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Reduction of Imidazo[4,5-*c*]pyridine and [1,2,3]Triazolo[4,5-*c*]pyridine Derivatives to Spinaceamines and 2-Azaspinaceamines

Yu. M. Yutilov, N. N. Smolyar, and N. V. Astashkina

Litvinenko Institute of Physical Organic and Coal Chemistry, National Academy of Sciences of Ukraine,
ul. R. Luxemburg 70, Donetsk, 83114 Ukraine

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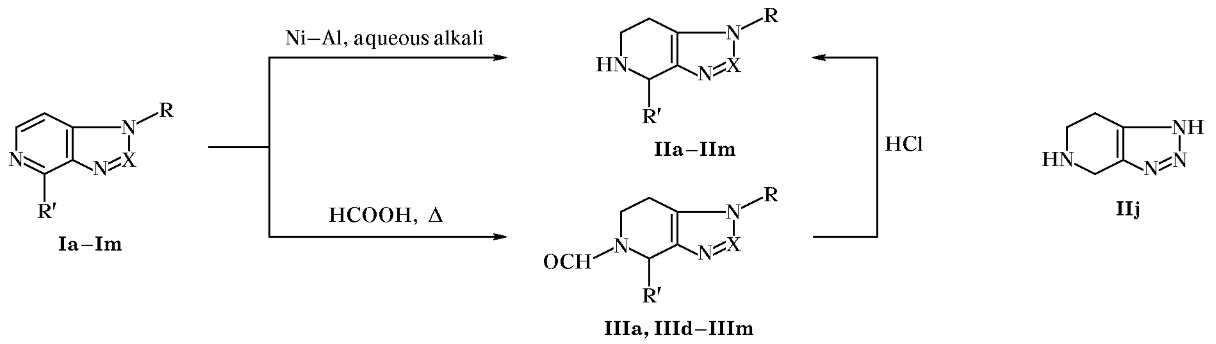
Abstract—Reduction of 1-substituted [1,2,3]triazolo[4,5-*c*]pyridines with nickel–aluminum alloy in aqueous alkali gave 2-azaspinaceamines. Reduction of imidazo[4,5-*c*]pyridine and [1,2,3]triazolo[4,5-*c*]pyridine derivatives with formic acid in the presence of triethylamine resulted in formation of 5-formylspinaceamines and 2-azaspinaceamines. The 5-formyl group in the latter can be removed by acid hydrolysis. Unsubstituted 2-azaspinaceamine, an aza analog of natural spinaceamine, was synthesized for the first time.

Development of new methods for synthesizing of spinaceamine (**Ia**) [1] and 2-azaspinaceamine derivatives [2] (4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridines and 4,5,6,7-tetrahydro[1,2,3]triazolo[4,5-*c*]pyridines, respectively), made it possible to vary over a wide range the substitution pattern in both imidazole (triazole) and partially saturated pyridine rings. In such a way various derivatives of spinaceamine and 2-azaspinaceamine were obtained, some of which exhibited analgetic, spasmolythic, psychosedative, myorelaxant, hypotensive, and antihypoxic activity [3–6]. However, these procedures do not ensure preparation of spinaceamines and 2-azaspinaceamines having no substituent on the nitrogen atom in the imidazole or triazole ring. Pharmacological properties of such compounds seem to be especially interesting. Therefore, we made an attempt to fill the above synthetic gap via direct reduction of imidazo[4,5-*c*]pyridine and [1,2,3]triazolo[4,5-*c*]pyridine derivatives.

It is known [7] that pyridine and isoquinoline derivatives react with nickel–aluminum alloy in aqueous alkali to give products of reduction of the pyridine ring. Under analogous conditions, the reduction of 1-substituted [1,2,3]triazolo[4,5-*c*]pyridines **Ia**–**Ic** afforded the corresponding tetrahydro derivatives **IIa**–**IIc** in 80–91% yield (Scheme 1, Table 1). The products were individual compounds, as followed from the data of thin-layer chromatography and elemental analysis. They are low-melting substances, readily soluble in various organic solvents. Some

Scheme 1.



X = N, R′ = H, R = Me (**a**), Et (**b**), CH_2Ph (**c**), Ph (**d**); R = R′ = Et (**e**); X = CH, R′ = H, R = Me (**f**), Ph (**g**); X = CMe, R′ = H, R = Me (**h**); X = CPh, R = Me, R′ = H (**i**); R = R′ = H, X = N (**j**), CH (**k**), CMe (**l**), CPh (**m**).

Table 1. Yields, melting points, and elemental analyses of spinaceamine and 2-azaspinaceamine derivatives **IIa–IIm**, **IIId–IIIf**, and **IIIj–IIIm**

Comp. no.	Yield, %	mp °C (solvent)	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
IIa[a]	80	101–103 (2-propanol)	33.97	5.64	26.38	$C_6H_{10}N_4 \cdot 2HCl$	34.11	5.72	26.52
IIb[b]	91	48–50 (ethanol)	40.82	3.82	25.60	$C_7H_{12}N_4 \cdot C_6H_3N_3O_7$	40.95	3.96	25.71
IIc	89	94–95[c] (heptane)	67.11	6.52	26.04	$C_{12}H_{14}N_4$	67.26	6.59	26.15
IId	94	84–85 (hexane)	65.79	6.00	27.89	$C_{11}H_{12}N_4$	65.98	6.04	27.98
IIe[a]	93	165–167 (2-propanol)	42.53	7.11	22.01	$C_9H_{16}N_4 \cdot 2HCl$	42.70	7.16	22.13
IIf[a]	92	225–228 (methanol)	39.85	6.11	19.87	$C_7H_{11}N_3 \cdot 2HCl$	40.02	6.24	20.00
IIg[a]	94	>250 (ethanol)	52.80	5.49	15.32	$C_{12}H_{13}N_3 \cdot 2HCl$	52.95	5.55	15.44
IIh[a]	91	249–252 (methanol)	42.69	6.68	18.59	$C_{18}H_{13}N_3 \cdot 2HCl$	42.87	6.75	18.75
IIi[a]	92	>250 (ethanol)	54.40	5.88	14.53	$C_{13}H_{15}N_3 \cdot 2HCl$	54.56	5.98	14.68
IIj[a]	93	118–120 (ethanol)	30.31	5.03	28.29	$C_5H_8N_4 \cdot 2HCl$	30.47	5.11	28.43
IIk[a]	93	>250 (methanol)	36.57	5.58	21.31	$C_6H_9N_3 \cdot 2HCl$	36.75	5.65	21.43
IIl[a]	90	210–212 (ethanol)	39.80	6.15	19.81	$C_7H_{11}N_3 \cdot 2HCl$	40.02	6.24	20.00
IIm[a]	92	>250 (ethanol)	52.78	5.46	15.29	$C_{12}H_{13}N_3 \cdot 2HCl$	52.96	5.55	15.44
IIId	88	153–155 (benzene)	62.94	5.20	24.43	$C_{12}H_{12}N_4O$	63.14	5.30	24.55
IIIe[b]	91	59–60 (ethanol)	43.86	4.32	22.27	$C_{10}H_{16}N_4O \cdot C_6H_3N_3O_7$	43.94	4.38	22.42
IIIf	90	79–80 (2-propanol)	58.01	6.65	25.31	$C_8H_{11}N_3O$	58.17	6.71	25.44
IIIj[b]	93	60–61 (ethanol)	37.68	2.83	25.59	$C_6H_8N_4O \cdot C_6H_3N_3O_7$	37.80	2.91	25.72
IIIk[b]	92	200–202 (ethanol)	40.88	3.11	22.02	$C_7H_9N_3O \cdot C_6H_3N_3O_7$	41.06	3.18	22.10
IIIl[b]	81	181–183 (2-propanol)	42.44	3.49	21.16	$C_8H_{11}N_3O \cdot C_6H_3N_3O_7$	42.65	3.58	21.31
IIIm[b]	95	178–180 (2-propanol)	49.72	3.45	18.28	$C_{13}H_{13}N_3O \cdot C_6H_3N_3O_7$	50.00	3.53	18.41

[a] The melting point and analytical data are given for the corresponding dihydrochloride.

[b] The melting point and analytical data are given for the corresponding picrate.

[c] Published data [5]: mp 93–94°C.

products were characterized as the corresponding dihydrochlorides (Table 1). The spectral parameters of free bases **IIa**–**IIc** and their dihydrochlorides are collected in Table 2. Unlike initial [1,2,3]triazolo-[4,5-*c*]pyridines **Ia**–**Ic**, their reduction products **IIa**–**IIc** show in the ^1H NMR spectra signals from aliphatic protons in positions *4*, *6*, and *7*. For example, the spectrum of **IIb** contains signals at δ 1.31 (CH_3) and 4.26 ppm (CH_2) from the $N^1C_2H_5$ group and also methylene proton signals at δ 4.59 (C^4H_2), 3.61 (C^6H_2), and 3.09 ppm (C^7H_2) (Table 2).

The proposed procedure for synthesizing 4,5,6,7-tetrahydro[1,2,3]triazolo[4,5-*c*]pyridines **IIa**–**IIc** is more advantageous than the known method [8] due to its experimental simplicity, accessibility of reagents, and high yields and purity of the products. However, bases **Id**–**Im** are insoluble in aqueous alkali. In order to increase their solubility, in some cases aqueous alkali was replaced by aqueous–alcoholic alkali, but the desired results were not obtained. Therefore, we tried to apply Lukes' procedure [9], according to which the pyridine fragment in quinoline or isoquinoline is reduced on heating in a boiling mixture of formic acid with triethylamine.

The reduction of substituted [1,2,3]triazolo[4,5-*c*]-pyridines **Ia**, **Id**, **Ie**, and **Ij** and imidazo[4,5-*c*]pyridines **If**–**Ii** and **Ik**–**Im** was carried out as described in [10] for isoquinoline. The yields of the resulting 5-formyl derivatives **IIIa** and **IIId**–**IIIm** were 88–95% (Table 1). Most products were light yellow low-melting or oily substances which were characterized as the corresponding picrates. Free bases **III** are readily soluble in alcohol, water, benzene, and chloroform. Their structure was confirmed by the IR and ^1H NMR spectra (Table 2). In the IR spectra of **III** we observed a strong absorption band at about 1660 cm^{-1} due to stretching vibrations of the aldehyde carbonyl group. The ^1H NMR spectra of these compounds differ from those of initial triazolopyridines **I** by the presence of signals from the methylene protons in positions *4*, *6*, and *7* and from the aldehyde proton as a doublet at δ 8.17–8.38 ppm, $J = 10$ Hz (Table 2).

Heating of compounds **III** in boiling concentrated hydrochloric acid results in elimination of the formyl

Table 2. ^{1}H NMR spectra of spinaceamine and 2-azaspinaceamine derivatives **IIa–IIm**, **IIIa**, **IIId–IIIf**, and **IIIj–IIIm**

Comp. no.	Chemical shifts δ,[a] ppm					
	N^1R	C^4H_2 or C^4HR'	X	N^5CHO	C^6H_2	C^7H_2
IIa	3.92 s (3H, CH_3)	4.62 t (2H, CH_2)	–	–	3.62 t	3.09 t
IIb	1.31 t (3H, CH_3), 4.26 q (2H, CH_2)	4.59 t (2H, CH_2)	–	–	3.61 t	3.10 t
IIc	5.42 s (2H, CH_2), 7.04 s (5H, C_6H_5)	4.58 t (2H, CH_2)	–	–	3.52 t	2.81 t
IId	7.48–7.55 m (5H, C_6H_5)	4.11 t (2H, CH_2)	–	–	3.14 t	2.82 t
IIe	1.37 t (3H, CH_3), 6.62 q (2H, CH_2)	1.13 t (3H, CH_3), 1.98 q (2H, CH_2)	–	–	3.14–3.67 m	2.99 t
IIf	3.80 s (3H, CH_3)	4.65 t (2H, CH_2)	8.99 s (1H, 2-H)	–	3.76 t	3.22 t
IIg	7.30 s (5H, C_6H_5)	4.80 t (2H, CH_2)	8.92 s (1H, 2-H)	–	3.92 t	3.20 t
IIh	3.37 s (3H, CH_3)	3,75 t (2H, CH_2)	2.47 s (3H, 2-CH_3)	–	3.12 t	2.94 t
IIi	3.78 s (3H, CH_3)	4.67 t (2H, CH_2)	7.27 s (5H, 2-C_6H_5)	–	3.66 t	3.17 t
IIj	10.12 d (1H, 1-H)	4.19 t (2H, CH_2)	–	–	3.68 t	3.14 t
IIk		4.32 t (2H, CH_2)	8.33 s (1H, 2-H)	–	3.42 t	2.85 t
IIl		4.46 t (2H, CH_2)	2.36 s (3H, 2-CH_3)	–	3.72 t	2.71 t
IIm		4.58 t (2H, CH_2)	7.30 s (5H, 2-C_6H_5)	–	3.67 t	2.73 t
IIIa	3.69 s (3H, CH_3)	4.58 s (1H, CH), 4.71 s (1H, CH)	– –	8.32 d[b]	3.72 t (1H), 3.89 t (1H)	2.66–2.69 m
IIId	7.26–7.55 m (5H, C_6H_5)	4.68 s (1H, CH), 4.82 s (1H, CH)	–	8.28 d[b]	3.72 t (1H), 3.90 t (1H)	2.89–2.94 m
IIIe	1.39 t (3H, CH_3), 4.23 q (2H, CH_2)	0.99 t (3H, CH_3), 1.73 q (2H, CH_2), 4.54–4.64 m (1H, CH)	–	8.17 s	3.45 t	2.74 t
IIIf	3.85 s (3H, CH_3)	4.29 t (2H, CH_2)	8.83 s (1H, 2-H)	8.34 d[b]	3.67 t	3.41 t
IIIj	–	4.55 s (1H, CH), 4.79 s (1H, CH)	–	8.38 d[b]	3.40 s (1H), 3.74 s (1H)	3.00 t
IIIk	–	4.60 s (2H, CH_2)	9.10 s (1H, 2-H)	8.48 d[b]	3.78 t	2.83 t
IIIl	–	4.54 s (2H, CH_2)	2.38 s (3H, 2-CH_3)	8.87 d[b]	3.68 t	2.74 t
IIIm	–	4.53 s (2H, CH_2)	7.20–7.30 m (5H, 2-C_6H_5)	8.90 d[b]	3.75 t	2.67 t

[a] Solvents: CF_3COOH (**IIa–IIc**, **IIf**, **IIg**, **IIk**, **IIl**); DMSO-d_6 (**IIe**, **IIh**, **IIj**); $CDCl_3$ (**IId**, **IIIa**, **IIId**, **IIIj**); CD_3CN (**IIIe**); CD_3OD (**IIIk–IIIm**).

[b] $J_{4,5}$ = 10 Hz.

group with formation of 5-unsubstituted tetrahydro derivatives **II** in 80–94% yield (Table 1). Compounds **IIg**–**IIi** can also be obtained without isolation of 5-formyl derivatives by reduction of **Ig**–**Ii** with formic acid and subsequent hydrolysis with concentrated hydrochloric acid. The structure of products **IIg**–**IIi** was proved by the ^{1}H NMR and IR spectra (Table 2). Their ^{1}H NMR spectra contain signals from protons of alkyl or aryl groups on N^1 and C^4 and from methylene or methine protons in positions *4*, *6*, and *7*. The chemical shifts are well consistent with those reported in [5] for 2-azaspinaceamines.

We were the first to synthesize unsubstituted 2-azaspinaceamine (**IIj**) (which is a 2-aza analog of natural spinaceamine [11]) by reduction of 1*H*-[1,2,3]triazolo-[4,5-*c*]pyridine (**Ij**) with formic acid. Spinaceamine was obtained in 93% yield by reduction of 1*H*-imidazo[4,5-*c*]pyridine (**Ij**) with formic acid. Starting from 2-methyl- and 2-phenylimidazo[4,5-*c*]pyridines **Il** and **Im** we synthesized 2-methyl- and 2-phenylspinaceamines **IIl** and **IIm**.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Tesla BS-467C spectrometer (80 MHz) in CF_3COOH and on a Varian Gemini-200 instrument (200 MHz) in $CDCl_3$, DMSO-d_6, or CD_3CN; HMDS was used as internal reference. The IR spectra were measured on a UR-20 spectrophotometer in mineral oil. The purity of the products was checked by TLC on Silufol UV-254 plates with alcohol as eluent; spots were visualized by UV light or iodine vapor.

Initial [1,2,3]triazolo[4,5-*c*]pyridines **Ia**–**Id** and **Ij** were synthesized by the procedure reported in [12, 13]; compound **Ie** was obtained as described in [14]. Imidazo[4,5-*c*]pyridines **If**–**Ii** and **Ik**–**Im** were prepared according to [15–21].

1-Alkyl-4,5,6,7-tetrahydro[1,2,3]triazolo[4,5-*c*]pyridines IIa–IIc. *a*. To a solution of 10 mmol of 1-alkyl[1,2,3]triazolo[4,5-*c*]pyridine **Ia**–**Ic** in 32 ml of 0.5 M aqueous KOH (or NaOH) we added in portons 3.9 g of a 1 : 1 nickel–aluminum alloy under vigorous stirring at room temperature. After 20–24 h, an additional 3.2 g of Raney nickel was added under the same conditions. The mixture was stirred for 4–5 h and filtered, and the filtrate was treated with chloroform. The organic phase was separated and dried over anhydrous sodium sulfate, and the solvent was distilled off. The residue was purified by recrystallization from heptane (or hexane). The corresponding picrate was prepared from equimolar amounts of the free base and picric acid, which were heated for a short time in ethanol (Table 1).

Compound **IIa**, 5 mmol, was dissolved in 10 ml of alcohol, and either gaseous hydrogen chloride was passed through the solution or 2 ml of concentrated hydrochloric acid was added. The mixture was then evaporated to dryness, and the residue was recrystallized from alcohol or reprecipitated with acetone from a solution in propanol (Table 1).

Free base **IIe** was obtained as follows. The corresponding dihydrochloride was dissolved in distilled water, and the solution was neutralized with sodium carbonate and evaporated to dryness. The residue was extracted with benzene, the solvent was distilled off from the extract, and the residue was recrystallized from heptane (Table 1).

b. A solution of 5 mmol of base **III** in 5 ml of concentrated hydrochloric acid was heated for 0.5–1 h under reflux and was then evaporated to dryness. The residue was recrystallized from alcohol to obtain colorless dihydrochloride of **IId**, **IIf**, or **IIg** (Table 1).

5-Formylspinaceamines and 5-formyl-2-azaspinaceamines IIIa and IIId–IIIg. To a solution of 10 mmol of base **Ia** or **Id**–**Ij** in 80 mmol of 99% formic acid we added in portions 20 mmol of triethylamine on cooling. The mixture was heated for 10 h at 100°C, cooled, diluted with 20 ml of distilled water, neutralized with sodium carbonate, and evaporated to dryness. The residue was extracted with isopropyl alcohol, and the solvent was distilled off from the extract to obtain light yellow bases **III** which were converted into the corresponding picrates (compounds **IIId** and **IIIf**) by heating with an equimolar amount of picric acid in alcohol for 3–5 min (Table 1).

Base **IIIa**, 5 mmol, was dissoloved in 10 ml of benzene or isopropyl alcohol, and 2 ml of a saturated solution of hydrogen chloride in isopropyl alcohol was added on cooling (8–10°C). The precipitate was filtered off and dried in a desiccator over calcium chloride at room temperature (Table 1).

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