, melting points, elemental analyses, and molecular weights 2,3-dihydro-1*H*-benzimidazoles **IIIa**–**III**α and **IVa**–**IV**γ

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %			*M*	
			C	H	N		C	H	N	found	calculated
IIIa	89	–	69.84	6.05	11.23	$C_{14}H_{14}N_2O_2$	69.41	5.82	11.56	227.7	242.3
IIIb	84	–	70.69	6.48	10.65	$C_{15}H_{16}N_2O_2$	70.29	6.29	10.93	242.3	256.3
IIIc	82	–	67.88	5.71	9.42	$C_{16}H_{16}N_2O_3$	67.59	5.57	9.85	267.9	284.3
IIId	88	–	68.76	6.20	8.97	$C_{17}H_{18}N_2O_3$	68.44	6.08	9.39	281.8	298.3
IIIe	88	–	69.45	6.49	8.68	$C_{18}H_{20}N_2O_3$	69.21	6.45	9.97	303.7	312.4
IIIf	83	–	69.60	6.61	8.74	$C_{18}H_{20}N_2O_3$	69.21	6.45	9.97	305.1	312.4
IIIg	85	–	71.97	7.85	7.15	$C_{22}H_{28}N_2O_3$	71.71	7.66	7.60	344.8	368.5
IIIh	82	–	72.64	8.08	6.95	$C_{23}H_{30}N_2O_3$	72.22	7.91	7.32	360.2	382.5
IIIi	84	–	72.98	8.43	6.64	$C_{24}H_{32}N_2O_3$	72.70	8.13	7.06	379.9	396.5
IIIj	85	92–93	75.87	10.20	5.16	$C_{32}H_{48}N_2O_3$	75.55	9.51	5.51	482.4	508.7
IIIk	83	–	70.04	6.03	8.59	$C_{18}H_{18}N_2O_3$	69.66	5.85	9.03	295.4	310.4
IIIl	89	–	71.96	7.11	7.58	$C_{21}H_{24}N_2O_3$	71.57	6.86	7.95	338.6	352.4
IIIm	85	105–106	73.14	5.87	7.28	$C_{22}H_{20}N_2O_3$	72.76	5.59	7.77	347.5	360.4
IIIn	88	111–112	74.05	6.12	7.01	$C_{23}H_{22}N_2O_3$	73.78	5.92	7.48	358.0	374.4
IIIo	82	78–79	74.62	6.45	6.90	$C_{24}H_{24}N_2O_3$	74.21	6.23	7.21	375.2	388.5
IIIp	85	187–188	72.89	5.05	10.17	$C_{24}H_{19}N_3O_3$	72.53	4.82	10.57	380.8	397.4
IIIq	85	148–149	73.10	5.44	7.85	$C_{21}H_{18}N_2O_3$	72.82	5.24	8.08	336.0	346.4
IIIr[a]	87	166–167	66.68	6.52	7.06	$C_{21}H_{17}ClN_2O_3$	66.23	4.50	7.36	369.3	380.0
IIIs[b]	84	193–194	61.05	3.97	6.25	$C_{21}H_{16}Cl_2N_2O_3$	60.74	3.88	6.75	401.1	415.3
IIIt[c]	81	146–147	59.81	4.30	5.94	$C_{22}H_{18}Cl_2N_2O_4$	59.34	4.07	6.29	422.7	445.3
IIIu[d]	82	180–181	59.72	4.12	6.30	$C_{21}H_{17}BrN_2O_3$	59.31	4.03	6.59	411.4	425.3
IIIv	86	202–203	64.87	4.51	10.52	$C_{21}H_{17}N_3O_5$	64.45	4.38	10.74	388.6	391.4
IIIw	82	246 (decomp.)	58.07	3.93	12.39	$C_{21}H_{16}N_4O_7$	57.80	3.70	12.84	413.6	434.4
IIIx	81	–	64.20	5.45	9.01	$C_{16}H_{16}N_2O_4$	63.99	5.37	9.33	289.6	300.3
IIIy	81	–	65.22	5.90	8.54	$C_{17}H_{18}N_2O_4$	64.96	5.77	8.91	300.8	314.3
IIIz	84	–	64.35	5.83	7.62	$C_{19}H_{20}N_2O_5$	64.05	5.66	7.86	344.2	356.4
IIIα[e]	81	–	52.61	3.20	6.35	$C_{18}H_{15}Cl_3N_2O_3$	52.26	3.65	6.77	398.6	413.7
IVa	88	–	70.43	6.51	10.54	$C_{15}H_{16}N_2O_2$	70.29	6.29	10.93	248.9	256.3
IVb	90	–	71.46	6.98	10.03	$C_{16}H_{18}N_2O_2$	71.09	6.71	10.36	261.3	270.3
IVc	88	–	68.77	6.29	9.05	$C_{17}H_{18}N_2O_3$	68.44	6.08	9.39	287.7	298.3
IVd	84	–	69.59	6.63	8.65	$C_{18}H_{20}N_2O_3$	69.21	6.45	8.97	298.6	312.4
IVe	87	–	70.26	6.80	8.16	$C_{19}H_{22}N_2O_3$	69.92	6.79	8.58	315.0	326.4
IVf	88	–	70.12	6.91	8.24	$C_{19}H_{22}N_2O_3$	69.92	6.79	8.58	318.5	326.4
IVg	86	–	70.83	7.24	7.93	$C_{20}H_{24}N_2O_3$	70.57	7.11	8.23	326.4	340.4
IVh	87	–	71.60	7.54	7.45	$C_{21}H_{26}N_2O_3$	71.16	7.39	7.90	339.1	354.4
IVi	84	–	72.03	7.85	7.21	$C_{22}H_{28}N_2O_3$	71.71	7.66	7.60	346.8	368.5
IVj	86	–	72.51	8.08	7.04	$C_{23}H_{30}N_2O_3$	72.22	7.91	7.32	360.2	382.5
IVk	85	–	73.12	8.29	6.85	$C_{24}H_{32}N_2O_3$	72.70	8.13	7.06	383.7	396.5
IVl	85	–	73.39	8.58	6.67	$C_{25}H_{34}N_2O_3$	73.14	8.35	6.82	394.8	410.6
IVm	81	74–75	74.74	9.14	5.85	$C_{28}H_{40}N_2O_3$	74.30	8.91	6.19	438.6	452.6
IVn	82	96–97	76.10	9.96	5.06	$C_{33}H_{50}N_2O_3$	75.82	9.64	5.36	502.6	522.8
IVo	87	–	72.47	7.39	7.20	$C_{22}H_{26}N_2O_3$	72.11	7.15	7.64	349.0	366.5
IVp	87	121–122	74.63	6.45	7.03	$C_{24}H_{24}N_2O_3$	74.21	6.23	7.21	379.3	388.5
IVq	84	85–86	74.98	6.64	6.52	$C_{25}H_{26}N_2O_3$	74.60	6.51	6.96	388.4	402.5
IVr	88	178–179	74.96	5.95	6.96	$C_{24}H_{22}N_2O_3$	74.59	5.74	7.25	369.9	386.4
IVs	83	180–181	73.31	5.36	9.98	$C_{25}H_{21}N_3O_3$	72.98	5.14	10.21	395.2	411.5

Table (Contd.)

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %			*M*	
			C	H	N		C	H	N	found	calculated
IVt	82	156–157	74.07	6.13	7.01	$C_{23}H_{22}N_2O_3$	73.78	5.92	7.48	364.2	374.4
IVu[f]	86	200–201	61.84	4.20	6.08	$C_{22}H_{18}Cl_2N_2O_3$	61.55	4.23	6.53	409.8	429.3
IVv[g]	81	152–153	60.53	4.54	5.70	$C_{23}H_{20}Cl_2N_2O_4$	60.14	4.39	6.10	442.3	459.3
IVw	84	198–199	65.02	4.83	10.05	$C_{22}H_{19}N_3O_5$	64.69	4.72	10.36	384.6	405.4
IVx	85	210–211	64.80	4.57	10.10	$C_{22}H_{19}N_3O_5$	64.69	4.72	10.36	388.4	405.4
IVy	87	250 (decomp.)	58.93	4.25	12.23	$C_{22}H_{18}N_4O_7$	58.67	4.03	12.44	325.1	450.4
IVz	83	–	65.28	5.96	8.63	$C_{17}H_{18}N_2O_4$	64.96	5.77	8.91	305.4	314.3
IVα	81	–	66.06	6.19	8.12	$C_{18}H_{20}N_2O_4$	65.84	6.14	8.53	314.8	328.4
IVβ	82	–	65.00	6.18	7.28	$C_{20}H_{22}N_2O_5$	64.85	5.99	7.56	360.3	370.4
IVγ[h]	81	–	53.42	3.97	6.20	$C_{19}H_{17}Cl_3N_2O_3$	53.36	4.01	6.55	409.6	427.7

[a] Found Cl, %: 9.04. Calculated Cl, %: 9.31; [b] Found Cl, %: 16.88. Calculated Cl, %: 17.07; [c] Found Cl, %: 15.70. Calculated Cl, %: 15.92; [d] Found Br, %: 18.36. Calculated Br, %: 18.79; [e] Found Cl, %: 25.34. Calculated Cl, %: 25.71; [f] Found Cl, %: 16.10. Calculated Cl, %: 16.52; [g] Found Cl, %: 15.08. Calculated Cl, %: 15.44; [h] Found Cl, %: 24.61. Calculated Cl, %: 24.87.

The IR spectra of 2,3-dihydro-1*H*-benzimidazoles **IIIa**–**III**α**, IVa**–**IV**γ contain absorption bands of the following bonds, cm^{-1}: N–H, 3420–3140; C–H_{arom}, 3100–3000, 870–740; C–H_{alk}, 2990–2870; C=O, 1770–1740 (**IIIc**–**III**α**, IVc**–**IV**γ); C–C_{arom}, 1600–1370 cm^{-1}; and C–O, 1280–1000. The presence of C≡N groups in compounds **IIIp, IVs** is confirmed by the observation of an absorption band at 2225–2224 cm^{-1}. The presence of NO_2 groups in compounds **IIIw, IIIv, IVv**–**IVy** is confirmed by the observation of characteristic IR bands at 1541–1525 and 1349–1343 cm^{-1}.

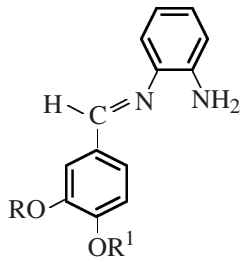
The UV spectra of 2,3-dihydro-1*H*-benzimidazoles **IIIa**–**III**α**, IVa**–**IV**γ show absorption bands with λ_{max} (log ε) at 238 nm (3.95) and 292 nm (4.00), assignable to the 2-[3-alkoxy-4-(hydroxy, alkoxy, acyloxy)-phenyl]-2,4-dihydro-1*H*-benzimidazole fragments. In the ^{1}H NMR spectra of 2,3-dihydro-1*H*-benzimidazoles **IIIa**–**III**α**, IVb**, the signals of MeO group appear as singlets at δ 3.85–3.92 ppm. In the spectra of compounds **IVa**–**IV**γ, the EtO group gives a triplet at 1.35–1.70 ppm (Me) and a quartet at 4.00–4.40 ppm (CH_2). The signals of aromatic protons of 2,3-dihydro-1*H*-benzimidazoles **IIIa**–**III**α**, IVa**–**IV**γ are in the range δ 6.50–8.35 ppm. The signals of methylidene protons at C(2) appear as a characteristic singlet at 8.45–8.55 ppm.

The IR, UV, and ^{1}H NMR spectra of 2,3-dihydro-1*H*-benzimidazoles **IIIa**–**III**α**, IVa**–**IV**γ provide evidence for the presence of the corresponding fragments of ester groups.

The 2,3-hydro-1*H*-benzimidazoles are unstable compounds quickly darkening on exposure to sunlight and air oxygen due to tarring. Apparently, first oxidative dehydration occurs to form 1*H*-benzimidazoles which undergo further transformations. In the IR s pectra of the samples of 2,3-dihydro-1*H*-benzimidazoles **IIIa**–**III**α**, IVa**–**IV**γ, handled for 1–2 days at 20–25°C, we observed appearance and gradual growth of the characteristic band at 1625–1622 cm^{-1} related to C=N absorption. At the same time, the ^{1}H NMR spectra showed gradual decrease in the intensity of the C(2)H proton signal at 8.45–8.55 ppm. These facts provide evidence for the above suggestions. Compounds **IIIa**–**III**α**, IVa**–**IV**γ can be handled for a long time in sealed ampules under argon in the absence of light and at temperatures below –5°C.

As known, aldehydes react with primary amines to form azomethines [4]. Among the reaction products of the vanillin and vanillal derivatives with 1,2-phenylenediamine (**II**), no corresponding azomethines were found. To explain this fact we carried out quantum-chemical calculations of the heats of formation (H_f) of 2-[3-alkoxy-4-(hydroxy, alkoxy, acyloxy)-phenyl]-2,3-dihydro-1*H*-benzimidazoles **IIIa, IIId, IIIq, IVb, IVc, IV**γ and their isomeric azomethines, (*E*)-[3-alkoxy-4(hydroxy, alkoxy, acyloxy)phenylmethylene](2-aminophenyl)amines **Va, Vd, Vq, VIb, VIc, VI**γ.

The quantum-chemical calculations were carried out by the semiempirical MNDO PM3 method with full optimization of interatomic distances and bond and dihedral angles, using GAMESS [5]. The follow-



Va, Vd, Vq, VIb, VIc, VIα

ing H_f values (kcal mol^{-1}) of 2,3-dihydro-1*H*-benzimidazoles were obtained (the H_f values for the isomeric (*E*)-azomethines are given in brackets): –25.5 (**IIIa**) [–12.9 (**Va**)]; –65.2 (**IIId**) [–54.8 (**Vd**)]; –24.6 (**IIIq**) [–13.6 (**Vq**)]; –20.5 (**IVb**) [–10.5 (**VIb**)]; –65.8 (**IVc**) [–55.2 (**VIc**)]; –109.5 (**IV**α) [–97.8 (**VI**γ)]. Hence, 2,3-dihydro-1*H*-benzimidazoles **IIIa, IIId, IIIq, IVb, IVc, IV**γ are 10.0–12.1 kcal mol^{-1} thermodynamically more stable than the corresponding isomeric (*E*)-azomethines **Va, Vd, Vq, VI b, VIc, VI**γ. This fact explains the formation of 2,3-dihydrobenzimidazoles **IIIa**–**III**α**, IVa**–**IV**γ, rather than azomethines in the reactions of aldehydes **I** with 1,2-phenylenediamine (**II**) under conditions of thermodynamic equilibrium [4].

EXPERIMENTAL

The IR spectra were recorded on a Nicolet Protege-460 Fourier spectrometer in thin layer or in KBr. The UV spectra were obtained on a Varian Cary-300 UV-Vis spectrophotometer for 1×10^{-4} M methanol solutions. The ^{1}H NMR spectra were taken on a Tesla BS-587A (100 MHz) spectrometer for 5% $CDCl_3$ solutions against internal TMS. Elemental analysis was performed on an Elementar Vario EL-III C,H,N,O,S-analyzer, determination error 0.1%. The molecular weights (*M*) were measured by cryoscopy in benzene.

Vanillin and vanillal esters **I** were obtained by the procedures in [6–9]. 1,2-Phenylenediamine of analytic grade was used, purity 98%, mp 102–103°C.

2-[3-Alkoxy-4-(hydroxy, alkoxy, acyloxy)phenyl-2,3-dihydro-1*H*-benzimidazoles IIIa–**III**α**, IVa**–**IV**γ *(general procedure).* A solution of 5 mmol of aldehyde of the vanillin series **I** and 5 mmol of 1,2-phenylenediamine (**II**) in 30 ml of methanol was refluxed for 0.5 h under argon. The solution was filtered while hot through a folded filter paper, cooled, and left for 10–15 h at 5°C. The crystals of compounds **IIIj, IIIm**–**IIIv, IVm, IVn, IVp**–**IVy** were filtered off on a glass frit, washed with a little methanol, and dried in a vacuum. The other 2,3-dihydro-1*H*-benzimidazoles **IIIa**–**IIIi, IIIk, IIIl, IIIx**–**IIIz, IVa**–**IVl, IVo, IVz**–**IV**γ were obtained as viscous glass-like compounds by removing methanol in a vacuum (1 mm Hg, *T* 30–35°C).

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