Chemistry of Heterocyclic Compounds, Vol. 36, No. 10, 2000

FORMYLATION OF 3,4-DIHYDRO-PYRROLO[1,2-*a*]PYRAZINES*

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Formylation of 3,4-dihydropyrrolo[1,2-a]pyrazines containing alkyl or aryl substituents at position 1 has been studied under the conditions of the Vilsmeier reaction. The direction of the reaction depends on the structure of 3,4-dihydropyrrolo[1,2-a]pyrazine starting materials. Formylation of 1-methyl-substituted 3,4-dihydropyrrolo[1,2-a]pyrazines occurs at the methyl group.

Keywords: 3,4-dihydropyrrolo[1,2-*a*]pyrazine, Vilsmeier formylation.

Derivatives of pyrrolodiazines have attracted the attention of researchers because of their broad spectrum of biological activity. Pyrrolo[1,2-*a*]pyrazine and its 1,2-dihydroanalog – 3,4-dihydropyrrolo[1,2-*a*]pyrazine systems (the only of the six possible isomers known) – have been studied unsufficiently [1]. Aromatic pyrrolo[1,2-*a*]pyrazines are known to be stable to the action of mild electrophiles. For example, unsubstituted pyrrolo[1,2-*a*]pyrazine gave a yield of 16% of 6-acetylpyrrolo[1,2-*a*]pyrazine on boiling with excess of acetic anhydride for 24 h [2]. According to the authors, formylation of unsubstituted pyrrolo[1,2-*a*]pyrazine under Vilsmeier reaction conditions gave 60% of the 8-formyl derivative, although the ^{1}H NMR spectrum cited leaves doubt as to the correctness of identification of its structure [1]. In earlier work a similar attempt to formylate pyrrolo[1,2-*a*]pyrazine was unsuccessful [3]. On the other hand pyrroles themselves are relatively easy to formylate and acetylate. Formation of products of substitution at either the α- or β-positions of the pyrrole ring depends on the structure of pyrrole and the reaction conditions [4].

We have shown [5] that trifluoroacetylation of 3,4-dihydropyrrolo[1,2-*a*]pyrazines, which are analogous to pyrroles with an imino group in the α-position of the pyrrole ring, occurs ambiguously and depends on the structure of the 3,4-dihydropyrrolo[1,2-*a*]pyrazine starting materials. In a continuation of this investigation we have studied the formylation of 3,4-dihydropyrrolo[1,2-*a*]pyrazines **1-7** containing alkyl or aralkyl substitutions in positions 1 and 6 of the heterocycle in DMF in the presence of phosphorus oxychloride (the Vilsmeier–Haack method).

The molecule of 1-substituted 3,4-dihydropyrrolo[1,2-*a*]pyrazine contains two reactive centers at which an electrophile is most likely to attack: the unbridged nitrogen atom of the pyrazine ring and the $C_{(6)}$ carbon atom (α-position of the pyrrole ring). However it was found that 1-methyl- (**1**) and 1,6-dimethyl-3,4-dihydropyrrolo-[1,2-*a*]pyrazine (**2**) formed formyl derivatives at the methyl group in position 1 – 2-(1,2,3,4-tetrahydropyrrolo-[1,2-*a*]pyrazin-1-ylidene)acetaldehyde (**10**) and 2-(6-methyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazin-1-ylidene)-acetaldehyde (**11**) respectively:

* Dedicated to A. N. Kost on his 85th birthday.

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, 1395-1402, October, 2000. Original article submitted July 11, 2000.

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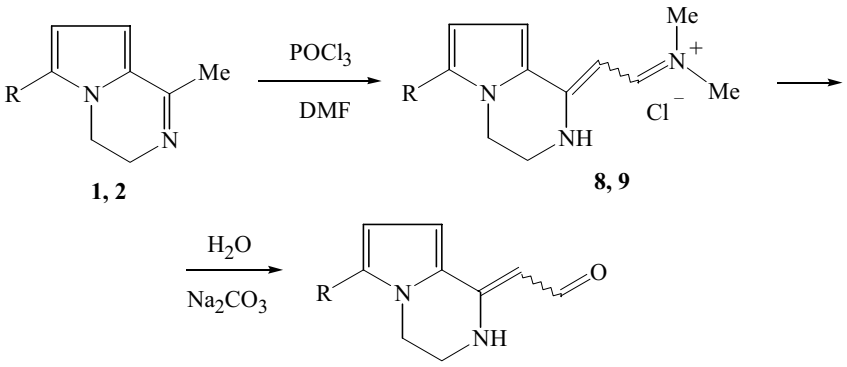
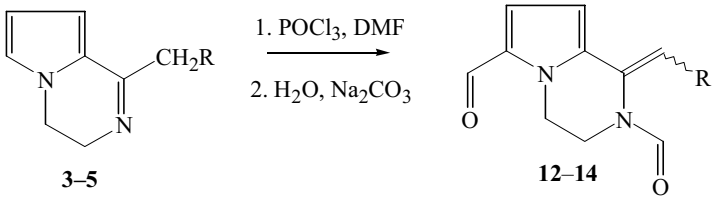


1, 2 **8, 9** **10, 11**

1, **8**, **10** R = H; **2**, **9**, **11** R = Me

When the reaction was carried out with an excess of reagent (DMF as solvent) at room temperature for 3-6 h the iminium salts **8** and **9** were formed, hydrolysis of which gave 1-methylideneformyl derivatives **10** and **11**.

On formylation of 3,4-dihydropyrrolo[1,2-*a*]pyrazines **3-7** containing substituents other than methyl at position 1, the direction of the reaction changed and formyl derivatives disubstituted at nitrogen atom $N_{(2)}$ and in the pyrrole ring were formed. Compounds **3-5**, in which the α-position of the pyrrole ring is free for electrophilic attack, gave formyl derivatives at $N_{(2)}$ and at $C_{(6)}$ – 1-ethylidene-, 1-propylidene-, and 1-(1-phenylmethylidene)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-2,6-dicarbaldehydes **12-14** respectively:



3–5 **12–14**

3, **12**, R = Me; **4**, **13** R =Et; **5**, **14** R = Ph

Compound **14** is a close to equimolar mixture of two isomers relative to the double bond at position 1 of the heterocycle, which are susceptible to the preparative isolation. The structure of each isomer was established by analysis of their ^{1}H NMR spectra. For example, the signal of the proton at position 8 of the *E* isomer **14a** underwent a considerable high field shift (~1 ppm) in comparison with the *Z* isomer **14b** since it fell within the region shielded by the phenyl substituent.

If the α-position in the pyrrole ring in the starting 3,4-dihydropyrrolo[1,2-*a*]pyrazine is occupied by methyl group then electrophilic attack occurs initially at $N_{(2)}$ atom and at carbon atoms $C_{(7)}$ or $C_{(8)}$ of the pyrrole ring. Only one product was observed in the case of 1-ethyl-6-methyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine (**6**) – 1-ethylidene-6-methyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-2,8-dicarbaldehyde (**15**). Formylation of 6-methyl-1-propyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine (**7**) gave a mixture of 2,7- and 2,8-dicarbaldehydes **16a** and **16b** with the 2,7-isomer **16a** predominating. When compounds **15**, **16a**, and **16b** were heated in aqueous sodium carbonate solution they were converted respectively into 1-ethyl-6-methyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine-8-carbaldehyde (**17**) and a mixture of 6-methyl-1-propyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine-7-carbaldehyde (**18a**) and the isomeric 8-carbaldehyde **18b**. According to the high resolution ^{1}H NMR spectroscopic data, compound **16a** is a mixture of two rotational isomers relative to the amide bond.

TABLE 1. ^{1}H NMR Spectral Characteristics of the Compounds Synthesized

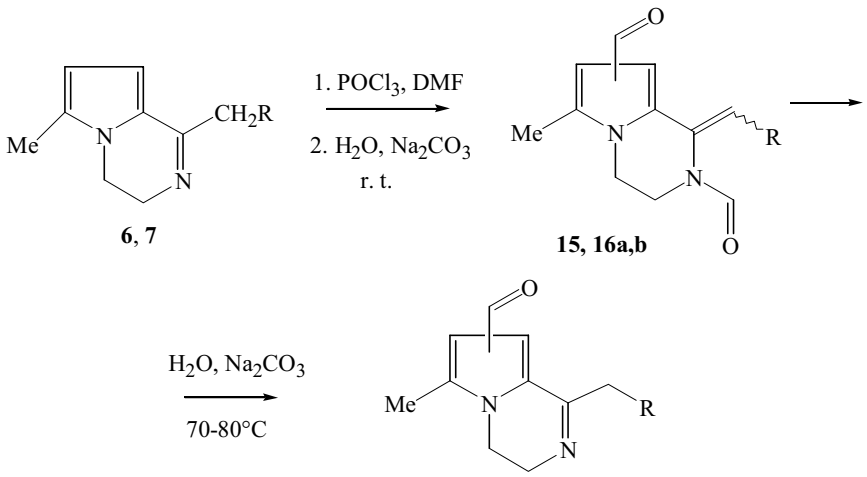
Compound	mp,°C	^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz)	^{13}C NMR spectrum ($CDCl_3$), δ, ppm	Yield, %
1	2	3	4	5
8	215	3.05 (3H, s, N^+-CH_3), 3.40 (3H, s, N^+-CH_3); 3.83 (2H, m, 3-H or 4-H); 4.18 (2H, t, *J* = 5.93, 4-H or 3-H); 5.19 (1H, d, *J* = 12.42, C<u>H</u>CHN$^+$); 6.33 (1H, dd, J_{78} = 3.77, J_{76} = 2.54, 7-H); 6.92 (1H, dd, J_{87} = 4.24, J_{86} = 1.17, 8-H); 7.00 (1H, dd, J_{67} = 2.47, J_{68} = 1.48, 6-H); 9.21 (1H, br. s, CHC<u>H</u>N$^+$); 11.20 (1H, s, HN)	37.17, 39.69, 43.28, 45.71 (<u>C</u>H_3–N^+, C-3,4); 83.76 (<u>C</u>HCHN$^+$); 110.94, 115.64 ($C_{(7,8)}$), 127.29 ($C_{(6)}$); 122.20($C_{(8a)}$), 155.31 ($C_{(1)}$); 156.16 (CH<u>C</u>HN$^+$)	58
9	254 (dec.)	2.17 (3H, s, 6-CH_3); 2.88 and 3.21 (6H, 2s, C<u>H</u>$_3$–N–C<u>H</u>$_3$); 3.66 (2H, m, 3-H or 4-H); 3.88 (2H, t, *J* = 5.96, 4-H or 3-H); 5.00 (1H, d, *J* = 12.56, C<u>H</u>CHN$^+$); 5.96 (1H, d, *J* = 3.46, 7-H or 8-H); 6.75 (1H, d, *J* = 3.68, 8-H or 7-H); 8.91 (1H, d, *J* = 12.25, CHC<u>H</u>N$^+$); 10.83 (1H, s, H-N)	11.49 (6-CH_3); 37.01, 39.44, 40.20, 45.52 ($C_{(3,4)}$, N^+–CH_3); 83.45 (<u>C</u>HCHN$^+$); 110.67, 116.10 ($C_{(7)}$, $C_{(8)}$); 122.10 ($C_{(8a)}$), 136.73 ($C_{(6)}$), 154.84 ($C_{(1)}$); 155.42 (CH<u>C</u>HN$^+$)	52
10	78-80	3.59···3.62 (2H, m, 4-H or H-3); 4.09 (2H, t, *J* = 5.98, 3-H or H-4); 5.42 (1H, d, *J* = 3.05, C<u>H</u>CH=O); 6.23 (1H, dd, J_{78} = 4.06, J_{76} = 2.46, 7-H); 6.72 (1H, dd, J_{87} = 4.09, J_{86} = 1.48, 8-H); 6.81 (1H, dd, J_{67} = 2.67, J_{68} = 1.66, 6-H); 9.04 (1H, d, *J* = 3.07, CHC<u>H</u>=O); 10.80 (1H, c, NH)		42
11	110-112	2.27 (3H, s, 6-CH_3); 3.64 (2H, t, *J* = 5.08, 3-H or 4-H); 3.98 (2H, t, *J* = 5.83, 4-H or 3-H); 5.37 (1H, d, *J* = 3.30, C<u>H</u>CH=O); 6.01 (1H, d, *J* = 3.85, 7-H or 8-H); 6.69 (1H, d, *J* = 3.98, 8-H or 7-H); 9.00 (1H, d, *J* = 2.81, CHC<u>H</u>=O); 10.86 (1H, s, H–N)	11.52 (6-CH_3); 39.32, 40.59 ($C_{(3,4)}$); 89.79 (<u>C</u>HCH=O); 109.34, 111.42 ($C_{(7,8)}$); 122.09, 133.56 ($C_{(6,8a)}$), 152.67 (C-1); 185.14 (CH<u>C</u>H=O)	58

TABLE 1 (continued)

1	2	3	4	5
12	97-99	2.05 (3H, d, *J* = 7.33, CHC<u>H</u>$_3$); 4.01 (2H, t, *J* = 5.83, 3-H or 4-H); 4.50 (2H, t, *J* = 5.72, 4-H or 3-H); 5.70 (1H, q, *J* = 7.66, C<u>H</u>CH$_3$); 6.58 (1H, d, *J* = 4.40, 7-H); 7.01 (1H, d, *J* = 4.28, 8-H); 8.44 (1H, s, O=CH–N); 9.58 (1H, s, 6-CHO)	14.05 (CH<u>C</u>H$_3$); 37.73, 44.54 ($C_{(3,4)}$); 110.76, 116.16, 123.92 ($C_{(7,8)}$, <u>C</u>HCH$_3$); 128.64, 130.77, 132.09 ($C_{(1,6,8a)}$); 160.07 (O=CH–N); 179.56 (6-CHO)	45
13		1.21 (3H, t, *J* = 7.62, CH$_2$<u>C</u>H$_3$); 2.46 (2H, q, *J* = 7.42, C<u>H</u>$_2$CH$_3$); 4.01 (2H, t, *J* = 5.59, 3-H or 4-H); 4.50 (2H, t, *J* = 5.87, 4-H or 3-H); 5.54 (1H, t, *J* = 7.12, C<u>H</u>CH$_2$CH$_3$); 6.54 (1H, d, *J* = 4.05, 7-H); 6.69 (1H, d, *J* = 4.55, 8-H); 8.44 (1H, s, O=CH–N); 9.57 (1H, s, 6-CHO)	13.85 (CH$_2$<u>C</u>H$_3$); 21.64 (<u>C</u>H$_2$CH$_3$); 37.83, 44.54 ($C_{(3,4)}$); 110.61, 123.89, 124.24 ($C_{(7,8)}$, <u>C</u>HCH$_2$CH$_3$); 127.16, 130.90, 132.04 ($C_{(1,6,8a)}$); 160.08 (O=CH–N); 179.51 (6-CHO)	50
14		**14a**: 4.07 (2H, t, *J* = 5.50, H-3 or H-4); 4.53 (2H, t, *J* = 5.38, H-4 or H-3); 5.92 (1H, d, *J* = 4.34, H-8); 6.54 (1H, s, C<u>H</u>–Ph); 6.68 (1H, d, *J* = 4.38, H-7); 7.33-7.43 (5H, m, Ph); 8.68 (1H, s, O=CH–N); 9.49 (1H, s, O=CH-6) **14b**: 4.13 (2H, t, *J* = 5.10, H-3 or H-4); 4.51 (2H, t, *J* = 4.93, H-4 or H-3); 6.66 (1H, d, *J* = 4.57, H-7); 6.81 (1H, s, C<u>H</u>-Ph); 6.96 (1H, d, *J* = 4.00, H-8); 7.32-7.41 (5H, m, Ph); 8.21 (1H, s, O=CH-N); 9.54 (1H, s, O=CH-6)		65
15		1.94 (3H, d, *J* = 7.37, CHC<u>H</u>$_3$); 2.21 (3H, s, CH$_3$-6); 3.89 (2H, t, *J* = 5.76, H-3 or H-4); 4.06 (2H, t, *J* = 5.78, H-4 or H-3); 6.42 (1H, s, H-7); 7.29 (1H, q, *J* = 7.33, C<u>H</u>CH$_3$); 8.26 (1H, s, O=CH–N); 9.82 (1H, s, O=CH-8)	11.53, 13.60 (6-CH$_3$, CH<u>C</u>H$_3$); 41.89, 37.45 ($C_{(3,4)}$); 111.92, 120.31 ($C_{(7)}$, <u>C</u>HCH$_3$); 127.78, 128.19, 129.19, 130.39 ($C_{(1,6,8,8a)}$); 161.96 (O=CH–N); 184.79 (8-CHO)	59

TABLE 1 (continued)

1	2	3	4	5
16	Oil	**16a** (major component): 1.18 (3H, t, *J* = 7.43, $CH_2C\underline{H}_3$); 2.40 (2H, m, *J* = 7.27, $C\underline{H}_2CH_3$); 2.50 (3H, s, 6-CH_3); 3.84-3.91 (2H, m, 3-H or 4-H); 4.00-4.05 (2H, m, 4-H or 3-H); 5.30 (1H, t, *J* = 6.81, $C\underline{H}CH_2CH_3$); 6.76 (1H, s, 8-H); 8.40 (1H, s, O=CH–N); 9.85 (1H, s, 7-CHO) **16a** (minor component): 1.09 (3H, t, *J* = 7.19, $CH_2C\underline{H}_3$); 2.26 (2H, m, *J* = 7.58, $C\underline{H}_2CH_3$); 2.46 (3H, s, 6-CH_3); 3.84-3.91 (2H, m, 3-H or 4-H); 4.00-4.05 (2H, m, 4-H or 3-H); 5.78 (1H, t, *J* = 7.52, $C\underline{H}CH_2CH_3$); 6.72 (1H, s, 8-H); 8.26 (1H, s, O=CH–N); 9.80 (1H, s, 7-CHO) **16b**: 1.12 (3H, t, *J* = 7.44, $CH_2C\underline{H}_3$); 2.20 (3H, s, 6-CH_3); 2.32 (2H, m, *J* = 7.55, $C\underline{H}_2CH_3$); 3.84-3.91 (2H, m, 3-H or 4-H); 4.00-4.05 (2H, m, 4-H or 3-H); 6.40 (1H, s, 7-H); 7.05 (1H, t, *J* = 7.50, $C\underline{H}CH_2CH_3$); 8.23 (1H, s, O=CH–N); 9.82 (1H, s, 8-CHO)		55
17	68-70	1.23 (3H, t, *J* = 7.55, $CH_2C\underline{H}_3$); 2.53 (3H, s, 6-CH_3); 2.62 (2H, q, *J* = 7.56, $\underline{CH}_2CH_3$); 3.81-3.90 (4H, m, 3,4-H); 6.83 (1H, s, 7-H); 9.89 (1H, s, 8-CHO)	9.94 ($CH_2\underline{C}H_3$); 11.26 (6-CH_3); 28.52 ($\underline{C}H_2CH_3$); 38.68, 46.99 ($C_{(3,4)}$); 109.32, 119.96, 122.20, 124.88 ($C_{(6,7,8,8a)}$); 162.84 ($C_{(1)}$); 185.38 (O=CH)	54
18	Oil	**18a**: 0.98 (3H, t, *J* = 7.31, $CH_2CH_2C\underline{H}_3$); 1.70 (2H, m, $CH_2C\underline{H}_2CH_3$); 2.53 (3H, s, 6-CH_3); 2.55 (2H, t, *J* = 7.65, $C\underline{H}_2CH_2CH_3$); 3.72-3.89 (4H, m, 3,4-H); 6.83 (1H, s, 8-H); 9.88 (1H, s, 7-CHO) **18b**: 0.99 (3H, t, *J* = 7.31, $CH_2CH_2\underline{CH}_3$); 1.70 (2H, m, *J* = 7.48, $CH_2\underline{CH}_2CH_3$); 2.25 (3H, s, 6-CH_3); 2.81 (2H, t, *J* = 7.77, $\underline{CH}_2CH_2CH_3$); 3.72-3.89 (4H, m, 3,4-H); 6.47 (1H, s, 7-H); 10.15 (1H, s, O=CH-8)		49



6 R = Me; **15**, **17** R = Me, 8-CHO; **7** R = Et,
16a, **18a** R = Et, 7-CHO; **16b**, **18b** R = Et, 8-CHO

TABLE 2. Elemental Analysis Results and Mass Spectral Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			Mass spectrum, *m/z* (*I*, %)
		C	H	N	
8	$C_{11}H_{16}N_3Cl$				190 (M^+, 14.42), 189 (100), 187 (41.75), 174 (66.86), 159 (56.51), 147 (27.82), 145 (35.84), 131 (16.91), 118 (19.55), 117 (17.21), 44 (12.38), 40 (22.51)
9	$C_{12}H_{18}N_3Cl$	60.08 / 60.12	7.21 / 7.57	17.37 / 17.53	204 (M^+, 17.38), 203 (100), 188 (85.19), 173 (73.62), 159 (45.07), 148 (18.52), 131 (20.77), 118 (16.33), 94 (11.01), 77 (11.40), 52 (10.85)
11	$C_{10}H_{12}N_2O$				176 (M^+, 100), 175 (69.68), 161 (33.22), 148 (27.75), 147 (22.04), 133 (13.08), 120 (14.40), 118 (18.83), 106 (16.24), 77 (10.59), 65 (9.71), 51 (10.66)
12	$C_{11}H_{12}N_2O_2$	62.09 / 64.69	5.60 / 5.92	12.92 / 13.72	204 (M^+, 94.69), 189 (100), 162 (16.56), 161 (27.26), 134 (6.64), 133 (10.13), 118 (4.19), 94 (6.64), 77 (4.49), 65 (2.57)
13	$C_{12}H_{14}N_2O_2$	62.17 / 66.03	5.90 / 6.47	12.09 / 12.84	218 (M^+, 57.49), 203 (45.82), 189 (25.67), 175 (62.50), 162 (100), 161 (35.67), 147 (10.87), 133 (10.90), 118 (9.51), 104 (8.49), 92 (9.87), 77 (9.17), 65 (9.31)
14	$C_{16}H_{14}N_2O_2$	71.96 / 72.16	5.14 / 5.30	10.49 / 10.52	266 (M^+, 40.37), 238 (20.77), 237 (98.02), 210 (16.65), 209 (100), 180 (13.12), 167 (16.50), 139 (11.21), 115 (11.11), 105 (17.57), 91 (18.45), 77 (15.41), 63 (10.34), 51 (10.60)
16	$C_{13}H_{16}N_2O_2$				232 (M^+, 3.31), 231 (4.43), 217 (7.19), 206 (44.32), 191 (21.39), 179 (25.36), 178 (94.49), 177 (100), 163 (19.80), 150 (47.53), 149 (32.17), 136 (22.19), 134 (41.82), 121 (29.75), 106 (15.69), 92 (21.70)
17	$C_{11}H_{14}N_2O$	69.62 / 69.45	7.51 / 7.42	15.19 / 14.73	190 (M^+, 94.69), 189 (100), 162 (16.56), 161 (27.26), 134 (6.64), 133 (10.13), 118 (4.19), 94 (6.64), 77 (4.49), 65 (2.57)

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded with a Varian VXR-400 instrument with TMS as internal standard. Mass spectra were obtained with a Kratos mass spectrometer, ionizing voltage 70 eV. Reactions were monitored by TLC on Silufol UV-254 strips. 3,4-Dihydropyrrolo[1,2-*a*]pyrazines were synthesized by a known method [6]. The yields, physical constants, and NMR spectroscopic data of the compounds obtained are given in Table 1 and their elemental analyses and mass spectral data – in Table 2.

General Method for Formylation. Dry DMF (25 mmol) was added dropwise, with stirring and cooling to phosphorus oxychloride (10 mmol), the mixture was stirred with cooling for 30 min, then solution of 3,4-dihydropyrrolo[1,2-*a*]pyrazine (2 mmol) in DMF (5 ml) was added dropwise. The reaction mixture was stirred at room temperature for 3-6 h and then poured onto crushed ice.

For compounds **1** and **2** the aqueous solution was extracted with chloroform, the chloroform extracts were dried over 3 Å molecular sieves, and the solvent was evaporated. Acetone was added and the precipitated salts **8** and **9** were filtered off, heated with aqueous sodium carbonate solution to 60-70°C, cooled, and extracted with benzene. The benzene extract was dried over 3 Å molecular sieves, and the solvent was evaporated. Compounds **10** and **11** were chromatographed on 100/160 silica gel column with benzene as eluent.

For compounds **3-5** the aqueous solution was neutralized with sodium carbonate solution, heated to 60-70°C, cooled and extracted with benzene. The benzene extract was dried and evaporated and the residue crystallized. Compounds **12** and **14b** were crystallized from 1:3 ethyl acetate–heptane, compounds **13** and **14a** – from heptane.

For compounds **6** and **7** the aqueous solution was neutralized with sodium carbonate solution, extracted with benzene, dried, and the solvent evaporated. The residue was chromatographed on column with 4:1 benzene–ethyl acetate solvent system to give compounds **15** and **16**. Compounds **17** and **18** were obtained by heating compounds **15** and **16** in aqueous sodium carbonate solution to 70-80°C. After cooling, the solution was extracted with benzene, dried, and the solvent was evaporated. Compound **17** was crystallized from heptane. Compound **18** was chromatographed on 100/160 silica gel column with 4:1 benzene–ethyl acetate as eluent.

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