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Synthesis of (*E*)-4-Ethoxyphenyliminomethylaryls and Their Hydrochlorides

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Abstract—Condensation of *p*-phenetidine with the substituted aromatic benzaldehydes in methanol results in (*E*)-4-methylethoxyphenyliminoaryl derivatives. The latter react with gaseous hydrogen chloride in diethyl ether to form 4-ethoxymethylphenyliminoaryl hydrochlorides.

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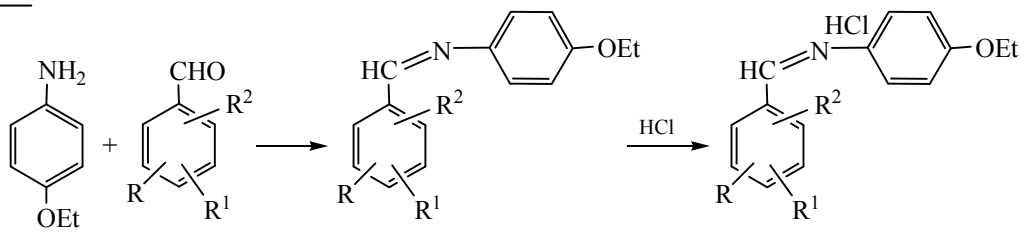
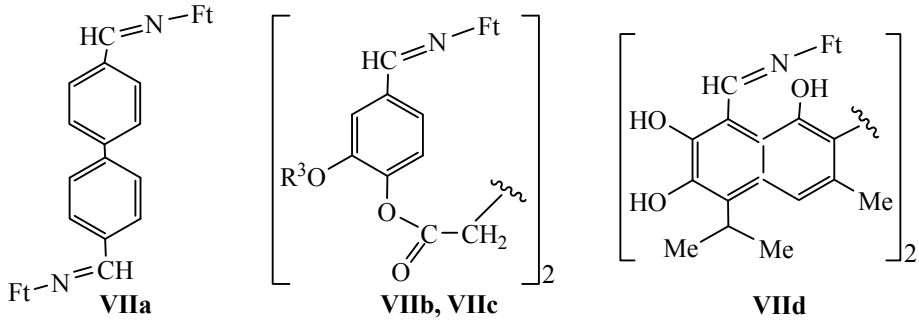
p-Phenetidine (4-ethoxyaniline) **I** has acquired special importance as the starting material for the synthesis of numerous febrifuge, antipyretic, and antineuralgic drugs, beginning with phenacetin (acetyl-*p*-phenetidine) obtained in 1887 [1].

In this work we have developed a preparative method for the synthesis of new (*E*)-4-ethoxyphenyliminomethylaryl derivatives **IIIa–IIIv**, **IVa–IVj**, **VIIa–VIId** in the yield of 87–93% via the condensation of *p*-phenetidine **I** with aromatic alde-



I **II** **IIIa–IIIv, IVa–IVj** **Va–Vv, VIa–VIj**

II, III, V, R = R^1 = R^2 = H (**a**); R = R^1 = H, R^2 = 4-OH (**b**), 4-OMe (**c**); R = H, R^1 = 2-OH, R^2 = 4-OH (**d**), 3-OMe (**e**); R = H, R^1 = 3-OH, R^2 = 4-OMe (**f**); R = H, R^1 = 3-OMe, R^2 = 4-OH (**g**), R^2 = 4-OMe (**h**); R = 3-OMe, R^1 = 4-OMe, R^2 = 6-Br (**i**); R = H, R^1 = 3-OMe, R^2 = 4-OOCMe (**j**), 4-OOCEt (**k**), 4-OOCPr (**l**), 4-OOC-*i*-Pr (**m**), 4-OOCBu (**n**), 4-OOC-*i*-Bu (**o**), 4-OOC$(CH_2)_8$Me (**p**), 4-OOC$(CH_2)_{11}$Me (**q**), 4-OOC$(CH_2)_{16}$Me (**r**), 4-OOCPh (**s**), 4-OOCPh-2,4-Cl_2 (**t**), 4-OCOOMe (**u**), 4-COO-Ad-1 (**v**); **IV, VI**, R = H, R^1 = 3-OEt, R^2 = 4-OH (**a**), 4-OMe (**b**), 4-OOCMe (**c**), 4-OOCEt (**d**), 4-OOCPr (**e**), 4-OOC-*i*-Pr (**f**), 4-OOCBu (**g**), 4-OOC-*i*-Bu (**h**), 4-OOCPh (**i**), 4-OOCPh-4-Me (**j**).



VIIa **VIIb, VIIc** **VIId**

VIIa–VIId, Ft = 4-OEtC_6H_4, R^3 = Me (**b**), Et (**c**).

Table 1. Yields, melting points, and elemental analysis data of azomethines **IIIa–IIIv, IVa–IVj, VIIa–VIId**

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %			*M*	
			C	H	N		C	H	N	found	calculated
IIIa	87	75–76	80.23	6.85	5.89	$C_{15}H_{15}NO$	79.97	6.71	6.22	219	225
IIIb	89	217–218	74.90	6.42	5.42	$C_{15}H_{15}NO_2$	74.67	6.27	5.81	234	241
IIIc	88	132–133	75.56	6.80	5.12	$C_{16}H_{17}NO_2$	75.27	6.71	5.49	246	255
IIId	92	167–168	70.39	6.02	5.05	$C_{15}H_{15}NO_3$	70.02	5.88	5.44	251	257
IIIe	90	99–100	71.13	6.38	4.87	$C_{16}H_{17}NO_3$	70.83	6.32	5.16	262	271
IIIf	92	142–143	71.20	6.44	4.91	$C_{16}H_{17}NO_3$	70.83	6.32	5.16	264	271
IIIg	93	106–107	71.17	6.45	4.80	$C_{16}H_{17}NO_3$	70.83	6.32	5.16	266	271
IIIh	91	105–106	71.84	6.87	4.65	$C_{17}H_{19}NO_3$	71.56	6.71	4.91	279	285
IIIi[a]	88	117–118	56.51	5.14	3.67	$C_{17}H_{18}BrNO_3$	56.06	4.98	3.85	357	364
IIIj	87	97–98	69.20	6.19	4.21	$C_{18}H_{19}NO_4$	68.99	6.11	4.47	306	313
IIIk	87	90–91	70.03	6.56	3.95	$C_{19}H_{21}NO_4$	69.71	6.47	4.28	319	327
IIIl	88	57–58	70.64	6.95	3.88	$C_{20}H_{23}NO_4$	70.36	6.79	4.10	333	341
IIIm	90	85–86	70.72	6.83	3.75	$C_{20}H_{23}NO_4$	70.36	6.79	4.10	336	341
IIIn	90	74–75	71.38	7.19	3.65	$C_{21}H_{25}NO_4$	70.96	7.09	3.94	348	355
IIIo	91	77–78	71.25	7.10	3.86	$C_{21}H_{25}NO_4$	70.96	7.09	3.94	346	355
IIIp	87	65–66	73.57	8.36	3.20	$C_{26}H_{35}NO_4$	73.38	8.29	3.29	409	426
IIIq	89	57–58	74.90	8.84	2.67	$C_{29}H_{41}NO_4$	74.48	8.84	3.00	450	468
IIIr	91	73–74	76.18	9.65	2.18	$C_{34}H_{51}NO_4$	75.94	9.56	2.60	527	538
IIIs	90	146–147	73.84	5.72	3.28	$C_{23}H_{21}NO_4$	73.58	5.64	3.73	366	375
IIIt[b]	92	114–115	62.41	4.33	2.80	$C_{23}H_{19}Cl_2NO_4$	62.17	4.31	3.15	431	444
IIIu	90	107–108	65.86	5.92	3.85	$C_{18}H_{19}NO_5$	65.64	5.81	4.25	322	329
IIIv	88	156–157	77.00	6.68	2.64	$C_{30}H_{31}NO_4$	76.73	6.65	2.98	456	470
IVa	90	109–110	71.86	6.78	4.62	$C_{17}H_{19}NO_3$	71.56	6.71	4.91	276	285
IVb	89	101–102	72.18	7.21	4.48	$C_{18}H_{21}NO_3$	72.22	7.07	4.68	284	299
IVc	93	88–89	69.92	6.51	4.03	$C_{19}H_{21}NO_4$	69.71	6.47	4.28	322	327
IVd	92	77–78	70.56	7.03	3.86	$C_{20}H_{23}NO_4$	70.36	6.79	4.10	332	341
IVe	91	83–84	71.15	7.16	3.81	$C_{21}H_{25}NO_4$	70.96	7.09	3.94	348	355
IVf	90	93–94	71.06	7.22	3.60	$C_{21}H_{25}NO_4$	70.96	7.09	3.94	346	355
IVg	89	73–74	71.87	7.40	3.29	$C_{22}H_{27}NO_4$	71.52	7.37	3.79	361	369
IVh	88	84–85	71.70	7.51	3.52	$C_{22}H_{27}NO_4$	71.52	7.37	3.79	363	369
IVi	90	138–139	74.25	6.14	3.28	$C_{24}H_{23}NO_4$	74.02	5.95	3.60	382	389
IVj	90	155–156	74.15	6.38	3.06	$C_{25}H_{25}NO_4$	74.42	6.25	3.47	389	403
VIIa	89	205–206	80.48	6.19	5.78	$C_{30}H_{28}N_2O_2$	80.33	6.29	6.25	Insoluble	449
VIIb	90	204–205	69.47	6.03	4.40	$C_{36}H_{36}N_2O_8$	69.22	5.81	4.48	603	625
VIIc	91	171–172	70.13	6.28	3.87	$C_{38}H_{40}N_2O_8$	69.92	6.18	4.29	640	653
VIId	87	282–283	73.50	6.36	3.38	$C_{46}H_{48}N_2O_8$	73.00	6.39	3.70	Insoluble	757

[a] Found Br, %: 21.46. Calculated Br, %: 21.94. [b] Found Cl, %: 15.58. Calculated Cl, %: 15.96.

hydes **II**: benzaldehyde, anisaldehyde, and veratraldehyde, aldehydes of the vanillin series, 4,4'-diformylbiphenyl and gossypol [2,2'-bis(1,6,7-trioxo-3-methyl-5-isopropyl-8-naphthaldehyde]. The synthesis was carried out in anhydrous methanol at reflux.

The reaction of the monobasic azomethines **IIIa–IIIv**, **IVa–IVj** with the gaseous hydrogen chloride in anhydrous ether results in the corresponding 4-ethoxyphenyliminomethylaryl hydrochlorides **Va–Vv**, **VIa–VIj** in the yield of 89–95%. Under the reaction conditions, the hydrolysis of the ester side groups in compounds **Vj–Vv**, **VIc–VIj** did not occur. We failed to obtain the hydrochlorides of dibasic Schiff bases **VIIa–VIId** because of their low solubility in diethyl ether and benzene.

Table 2. Yields, melting points, and elemental analysis data of hydrochlorides **Va–Vv, VIa–VIj**

Comp. no.	Yield, %	mp, °C	Found, %				Formula	Calculated, %			
			C	H	Cl	N		C	H	Cl	N
Va	91	112–113	69.24	6.28	13.10	5.14	$C_{15}H_{16}ClNO$	68.83	6.16	13.54	5.35
Vb	92	229–230	65.09	5.73	12.22	4.86	$C_{15}H_{16}ClNO_2$	64.87	5.81	12.76	5.04
Vc	90	192–193	66.13	6.08	12.04	4.66	$C_{16}H_{18}ClNO_2$	65.86	6.22	12.15	4.80
Vd	93	134–135	61.50	5.28	11.70	4.45	$C_{15}H_{16}ClNO_3$	61.33	5.49	12.07	4.77
Ve	94	177–178	62.81	6.10	11.19	4.30	$C_{16}H_{18}ClNO_3$	62.44	5.89	11.52	4.55
Vf	93	184–185	62.19	5.99	11.40	4.21	$C_{16}H_{18}ClNO_3$	62.44	5.89	11.52	4.55
Vg	93	119–120	62.60	6.05	11.28	4.62	$C_{16}H_{18}ClNO_3$	62.44	5.89	11.52	4.55
Vh	89	237–238	63.78	6.41	10.59	4.03	$C_{17}H_{20}ClNO_3$	63.45	6.26	11.02	4.35
Vi	90	189–190	51.15	4.22	28.60	3.23	$C_{17}H_{19}BrClNO_3$	50.96	4.78	28.79	3.50
Vj	94	197–198	62.12	5.48	10.19	3.68	$C_{18}H_{20}ClNO_4$	61.80	5.76	10.13	4.00
Vk	94	176–177	63.20	6.18	9.31	3.44	$C_{19}H_{22}ClNO_4$	62.72	6.09	9.74	3.85
Vl	93	168–169	63.93	6.45	9.02	3.73	$C_{20}H_{24}ClNO_4$	63.57	6.40	9.38	3.71
Vm	92	177–178	63.84	6.61	8.99	3.36	$C_{20}H_{24}ClNO_4$	63.57	6.40	9.38	3.71
Vn	95	163–164	64.65	6.40	8.73	3.25	$C_{21}H_{26}ClNO_4$	64.36	6.69	9.05	3.57
Vo	93	169–170	64.10	6.92	8.87	3.19	$C_{21}H_{26}ClNO_4$	64.36	6.69	9.05	3.57
Vp	93	157–158	67.88	8.04	7.18	2.76	$C_{26}H_{36}ClNO_4$	67.59	7.85	7.67	3.03
Vq	94	151–152	69.54	8.57	6.65	2.41	$C_{29}H_{42}ClNO_4$	69.10	8.40	7.03	2.78
Vr	92	84–85	71.37	9.35	5.80	2.07	$C_{34}H_{52}ClNO_4$	71.11	9.13	6.17	2.44
Vs	92	221–222	67.39	5.46	8.19	3.20	$C_{23}H_{22}ClNO_4$	67.07	5.38	8.61	3.40
Vt	90	203–204	57.82	4.18	21.91	2.66	$C_{23}H_{20}Cl_3NO_4$	57.46	4.19	22.12	2.91
Vu	89	186–187	59.45	5.73	9.58	3.47	$C_{18}H_{20}ClNO_5$	59.10	5.51	9.69	3.83
Vv	91	206–207	71.53	6.41	6.86	2.53	$C_{30}H_{32}ClNO_4$	71.21	6.37	7.01	2.77
VIa	90	117–118	63.56	6.38	10.62	3.99	$C_{17}H_{20}ClNO_3$	63.45	6.26	11.02	4.35
VIb	93	223–224	64.58	6.47	10.23	3.85	$C_{18}H_{22}ClNO_3$	64.38	6.60	10.56	4.17
VIc	93	173–174	62.95	6.24	9.51	3.54	$C_{19}H_{22}ClNO_4$	62.72	6.09	9.74	3.85
VId	92	183–184	63.49	6.61	9.18	3.37	$C_{20}H_{24}ClNO_4$	63.57	6.40	9.38	3.71
VIe	92	180–181	64.76	6.92	8.46	3.22	$C_{21}H_{26}ClNO_4$	64.36	6.69	9.05	3.57
VIf	93	188–189	64.25	6.78	8.59	3.15	$C_{21}H_{26}ClNO_4$	64.36	6.69	9.05	3.57
VIg	92	161–162	65.65	7.09	8.34	3.05	$C_{22}H_{28}ClNO_4$	65.10	6.95	8.73	3.45
VIh	95	169–170	65.70	7.24	8.19	3.41	$C_{22}H_{28}ClNO_4$	65.10	6.95	8.73	3.45
VIi	94	191–192	68.11	5.43	8.38	2.92	$C_{24}H_{24}ClNO_4$	67.68	5.68	8.32	3.29
VIj	90	205–206	68.72	6.13	7.76	2.84	$C_{25}H_{26}ClNO_4$	68.25	5.96	8.06	3.18

The synthesized compounds **IIIa–IIIv**, **IVa–IVj**, **Va–Vv**, **VIa–VIj**, **VIIa–VIId** are stable yellow or orange crystalline substances with the clear melting points (Tables 1, 2). Azomethines **IIIa–IIIv**, **IVa–IVj** are soluble in diethyl ether, benzene, chloroform, and DMSO, and insoluble in water. The hydrochlorides **Va–Vv**, **VIa–VIj** are insoluble in nonpolar aprotic solvents, but they are soluble in alcohol, acetone, DMSO, and moderately soluble in water. This fact makes convenient and promising the study of their biological activity [2, 3].

The IR spectra of the Schiff bases **IIIa–IIIv**, **IVa–IVj**, **VIIa–VIId** contain the characteristic absorption bands (ν, cm^{-1}): 3100–3030, 880–690 (CH_{arom}), 2980–2850 (CH_{aliph}), 1770–1720 ($C{=}O_{ester}$) (**IIIj–IIIv**, **IVc–IVj**, **VIIc**, **VIId**), 1610–1460 ($C{=}C_{arom}$), 1630–1615 (C=N), 1275–1020 (C–O). There is no absorption band $\nu(C{=}O_{aldehyde})$ at 1700–1680 cm^{-1}, characteristic of the original benzaldehydes **II** . In the IR spectra of the hydrochlorides **Va–Vv**, **VIa–VIj** there are additional absorption bands at 2750–2250 (N^+H) and 1670–1650 cm^{-1} ($C{=}N^+$). The IR spectra of the hydrochlorides **Vj–Vv**, **VIc–VIj** contain the absorption band $\nu(C{=}O_{ester})$, the position and intensity of which have not changed in comparison with the starting azomethines **IIIj–IIIv**, **IVc–IVj**.

In the ^{1}H NMR spectra of the Schiff bases **IIIa–IIIv**, **IVa–IVj**, **VIIa–VIId** there are the proton signals of the *p*-phenetidine fragment (δ, ppm): 1.2–1.7 t (Me), 3.8–4.3 q (CH_2), 6.7–7.4 m (C_6H_4), 8.4–8.7 s (HC=N), which indicates their *E*-configuration [4]. The MeO proton signals are singlets in the range of 3.8–4.0 ppm (**IIIc**, **IIIe–IIIv**, **IVb**, **VIIb**). The EtO proton signals in **IVa–IVj**, **VIIc** are observed in the range of 1.2–1.7 (t, Me) and 3.8–4.3 (q, CH_2). In the ^{1}H NMR spectra of the hydrochlorides **Va–Vv**, **VIa–VIj** the singlet signals in the ranges of 10.0–10.2 and 10.1–11.2 ppm belong to the $HC{=}N^+$ and HN^+Cl^- groups.

The IR and ^{1}H NMR spectra of compounds **IIIa–IIIv**, **IVa–IVj**, **Va–Vv**, **VIa–VIj**, **VIIa–VIId** contain the absorption band and the proton signals confirming the presence of all the corresponding structural fragments of the ester groups.

EXPERIMENTAL

The IR spectra were recorded on a spectrophotometer Protege-460 Nicolet FTIR (thin layer, KBr). The ^{1}H NMR spectra were registered on a spectrometer Tesla BS-587A (100 MHz) relative to internal TMS using deuterochloroform or DMSO-d_6 as the solvents. The molecular weights of the azomethines obtained were determined by the cryoscopy in benzene.

(*E*)-4-Ethoxyphenyliminomethylaryles (IIIa–IIIv, IVa–IVj). A solution of 5 mmol of *p*-phenetidine **I** and 5 mmol of the appropriate aromatic aldehyde **II** in 40 ml of anhydrous methanol was refluxed for 30–45 min. The solution was cooled to 0–5°C. The azomethines were filtered off, washed with cold methanol, and dried in air for 6–8 h.

Bisazomethines (VIIa–VIId). A solution of 10 mmol of *p*-phenetidine **I** and 5 mmol of the appropriate dibasic aromatic aldehyde **II** in 50 ml of anhydrous methanol was refluxed for 45 min. The target products were isolated as described above.

4-Ethoxyphenyliminomethylaryles hydrochlorides (Va–Vv, VIa–VIj). Dry hydrogen chloride [5] was bubbled through a cooled (0–5°C) solution of 1 mmol of azomethine **IIIa–IIIv** or **IVa–IVj** in 30–50 ml of anhydrous ether for 10–15 min. The formed precipitate was filtered off, washed with cold ether, and dried in air for 3–4 h.

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