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Hydrogenation of 4-Phenylspinaceamines and Synthesis of 5-Benzylhistamines

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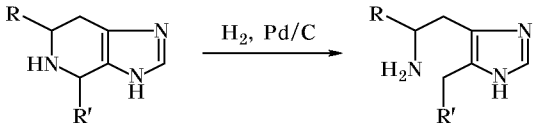
Abstract—4-Phenyl derivatives of spinaceamine and spinacine undergo mild catalytic hydrogenation under atmospheric pressure with cleavage of the C^4-N^5 bond to give 5-benzyl-substituted histamines and histidines. The process is likely to be facilitated by the double benzylic effect on the C–N bond of the imidazole and benzene rings.

Spinaceamines (4,5,6,7-tetrahydroimidazo[4,5-*c*]-pyridines **I**) can be regarded as cyclic analogs of histamine. They are obtained in good yields by the Pictet–Spengler reaction from histamine and carbonyl compounds [1, 2]. In 1982, Emmett *et al.* [3] showed that the hydrogenation of 4-phenylspinaceamine dihydrochloride (**Ia**) (as the only example) over palladium catalyst under severe conditions (hydrogen presure 100 atm, reaction time 26 h) leads to cleavage of the C^4-N^5 bond and formation of 79% of 5-benzylhistamine (**IIIa**) which was isolated as the corresponding dihydrobromide. Thus the possibility for introducing a benzyl group into position *5* of the histamine molecule starting from 4-phenylspinaceamine was demonstrated for the first time. However, realization of this process involves serious technical difficulties associated with high pressure of hydrogen. Therefore, the preparative value of this procedure is not high; moreover, one cannot be sure that the reaction is of general character, for only one example has been reported.

We focused on one structural feature of 4-phenylspinaceamine molecule in which the C^4-N^5 occupies benzylic position with respect to both benzene and imidazole rings. Such a double effect of aromatic rings should strongly facilitate hydrogenolysis of the above bond, as compared with common benzylamines, and acid medium should favor the process.

In fact, 4-phenylspinaceamine dihydrochloride (**Ia**) in a mixture of methanol with glacial acetic acid (1 : 1) readily absorbed a required amount of hydrogen (during 3–5 h) over palladium catalyst (Pd/C, 25% of Pd) under atmospheric pressure at room temperature. The yield of of 5-benzylhistamine (**IIIa**) was almost quantitative [4]. The ^{1}H NMR spectrum and melting point of **IIIa** dihydrobromide were the same as those reported in [3]. A similar ^{1}H NMR pattern was observed for 4-benzylimidazole [5] (as concerns the position and intensity of signal from the benzylic methylene protons).

We have found that 4-phenylspinaceamines **Ib**–**Ih** having a substituent in the benzene ring, as well as 4-(4-pyridyl)spinaceamine (**Ii**) (Table 1), also readily undergo catalytic hydrogenation under atmospheric pressure to afford the corresponding 5-benzylhistamines **IIIb**–**IIIh** and 5-(4-pyridylmethyl)histamine (**IIIi**) in high yields (Table 2). The best results were obtained when the hydrogenation was performed in a mixture of glacial acetic acid with methanol.



Ia–Ii, IIa–IIj **IIIa–IIIi, IVa–IVj**

Ia–**Ii**, **IIIa**–**IIIi**, R = H; **IIa**–**IIj**, **IVa**–**IVj**, R = COOH; **Ia**, **IIa**, **IIIa**, **IVa**, R′ = C_6H_5; **IIb**, **IVb**, R′ = 3-HOC_6H_4; **Ib**, **IIc**, R′ = 4-$PhCH_2OC_6H_4$; **IIIb**, **IVc**, R′ = 4-HOC_6H_4; **Ic**, **IId**, R′ = 3-$NO_2C_6H_4$; **IIIc**, **IVd**, R′ = 3-$H_2NC_6H_4$; **Id**, **IIe**, **IIId**, **IVe**, R′ = 4-$CH_3OC_6H_4$; **Ie**, **IIIe**, R′ = 2,4-$(CH_3O)_2C_6H_3$; **If**, **IIIf**, R′ = 2,5-$(CH_3O)_2C_6H_3$; **IIf**, **IVf**, R′ = 4-BrC_6H_4; **IIg**, **IVg**, R′ = 4-FC_6H_4; **Ig**, **IIh**, **IIIg**, **IVh**, R′ = 3,4-$(OCH_2O)C_6H_3$; **Ih**, **IIIh**, R′ = 3,4,5-$(CH_3O)_3C_6H_2$; **Ii**, **IIi**, **IIIi**, **IVi**, R′ = 4-pyridyl; **IIj**, **IVj**, R′ = 3-hydroxy-5-hydroxymethyl-2-methyl-4-pyridyl.

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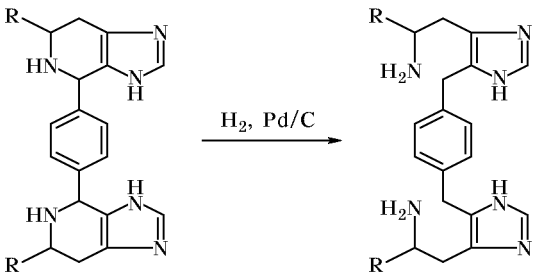
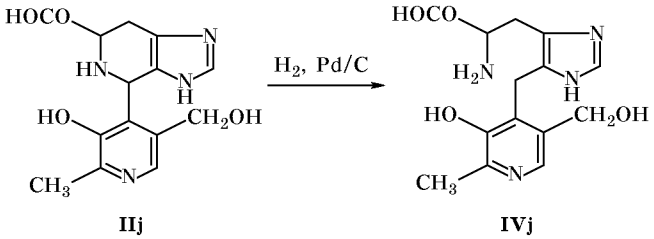
Taking into account structural analogy between spinacines and spinaceamines, we applied the proposed procedure to 4-phenylspinacines [4]. The C^4-N^5 bond in these compounds also suffers double influence of the imidazole and benzene (or pyridine) rings. The hydrogenation of 4-phenylspinacines **IIa**–**IIi** (Table 1) over Pd/C under atmospheric pressure at room temperature gave the corresponding 5-benzylhistidines **IVa**–**IVi** in high yield (Table 2).

The hydrogenolysis of compounds **Ib** and **IIc** was accompanied by elimination of the *O*-benzyl group; as a result, 5-*p*-hydroxybenzyl-substituted hystamine **IIIb** and histidine **IVc** were formed; the hydrogenation of **Ic** and **IId** also involved the nitro group and yielded 5-*m*-aminobenzylhystamine (**IIIc**) and 5-*m*-aminobenzylhistidine (**IVd**). *p*-Phenylenebisspinaceamine and spinacine derivatives **Ij** and **IIk** were converted into the corresponding histamine and histidine derivatives with unusual stucture (**IIIj** and **IVk**):



Ij, **IIIj**, R = H; **IIk**, **IVk**, R = COOH.

By mild hydrogenation of spinacine **IIj**, which was synthesized from histidine and pyridoxal [6, 7], we obtained for the first time a histidine–vitamin B_6 hybrid **IVj**:



5-Substituted histamines **IIIa**–**IIIj** show similar patterns in the ^{1}H NMR spectra (Table 4). In all cases the intensity of the singlet of the benzylic methylene protons is twice as large as that of the 4-H proton in the spectra of the corresponding 4-substituted spinaceamines **Ia**–**Ij**. The positions and intensities of the other signals of **IIIa**–**IIIj** differ only slightly from those observed for initial spinaceamines **Ia**–**Ij** (Table 3). For example, the difference between the chemical shifts of 4-H in **Ia** and 5-CH_2 in **IIIa** is a few hundredth ppm. The chemical shifts of 5-CH_2 in **IIIa**–**IIIj** dihydrochlorides vary within a relatively narrow range, from 3.81 to 4.16 ppm. In going from base **IIIa** to the corresponding dihydrochloride, the 5-CH_2 signal shifts downfield by 0.82 ppm. However, the difference between the chemical shifts of 4-H of 4-phenylspinaceamine **Ia** in a neutral solvent and in an acid (CF_3COOH) is considerably smaller, –0.06 ppm. The position of the other signals (2-H, aromatic, and other CH_2 protons) almost does not change in going from spinaceamines **Ia**–**Ij** to histamines **IIIa**–**IIIj**.

5-Benzylhistidines **IVa**–**IVk** show in the ^{1}H NMR spectra (Table 4) stronger differences from the initial 4-arylspinacines (Table 3). The 5-CH_2 signal of **IVa** is located in a stronger field (δ 3.91 ppm) than the 4-H signal of **IIa** (δ 4.20 ppm). The upfield shift of the 5-CH_2 signal relative to the 4-H signal of initial spinacines **IIa**–**IIk** is also typical of 5-benzylhistidine **IVa**–**IVk** dihydrochlorides. However, the most characteristic are the positions of the 7-H (α-proton with respect to the carboxy group) signal of **II** and 4-β-CH of **IV**. The chemical shifts of 7-H in the ^{1}H NMR spectra of spinacine **IIa**–**IIk** dihydrochlorides range from 5.56 to 6.30 ppm, whereas the 4-β-CH signal in the spectra of **IVa**–**IVk** dihydrochlorides (Table 4) appears in the region δ 3.56–3.85 ppm. Thus the difference attains ~2–2.5 ppm, and these signals can be used to distinguish 5-benzylhistidines from initial 4-phenylspinacine. The intensity of the benzylic methylene proton signal in the spectra of 5-benzylhistidines is twice as large as the intensity of the 4-H signal of initial spinacine.

We can conclude that only absorption of a required amount of hydrogen and appearance of a double-intensity peak in the ^{1}H NMR spectra of the products ensure reliable monitoring of the progress of hydrogenation of spinaceamines **Ia**–**Ij**.

It is known that synthesis of substituted histamines always involves difficulties. First of all, this applies to C-substituted histamines which are promising as H_1-, H_2-, and H_3-histamine receptor antagonists [3, 8–11]. Histamine itself is a vitally important physiological mediator exhibiting versatile activity. At a normal concentration, histamine shows properties of a hormone; however, its presence in excess concentrations can lead to various heavy disorders [12, 13]. Synthesis of new histamine antagonists is

Table 1. Yields, melting points, and elemental analyses of 4-aryl(pyridyl)spinaceamines **Ib**, **Ie**, and **If** and 4-aryl-spinacines **IIb**–**IIi** and **IIk**

Comp. no.	Yield, %	mp, °C (solvent)	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
Ib	71	118–120 (MeOH–H_2O)	74.75	6.35	13.70	$C_{19}H_{19}N_3O$	74.73	6.27	13.75
Ie	63	132–133 (MeOH–H_2O)	64.75	6.55	16.22	$C_{14}H_{17}N_3O_2$	64.85	6.61	16.20
If	88	103–105 (H_2O)	64.72	6.80	16.11	$C_{14}H_{17}N_3O_2$	64.85	6.61	16.20
IIb	90	>250 (decomp.) (alcohol)	46.92	4.68	12.50	$C_{13}H_{13}N_3O_3 \cdot 2HCl$	47.00	4.55	12.65
IIc	~99	190–193 (*i*-PrOH)	68.66	5.62	11.99	$C_{20}H_{19}N_3O_3$	68.75	5.48	12.03
IId	92	224–226 (alcohol)	43.38	3.79	15.55	$C_{13}H_{12}N_4O_4 \cdot 2HCl$	43.20	3.90	15.51
IIe	92	222–224 (alcohol)	48.39	5.06	12.01	$C_{14}H_{15}N_3O_3 \cdot 2HCl$	48.57	4.95	12.14
IIf	75	207–209 (alcohol)	39.43	3.68	10.50	$C_{13}H_{12}BrN_3O_2 \cdot 2HCl$	39.52	3.57	10.63
IIg	65	219–221 (alcohol)	46.65	4.35	12.50	$C_{13}H_{12}FN_3O_2 \cdot 2HCl$	46.72	4.22	12.57
IIh	92	216 (decomp.) (alcohol)	46.59	4.32	11.52	$C_{14}H_{13}N_3O_4 \cdot 2HCl$	46.68	4.20	11.68
IIi	66	209–211 (alcohol)	45.35	4.53	17.58	$C_{12}H_{12}N_4O_2 \cdot 2HCl$	45.44	4.45	17.67
IIk	97	>300 (decomp.) (alcohol)	58.60	5.17	20.32	$C_{20}H_{20}N_6O_4$	58.81	4.94	20.58

Table 2. Yields, melting points, and elemental analyses of 5-benzylhistamines **IIIa**–**IIIj** and 5-benzylhistidines **IVa**–**IVk**

Comp. no.	Yield, %	mp, °C (solvent)	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
IIIa	~100	64–65 (*i*-PrOH)				$C_{12}H_{15}N_3$			
IIIb	70	195–197 (alcohol)	49.52	6.01	14.28	$C_{12}H_{15}N_3O \cdot 2HCl$	49.66	5.90	14.48
IIIc	80	225–227 (alcohol)	45.09	5.75	17.38	$C_{12}H_{16}N_4 \cdot 2HCl$	45.15	5.68	17.55
IIId	~100	91–93 (*i*-PrOH)	67.49	7.52	18.15	$C_{13}H_{17}N_3O$	67.50	7.41	18.14
IIIe	80	88–89 (*i*-PrOH)	64.41	7.35	16.15	$C_{14}H_{19}N_3O_2$	64.35	7.33	16.03
IIIf	72	225–228 (alcohol)	50.22	6.50	12.38	$C_{14}H_{19}N_3O_2 \cdot 2HCl$	50.31	6.39	12.57
IIIg	80	242–245[a] (alcohol)	49.02	5.45	13.12	$C_{13}H_{15}N_3O_2 \cdot 2HCl$	49.07	5.39	13.21
IIIh	71	240[a] (alcohol)	49.32	6.45	11.39	$C_{15}H_{21}N_3O_3 \cdot 2HCl$	49.46	6.36	11.54
IIIi	75	155–157 (alcohol)	47.95	5.99	20.28	$C_{11}H_{14}N_4 \cdot 2HCl$	48.01	5.80	20.36
IIIj	90	270[a] (alcohol)	45.82	6.13	17.68	$C_{18}H_{24}N_6 \cdot 4HCl$	45.97	6.00	17.87
IVa	77	222–224 (alcohol)	49.15	5.51	13.29	$C_{13}H_{15}N_3O_2 \cdot 2HCl$	49.07	5.39	13.20
IVb	75	152–154 (alcohol)	46.66	5.17	12.52	$C_{13}H_{15}N_3O_3 \cdot 2HCl$	46.72	5.13	12.57
IVc	77	221–223 (*i*-PrOH)	59.68	5.80	16.28	$C_{13}H_{15}N_3O_3$	59.76	5.78	16.08
IVd	77	151–153 (alcohol)	46.75	5.42	16.70	$C_{13}H_{16}N_4O_4 \cdot 2HCl$	46.86	5.44	16.82
IVe	70	171–173 (alcohol)	48.39	5.67	12.14	$C_{14}H_{17}N_3O_3 \cdot 2HCl$	48.28	5.50	12.07
IVf	75	134–136[a] (alcohol)	39.28	4.17	10.43	$C_{13}H_{14}N_3O_2Br \cdot 2HCl$	39.32	4.06	10.58
IVg	81	206–208[a] (alcohol)	46.38	4.92	12.39	$C_{13}H_{14}N_3O_2F \cdot 2HCl$	46.44	4.80	12.50
IVh	90	157–159 (alcohol)	46.30	4.82	11.51	$C_{14}H_{15}N_3O_4 \cdot 2HCl$	46.43	4.73	11.60
IVi	90	197–199[a] (alcohol)	45.05	5.17	10.39	$C_{12}H_{14}N_4O_2 \cdot 2HCl$	45.15	5.05	17.55
IVj	60	196–197 (alcohol)	44.46	5.38	14.90	$C_{14}H_{18}N_4O_4 \cdot 2HCl$	44.33	5.33	14.77
IVk	68	244–246[a] (alcohol)	42.87	5.32	15.01	$C_{20}H_{24}N_6O_4$	43.02	5.05	15.05

[a] With decomposition.

Table 3. ^{1}H NMR spectra of 4-arylspinaceamines **Ia**–**Ij** and 4-arylspinacines **IIa**–**IIk**, δ, ppm

Comp. no.	2-H, s	7-CH_2	6-CH_2 (**I**) or 6-CH (**II**), t	4-CH, s	H_{arom}
Ia	7.50	2.62–2.87 t	3.00–3.40	4.91	7.20–7.35 m (5H, C_6H_5)
Ia[a]	7.32	2.33–2.73 t	2.73–3.12	4.85	7.27 s (5H, C_6H_5)
Ib	8.15	3.00 t	3.84	5.10	4.85 s (2H, OCH_2), 6.81–7.69 m (9H, C_6H_5, C_6H_4)
Ic	8.17	2.77 t	3.13	5.16	7.59–7.77 m (3H, 4-H, 5-H, 6-H, C_6H_3), 8.23 s (1H, 2-H)
Id	7.58	2.80 t	2.96–3.32	5.13	3.89 s (3H, OCH_3), 6.97 d (2H, 3-H, 5-H, *J* = 8.0 Hz), 7.25 d (2H, 2-H, 6-H, *J* = 8.0 Hz)
Ie[b]	7.52	2.75 t	3.10	5.32	3.90 s (6H, $2OCH_3$), 6.47 d (1H, 5-H), 6.67 s (1H, 3-H), 6.85 d (1H, 6-H)
If	7.57	2.74 t	2.95–3.12	5.10	3.61 s (3H, 2-OCH_3), 3.87 s (3H, 5-OCH_3), 6.45 d (1H, 6-H, *J* = 3.0 Hz), 6.86 d (1H, 3-H, *J* = 9.0 Hz), 6.97 d (1H, 4-H, *J* = 9.0 Hz)
Ig	7.50	2.60–2.90 t	2.92–3.30	4.95	5.95 s (2H, OCH_2), 6.60–6.90 m (3H, 2-H, 5-H, 6-H, C_6H_3)
Ih	7.60	2.66–2.87 t	2.98–3.12	5.05	3.80 s (3H, OCH_3), 3.90 s (6H, $2OCH_3$), 6.65 s (2H, C_6H_2)
Ii	8.63	3.35 t	3.84	4.96	8.39 d (2H, 3-H, 5-H, *J* = 6.0 Hz), 9.15 d (2H, 2-H, 6-H, *J* = 6.0 Hz)
Ij	7.58	2.72–2.83 t	2.95–3.26	5.11	7.30 s (4H, C_6H_4)
IIa	8.92	3.36 d	5.56	4.20	7.60 s (5H, C_6H_5)
IIa[a]	8.37	3.33 d	5.67	4.37	7.05 s (5H, C_6H_5)
IIb[c]	9.10	3.55 d	5.95	4.05	6.81–7.41 m (3H, 4-H, 5-H, 6-H), 7.51 t (1H, 2-H)
IIc[c]	8.31	3.34 d	5.85	4.65	4.88 s (2H, CH_2), 7.25–7.48 m (9H, C_6H_5, C_6H_4)
IId[c]	9.03	3.50 d	6.30	4.87	7.90–8.13 m (2H, 5-H, 6-H), 8.51–8.59 m (2H, 2-H, 4-H)
IIe[c]	8.52	3.30 d	5.90	4.62	3.86 s (3H, OCH_3), 7.06 q (2H, 2-H, 6-H, *J* = 5.0 Hz), 7.40 q (2H, 3-H, 5-H, *J* = 8.6 Hz)
IIf[c]	8.42	3.25 d	5.85	4.45	7.49 d (2H, 2-H, 6-H, *J* = 8.0 Hz), 7.74 d (2H, 3-H, 5-H, *J* = 8.0 Hz)
IIg[c]	8.96	3.60 d	6.11	4.93	7.41 d (2H, 2-H, 6-H, *J* = 8.0 Hz), 7.70 d (2H, 3-H, 5-H, *J* = 8.0 Hz)
IIh[c]	8.86	3.31 d	6.00	4.42	6.06 s (2H, OCH_2), 6.75–7.05 m (3H, 2-H, 5-H, 6-H)
IIi[c]	8.91	3.40 d	6.05	4.68	7.35 d (2H, 3-H, 5-H, *J* = 6.0 Hz), 7.95 d (2H, 2-H, 6-H, *J* = 6.0 Hz)
IIj[c]	9.04	3.39 d	6.30	4.75	2.74 s (3H, CH_3), 4.71 s (2H, CH_2), 8.46 s (1H, 2-H)
IIk[c]	8.95	3.40 d	6.11	4.60	7.60–7.80 m (4H, C_6H_4)

[a] In CF_3COOH.
[b] In DMF-d_7.
[c] Dihydrochloride.

one of the most important fields of medicinal chemistry from the viewpoint of treatment of erosive and ulcerative gastrointestinal and also allergic and many other disorders.

L-Histidine is classed with the most important gene-coded amino acids [14]; it is a biosynthetic precursor of histamine and is used in medicine for treatment of hepatitis and ulcerative disease of the stomach; L-histidine also stimulates lipoprotein exchange in atherosclerosis [15]. Histidine derivatives have always been the subject of increased interest as potential highly biologically active compounds. On the other hand, synthetic procedures for a number of histidine derivatives are very laborious, especially for C-substituted histidines.

Thus we have shown for the first time that hydrogenation of 4-phenylspinaceamines and 4-phenylspinacines with cleavage of the C^4-N^5 bond can be

Table 4. ^{1}H NMR spectra of 5-benzylhistamines **IIIa**–**IIIj** and 5-benzylhistidines **IVa**–**IVk**, δ, ppm

Comp. no.	2-H, s	4-β-$H_2NCH_2CH_2$ (**III**) or 4-β-H_2NCH_2CH (**IV**)		5-CH_2, s	H_{arom}
		α-CH_2	β-CH_2 or β-CH, t		
IIIa	7.48	2.61–2.78 t	2.91–3.25	4.98	7.21–7.33 m (5H, C_6H_5)
IIIa[a]	8.64	3.21 t	3.21	4.16	7.27–7.37 m (5H, C_6H_5)
IIIb[a]	8.99	3.25 t	3.39	4.10	6.85 d (2H, 2-H, 6-H, *J* = 8.4 Hz), 7.60 d (2H, 3-H, 5-H, *J* = 8.4 Hz)
IIIc[a]	9.13	3.40 t	3.40	3.90	6.18 s (1H, 2-H), 7.67–7.79 m (3H, 4-H, 5-H, 6-H, C_6H_3)
IIId[a]	8.87	3.25 t	3.38	4.15	3.85 s (3H, OCH_3), 6.97–7.30 m (4H, C_6H_4)
IIIe[b]	7.60	2.86 t	3.21	4.10	3.79 s (6H, $2OCH_3$), 6.35–6.51 m (2H, 5-H, 6-H, C_6H_2), 7.31 s (1H, 3-H)
IIIf[a]	9.04	3.31 t	3.75	3.81	3.91 d (6H, $2OCH_3$), 6.91 s (1H, 6-H), 7.24 s (2H, 3-H, 4-H, C_6H_2)
IIIg[a]	9.00	3.20–3.40 t	3.66–3.78	4.10	6.10 s (2H, CH_2), 6.90–7.20 m (3H, 2-H, 5-H, 6-H, C_6H_3)
IIIh[a]	9.06	3.30 t	3.45	4.06	6.96 s (2H, C_6H_2), 3.95 s (9H, $3OCH_3$)
IIIi[a]	9.03	3.38 t	3.43	3.90	8.36 d (2H, 3-H, 5-H, *J* = 7.0 Hz), 9.14 d (2H, 2-H, 6-H, *J* = 7.0 Hz)
IIIj	9.00	3.23 t	3.73	4.20	7.35–7.80 m (4H, C_6H_4)
IVa	7.55	3.02 d	3.20	3.91	7.19 s (5H, C_6H_5)
IVa[a]	8.54	3.35 d	3.77	4.12	7.23–7.41 m (5H, C_6H_5)
IVb[a]	8.91	3.42 d	3.56	3.91	6.81–7.06 m (3H, 4-H, 5-H, 6-H), 7.39 s (1H, 2-H)
IVc[b]	8.14	3.22 d	3.82	4.11	6.85–6.96 (2H, 2-H, 6-H), 7.26–7.38 (2H, 3-H, 5-H)
IVd[a]	8.86	3.39 d	3.67	4.19	7.03 q (3H, 4-H, 5-H, 6-H), 7.39 t (1H, 2-H)
IVe[a]	9.02	3.38 d	3.85	3.94	3.92 s (3H, OCH_3), 7.16 q (2H, 3-H, 5-H), 7.54 q (2H, 2-H, 6-H)
IVf[a]	8.93	3.50 d	3.67	4.33	7.34 d (2H, 2-H, 6-H, *J* = 8.0 Hz), 7.43 d (2H, 3-H, 6-H, *J* = 8.0 Hz)
IVg[a]	9.10	3.45 d	3.61	4.17	7.34–7.43 m (2H, 2-H, 6-H), 7.69–7.75 m (2H, 3-H, 5-H)
IVh[a]	10.27	3.54 d	3.81	4.86	6.50 s (2H, OCH_3), 8.45–8.81 m (3H, 2-H, 5-H, 6-H)
IVi[a]	9.03	3.38 d	3.56	4.47	8.33 d (2H, 3-H, 5-H, *J* = 6.8 Hz), 8.30 d (2H, 2-H, 6-H, *J* = 6.8 Hz)
IVj[a]	8.94	3.36 d	3.63	3.90	2.71 s (3H, CH_3), 4.51 t (2H, CH_2OH), 8.40 s (1H, 3-H)
IVk[a]	8.90 (2H)	3.46 d (4H, $2CH_2$)	3.60 (2H)	4.19 (4H)	7.70–7.90 m (4H, C_6H_4)

[a] Dihydrochloride; for **IIIj**, tetrahydrochloride.

[b] In $CDCl_3$.

effected under mild conditions. The ease of this transformation was explained in terms of the double effect of the benzene (or pyridine) and imidazole rings on the C^4-N^5 bond. The general character of the process opens new possibilities for synthesizing substituted histamine and histidine derivatives.

EXPERIMENTAL

The ^1H NMR spectra were recorded on Gemini-200 (200 MHz) and Tesla BS-467C (80 MHz) spectrometers using CD_3OD, DMF-d_7, $CDCl_3$, or CF_3COOH as solvent and HMDS as internal reference. The purity of the products was checked by TLC on Silufol UV-254 plates using alcohol as eluent; spots were visualized with UV light or iodine vapor.

Initial spinaceamines **Ia**, **Ic**, **Id**, **Ig**, and **Ii** were synthesized by the procedure reported in [1]; compounds **Ih** and **Ij** were obtained as described in [2]. Spinacines **IIa** and **IIj** were synthesized according to [1, 2, 6, 7, 16].

4-Arylspinaceamines Ib, Ie, and If. To a solution of 10 mmol of histamine dihydrochloride in 10 ml of water we added 25 mmol of sodium hydroxide in 2–3 ml of water and a solution of 10 mmol of appropriate benzaldehyde in 25–50 ml of methanol. The mixture was heated for 12 h on a boiling water bath, methanol was distilled off, the residue was cooled, and the product was filtered off and recrystallized from alcohol or aqueous alcohol (Table 1).

4-Arylspinacines IIb–IIi and IIk. To a suspension of 20 mmol of L-histidine in 10 ml of water we added a solution of 60 mmol of KOH in 10 ml of water, and a solution of 20 mmol of substituted benzaldehyde in a mixture of 25 ml of water and 25 ml of methanol was then added. The mixture was heated for 12 h at a bath temperature of 90°C, cooled, carefully neutralized with hydrochloric acid, and evaporated to dryness. The residue was ground in isopropyl alcohol, and the precipitate was filtered off, dried, and recrystallized from appropriate alcohol (Table 1).

5-Benzylhistamines IIIa–IIIj and 5-benzylhistidines IVa–IVk. A solution of 20 mmol of 4-phenyl-(or pyridyl)spinaceamine **Ia–Ij** or spinacine **IIa–IIk** in 20 ml of methanol and 20 ml of glacial acetic acid was hydrogenated at room temperature and hydrogen pressure equal to atmospheric over 0.5 g of 25% Pd/C. The reaction time was 3–5 h (until a required amount of hydrogen was absorbed). The catalyst was filtered off, the filtrate was evaporated under reduced pressure (water-jet pump), and the residue was recrystallized from appropriate solvent (Table 2).

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