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DIPYRROLO[1,2-a; 2′,1′-c]PYRAZINES. 4.* AMINOMETHYLATION OF ALKYL SUBSTITUTED DIPYRROLO[1,2-a; 2′,1′-c]PYRAZINES AND 5,6-DIHYDRODIPYRROLO[1,2-a; 2′,1′-c]PYRAZINES

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We have studied the aminomethylation reaction of alkyl substituted dipyrrolo[1,2-a; 2′,1′-c]pyrazines and their 5,6-dihydro analogs using different aminomethylating agents. Use of alkoxydialkylaminomethanes (amino-acetals) as Mannich reagents leads to the highest yields of the aminomethylated dipyrrolopyrazines. The compounds prepared have been studied by mass spectrometry.

With the aim of finding biologically active compounds, we have continued our investigation of dipyrrolopyrazines [1, 2] by studying the aminomethylation of the alkyl substituted dipyrrolopyrazines IIa, b and their 5,6-dihydro analogs Ia, b. C-Aminoalkylation of π-electron excessive heterocyclic systems is usually carried out by refluxing the amine, formaldehyde, and the corresponding heterocycle in alcohol [3] or by reaction of the amine hydrochloride or amine in acetic acid and formaldehyde medium with the heterocycle [4-7]. The most commonly used reagents for the given substrates are bis(dialkylamino)methanes (aminals) [8, 9], N,N-dialkylmethyleneiminium salts [10-12], or alkoxydialkylaminomethanes (aminoacetals) [13]. It is proposed that the mechanism of the Mannich reaction can depend both on the nucleophilicity of the substrate and on the pH of the medium. Thus, N,N-dialkyliminium salts behave as electrophiles at pH less than 7 but as aminals they can take part in a Mannich reaction at pH greater than 7 [13].

We have found that the aminomethylation of dipyrrolopyrazines and their 5,6-dihydro analogs depends on the medium acidity. Attempts to carry out the reaction at pH greater than 7 did not give the expected result since the Mannich base formed is unstable in the conditions indicated. Hence the choice of aminomethylating reagents was dictated by the pH of the reaction medium. Reaction of the dipyrrolopyrazine IIb with bisdimethylaminomethane in acetonitrile led only to separation of 3-[(2,8-dimethyldipyrrolo[1,2-a; 2′,1′-c]pyrazin-3-yl)methyl]-2,8-dimethyldipyrrolo[1,2-a; 2′,1′-c]pyrazine (IVg) from the reaction mixture. Hence ethoxydialkylaminomethanes (aminoacetals) were used as aminomethylating reagents and this allowed the reaction to be carried out in quite mild conditions in a neutral medium. In fact, heating the dipyrrolopyrazines IIa, b and their 5,6-dihydro analogs Ia, b with the corresponding aminoacetals in benzene gave good yields of the aminomethyl derivatives of the given substrates. In almost all cases the reaction time did not exceed 1 h.

On the basis of quantum chemical calculations we have previously shown that, in dipyrrolopyrazines with single and double bonds between the C_5-C_6 carbon atoms, the free α-position of the pyrrole rings is the most reactive towards electrophilic substitution [14]. Study of the aminomethylation reaction also confirms the theoretical data in that, independently of the substrate-reagent ratio, the aminomethylating group attacks the free α-position of the pyrrole rings in the dipyrrolopyrazine molecule.

Thus, reaction of 2-methyl substituted dipyrrolopyrazines Ia, IIa with ethoxymethylpiperidine and ethoxymethylmorpholine gives products disubstituted at the free α-pyrrolyl positions of the molecules (IIIa, b and IVa, b respectively).

*For Communication 3, see [1].

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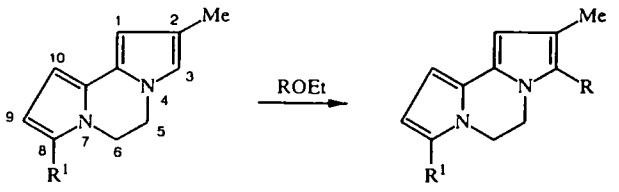
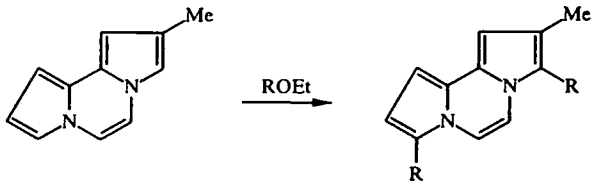


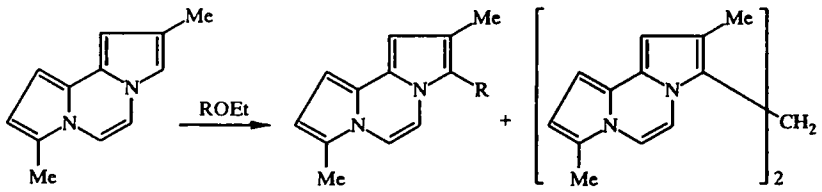
Ia, b IIIa-g

Ia R^1 = H; Ib R^1 = Me; IIIa R^1 = R = $-CH_2NC_5H_{10}$; b R^1 = R = $-CH_2NC_4H_8O$; c R^1 = R = $-CH_2NEt_2$; d R^1 = H, R = $-CH_2NEt_2$; e R^1 = Me, R = $-CH_2NC_5H_{10}$; f R^1 = Me, R = $-CH_2NC_4H_8O$; g R^1 = Me, R = $-CH_2NEt_2$



IIa IVa-c

IV a R = $-CH_2NC_5H_{10}$; b R = $-CH_2NC_4H_8O$; c R = $-CH_2NEt_2$



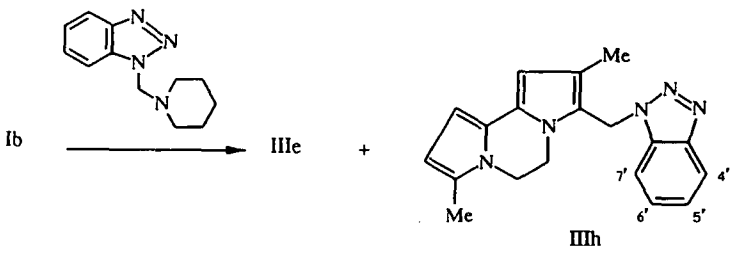
IIb IVd-f IVg

IV d R = $-CH_2NC_5H_{10}$; e R = $-CH_2NC_4H_8O$; f R = $-CH_2NEt_2$

Attempts to vary the substrate-reagent ratio for reaction of Ia with ethoxymethylpiperidine from 1:2.5 to 1:1 led to the disubstituted reaction product IIIa. However, in the latter case the yield of IIIa is lowered. High resolution ^1H NMR spectroscopy shows both the basic signals for isomer IIIa and low intensity signals for what can evidently be assigned as the mono substituted compound. Formation of 3-mono substituted aminomethylation products is also observed when treating 2-methyldipyrrolopyrazine IIa and its 5,6 dihydro analog Ia with ethoxymethyldiethylamine. However, the basic product for substrate IIa is the disubstituted IVc and for 5,6-dihydrodipyrrolopyrazine Ia the mono- and disubstituted products IIId and IIIc are present in the reaction mixture in the ratio 1:1. When the molar fraction of reagent to substrate used in the reaction is increased by 4 times the ratio of isomers is unchanged.

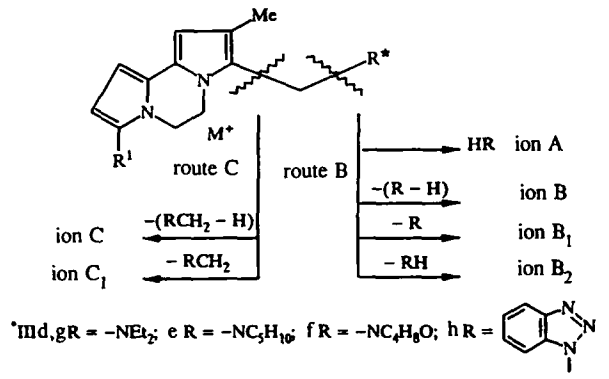
Hence, in spite of the principal formation of disubstituted products in the aminomethylation reactions of dipyrrolopyrazines Ia, IIa, the first electrophilic attack in fact occurs at position 3 of the dipyrrolopyrazine molecule and this is not in conflict with calculated data [14].

The aminomethylation of 2,8-dimethyl substituted dipyrrolopyrazines Ib, IIb is also in agreement with quantum chemical calculations and gives compounds IIIe-g and IVd-f respectively. Although, as referred to earlier, the aminomethyl derivatives can be formed in good yields from dipyrrolopyrazines Ia, b and IIa, b using aminoacetals we have used piperidinomethylbenzotriazole as an alternative aminomethylating reagent. It has been shown [15] that π-excessive heterocycles in the presence of a Lewis acid can take part in an aminomethylating reaction with different aminoalkylbenzotriazoles to give 70-96% yields of the corresponding Mannich base. However, in the case of the dipyrrolopyrazine Ib, besides the expected piperidinomethyldipyrrolopyrazine IIIe there is formed 3-(1H-1,2,3-benzotriazol-1-ylmethyl)-2,8-dimethyl-5,6-dihydro-dipyrrolo[1,2-a; 2′,1′-c]pyrazine (IIIh), the yield of the latter being higher. We were unable to optimize the product yield in the given reaction since, besides derivatives IIIe and IIIh, there was present in the reaction mixture a further unidentified compound. Separation of this mixture needed column chromatography which is not the most useful method for the separation of aminomethyl dipyrrolopyrazines. On the other hand, with the use of aminoacetals as Mannich reagents, there is formed only one reaction product in almost all cases and this considerably simplifies work up of the reaction mixture. However, the reaction



of 2,8-dimethyldipyrrolopyrazine IIb with ethoxydialkylaminomethanes gives both the expected aminomethyl derivatives IVd-f and IVg. The formation of substances like IVg in the course of the Mannich reaction was commented on in [16], moreover the amount of the products of this structure increased with increase in medium pH. For the dipyrrolopyrazine IIb the yield of IVg depends on the substrate-reagent ratio and decreases with increase in the molar fraction of aminomethylating reagent.

We carried out a mass spectral investigation of IIIa-h and IVa-g further to study their structure. The mass spectra of the given heterocyclic systems were obtained under electron impact and the results are given in Table 4. In most cases the molecular ion peaks for the aminomethyl derivatives of the dipyrrolopyrazines are of low intensity. The molecular ions of all the investigated compounds can undergo two main routes of electron impact bond fission. These are represented in the scheme for the mono substituted 5,6-dihydrodipyrrolopyrazines IIId-h.



The α- and β-fission in the $-CH_2R$ substituent, accompanying prototropic rearrangements, typify the breakdown routes. The positive charge is localized both on R (ion A) and on the polyheterocyclic part of the molecule (ions B, B_1, B_2, C, C_1). It should also be noted that peaks are absent in all cases for $CH_2{=}R$ fragments which usually indicate the presence of a dialkylaminomethyl substituent in the molecule. In the spectra of all the aminomethyl derivatives, the maximum peaks for the amine fragments formed by fission of the $HR_1^{+\cdot}$ correspond to the molecular ions of the corresponding amines.

In the spectra of the disubstituted derivatives III, IVa-c fission of the molecular ion by route C is absent. Moreover, there appears an additional route for fragmentation of ion B_1 with fission of a second amino group and hydrogen rearrangement. This leads to formation of a series of homologous peaks with m/z 214, 213, 212, m/z 200, 199, 198, and m/z 186, 185, 184 for compounds IIIa-c and with m/z 212, 211, 210, m/z 198, 197, 196, and m/z 184, 183, 182 for compounds IVa and IVc.

Fission of the molecular ion of dipyrrolopyrazine IVg under electron impact also occurs according to the scheme given for IIId-h.

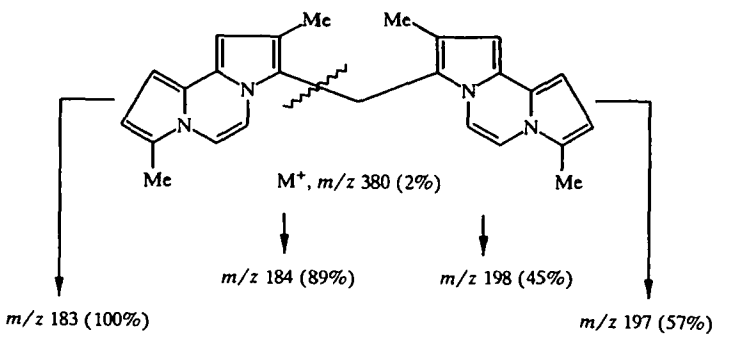


TABLE 1. Properties of Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, % (time h)
		C	H	N		
IIIa	$C_{23}H_{34}N_4$	75,01 / 75,41	9,25 / 9,28	15,47 / 15,30	174,7...175,8	84(1) 13(9)*
IIIb	$C_{21}H_{30}N_4O_2$	67,96 / 68,10	8,08 / 8,10	15,27 / 15,13	150,7...152,7	79(2)
IIIc	$C_{21}H_{34}N_4$					37,5(1)*2
IIId	$C_{16}H_{23}N_3$					37,5(1)*2
IIIe	$C_{18}H_{25}N_3$	76,32 / 76,30	8,86 / 8,80	14,47 / 14,80	171,7...176,2 (chars)	83(1) 11(17...20)*3
IIIf	$C_{17}H_{23}N_3O$	71,47 / 71,57	7,85 / 8,07	14,63 / 14,73	190,8...197,1 (chars)	84(3)
IIIg	$C_{17}H_{25}N_3$	74,79 / 75,27	8,95 / 9,23	15,73 / 15,49	115,1...121,2 (chars)	75(1)
IIIh	$C_{19}H_{19}N_5$				140...145,8 (chars)	37,8(17...20)
IVa	$C_{23}H_{32}N_4$	76,01 / 75,80	8,77 / 8,79	15,97 / 15,38	190,3...194,5 (decomp.)	88(1)
IVb	$C_{21}H_{28}N_4O_2$	68,47 / 68,35	7,60 / 8,25		190,6...196,5 (decomp.)	84(1)
IVc	$C_{21}H_{32}N_4$				54,1...60,7 (decomp.)	76(1)*2
IVd	$C_{18}H_{23}N_3$	76,69 / 76,86	8,49 / 8,18	14,92 / 14,94	126,9...133,8 (decomp.)	92,5(1)
IVe	$C_{17}H_{21}N_3O$	72,34 / 72,08	7,40 / 7,42		160,2...163,0	83(1)*2
IVf	$C_{17}H_{23}N_3$				Sticky crystals	78(1)*2

*Ratio of substrate to reagent 1:1.

*2Compounds IIIc, d separated as a 1:1 mixture; in compound IVc there was a small admixture of the 3-mono substituted reaction product; in compounds IVe and IVf a 4% admixture of compound IVg.

*3Prepared by method B.

TABLE 2. Dependence of the Yields of Compounds IVd-g on the Substrate-Reagent Ratio

Compound	Yield (%) with substrate–reagent ratio, mmole		
	1 : 1	1 : 1,5	1 : 3
IVd	85	92,5	
IVg	8	0	
IVe	72	80	83
IVg	12	8	4
IVf	51	72	78
IVg	17	12	4

TABLE 3. Chemical Shifts (δ, ppm) and Spin-Spin Couplings (J, Hz) in the PMR Spectra of Compounds IIIa-h and IVa-g in $CDCl_3$

Compound	Pyrrole ring protons and substituents						Pyrazine ring protons
	1H	2-CH_3	3-R	8-R(H)	9-H	10-H	
1	2	3	4	5	6	7	8
IIIa	6,028 s	2,043 s	1,410 m (2H, γ-CH_2); 1,505 m (4H, β-CH_2); 2,318 m (4H, α-CH_2); 3,356 s (2H, $-CH_2N$)	1,410 m (2H, γ-CH_2); 1,505 m (4H, β-CH_2); 2,318 m (4H, α-CH_2); 3,415 s (2H, $-CH_2N$)	5,970 d, J_{910} = 3,24	6,100 d	4,210 m (4H, 5,6-CH_2)
IIIb	6,046 s	2,056 s	2,400 m (4H, $N(CH_2)_2$); 3,423 s (2H, $-CH_2N$); 3,660 m (4H, $(CH_2)_2O$)	2,400 m (4H, $N(CH_2)_2$); 3,469 s (2H, $-CH_2N$); 3,660 m (4H, $(CH_2)_2O$)	6,010 d, J_{910} = 3,53	6,110 d	4,200 m (4H, 5,6-CH_2)
IIIc	6,030 s	2,055 s	0,989 t (3H, $CH_2\underline{CH_3}$)*, $J_{CH3,CH2}$ = 7,14; 2,450 q (2H, $\underline{CH_2}CH_3$); 3,461 s (2H, $-CH_2N$)	0,992 t (3H, $CH_2\underline{CH_3}$)*, $J_{CH3,CH2}$ = 7,14; 2,450 q (2H, $\underline{CH_2}CH_3$); 3,517 s (2H, $-CH_2N$)	5,980 d, J_{910} = 3,47	6,100 d	4,210 m (4H, 5,6-CH_2)
IIId	6,050 s	2,055 s	0,998 t (3H, $CH_2\underline{CH_3}$), $J_{CH3,CH2}$ = 7,15; 2,470 q (2H, $\underline{CH_2}CH_3$); 3,457 s (2H, $-CH_2N$)	6,560 d.d, J_{89} = 2,61, J_{810} = 1,53	6,160 dd, J_{910} = 3,57	6,190 dd	4,110 m (2H, 6-CH_2)*; 4,250 m (2H, 5-CH_2)*
IIIe	6,006 s	2,041 s	1,420 m (2H, γ-CH_2); 1,480 m (4H, β-CH_2); 2,310 m (4H, α-CH_2); 3,356 s (2H, $-CH_2N$)	2,240 d, $J_{CH3,9-H}$ = 0,74	5,870 dq, J_{910} = 3,46	6,110 d	3,990 m (2H, 6-CH_2)*; 4,210 m (2H, 5-CH_2)*
IIIf	6,011 s	2,052 s	2,388 m (4H, $N(CH_2)_2$); 3,419 s (2H, $-CH_2N$); 3,638 m (4H, $(CH_2)_2O$)	2,247 s	5,880 d, J_{910} = 3,35	6,120 d	4,010 m (2H, 6-CH_2)*; 4,190 m (2H, 5-CH_2)*
IIIg	6,007 s	2,052 s	0,988 t (3H, $CH_2\underline{CH_3}$), $J_{CH3,CH2}$ = 7,15; 2,450 q (2H, $\underline{CH_2}CH_3$); 3,461 s (2H, $-CH_2N$)	2,441 s	5,880 d, J_{910} = 3,40	6,110 d	3,990 m (2H, 6-CH_2)*; 4,240 m (2H, 5-CH_2)*

TABLE 3 (continued)

1	2	3	4	5	6	7	8
IIIh	6,110 s	2,200 s	5,885 br. s (2H, $^{-}CH_2N$); 7,200 m (1H, 7'-H); 7,310, 7,360 m (2H, 5',6'-H); 8,020 m (1H, 4'-H)	2,350 s	5,885 d	6,160 d, J_{109} = 3,76	3,900 m(4H, 5,6-CH_2)
IVa	6,281 s	2,186 s	1,428 m (2H, γ-CH_2); 1,527 m (4H, β-CH_2); 2,348 m (4H, α)-CH_2); 3,545 s (2H, $^{-}CH_2N$)	1,428 m (2H, γ-CH_2); 1,527 m (4H, β-CH_2); 2,348 m (4H, α-CH_2); 3,603 s (2H, $^{-}CH_2N$)	6,310 d, J_{910} = 3,69	6,340 d	7,400 d (1H, 5H)*, J_{56} = 6,17; 7,450 d (1H, 6-H)*
IVb	6,306 s	2,202 s	2,425 m (4H, $N(CH_2)_2$); 3,616 s (2H, $^{-}CH_2N$); 3,668 m (4H, $(CH_2)_2O$)	2,425 m (4H, $N(CH_2)_2$); 3,668 m (6H, $^{-}CH_2N$, $(CH_2)_2O$)	6,361 s	6,361 s	7,370 d (1H, 5H)*, J_{56} = 6,08; 7,420 d (1H, 6-H)*
IVc	6,284 s	2,200 s	1,016 t (3H, $CH_2\underline{CH_3}$)*, $J_{CH3,CH2}$ = 7,12; 2,488 q (2H, $\underline{CH_2}CH_3$)*2; 3,655 s (2H, $^{-}CH_2N$)	1,023 t 3H, $CH_2\underline{CH_3}$)*, $J_{CH3,CH2}$ = 7,14; 2,501 q (2H, $\underline{CH_2}CH_3$)*2; 3,714 s (2H, $^{-}CH_2N$)	6,330 d, J_{910} = 3,56	6,350 d	7,455 s (2H, 5,6-H)
IVd	6,259 s	2,182 s	1,420 m (2H, γ-CH_2); 1,508 m (4H, β-CH_2); 2,343 m (4H, α-CH_2); 3,546 s (2H, $^{-}CH_2N$)	2,380 d, $J_{CH3,9-H}$ = 0,74	6,210 dq, J_{910} = 3,51	6,350 d	6,890 d (1H, 6H)*, J_{65} = 6,14; 7,440 d (1H, 5-H)*
IVe	6,267 s	2,200 s	2,420 m (4H, $N(CH_2)_2$); 3,620 s (2H, $^{-}CH_2N$); 3,660 m (4H, $(CH_2)_2O$)	2,420 d, $J_{CH3,9-H}$ = 0,34	6,230 dq, J_{910} = 3,54	6,370 d	6,920 d (1H, 6H)*, J_{65} = 6,12; 7,390 d (1H, 5-H)*
IVf	6,261 s	2,195 s	1,010 t (3H, $CH_2\underline{CH_3}$), $J_{CH3,CH2}$ = 7,12; 2,480 q (2H, $\underline{CH_2}CH_3$); 3,660 s (2H, $^{-}CH_2N$)	2,380 d, $J_{CH3,9-H}$ = 0,56	6,220 dq, J_{910} = 3,42	6,350 d	6,890 d (1H, 6H)*, J_{65} = 6,20; 7,500 d (1H, 5-H)*
IVg	6,316 s (2H)	2,187 s (6H)	4,261 s (2H, 3-CH_2)	2,320 d (6H), $J_{CH3,9-H}$ = 0,42	6,190 dq (2H), J_{910} = 3,44	6,340 d (2H)	6,730 d (2H, 6H)*, J_{65} = 6,33; 6,750 d (2H, 5-H)*

*,*2Assignments may be reversed.

TABLE 4. Partial Mass Spectra of Synthesized Compounds

Compound	Characteristic ion peaks													
	M+		A		B_1		B		B_2		C		C_1	
	m/z	I*	m/z	I	m/z	I	m/z	I	m/z	I	m/z	I	m/z	I
IIIa	366	0,4	85	51	282	3			281	0,8				
IIIb	370	0,3	87	69	284	2	284	0,4						
IIIc	342		73	21	270	3	271	2						
IIId	257	1	73	10	185	25	186	8	184	3	172	3	171	2
IIIe	283	15	85	52	199	70	200	10	198	2	186	1	185	1
IIIf	285	6	87	74	199	71	200	41	148	9	186	20	185	18
IIIg	271	4	73	31	199	30	200	10	198	10	186	6	185	7
IIIh	317	23	119	100	199	52	200	17	198	2	186	6	185	5
IVa	364	0,7	85	62	280	6	281	0,9						
IVb	368	0,2	87	51	282	3								
IVc	340	1	73	20	268	9	269	3						
IVd	281	2	85	52	197	6	198	1			184	6	183	7
IVe	283	1	87	50	197	26	198	9	196	1	184	3	183	4
IVf	269	3	73	18	197	44	198	14	196	4	184	2	183	4

*Intensity, % relative to spectral peak maximum.

EXPERIMENTAL

PMR Spectra for IIIa-h and IVa-g in $CDCl_3$ solution were taken on a Varian VXR-400 instrument with TMS as internal standard. Mass spectra for IIIa-h and IVa-g were recorded on a Kratos MS-890 instrument with ionization energy 70 eV. Monitoring of the course of the reactions was carried out by TLC on Silufol UV-254 plates with hexane–ethyl acetate (6:1) eluent. Melting points were measured in an open capillary on an Electrothermal apparatus. Yields and parameters for the compounds synthesized are given in Tables 1 and 2 and spectral parameters in Tables 3 and 4.

2-Methyl-5,6-dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazine (Ia), 2,8-dimethyl-5,6-dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazine (Ib), 2-methyldipyrrolo[1,2-a; 2′, 1′-c]pyrazine (IIa), and 2,8-dimethyldipyrrolo[1,2-a; 2′,1′-c]pyrazine (IIb) were prepared by method [1], ethoxymethylpiperidine, ethoxymethylmorpholine, and ethoxymethyldiethylamine by method [17], and 1-(piperidinomethyl)-1H-1,2,3-benzotriazole by [15].

Aminomethylation of 2-Methyl-5,6-dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazines (IIIa-d) and 2-Methyldipyrrolo[1,2-a; 2′,1′-c]pyrazines (IVa-c). The corresponding ethoxymethyldialkylamine (2.5 mmole) was added to a solution of 2-methyl-5,6-dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazine Ia or 2-methyldipyrrolo[1,2-a; 2′,1′-c]pyrazine IIa (1 mmole) in benzene (10 ml). The reaction mixture was refluxed for 1-2 h until starting compound had disappeared on TLC. Compounds IVa, IVb were left overnight at room temperature in benzene solution, then the solution was evaporated and the precipitated crystals were filtered, the residue evaporated, and chromatographed on a small plug (2-2.5 cm) of basic alumina with benzene eluent. The evaporated reaction mixture of IIIa was washed with acetone, the crystals filtered off, and the evaporated residue chromatographed on basic alumina with benzene eluent. The evaporated reaction mixtures of compounds IIIb, IIIc, d, and IVc were chromatographed on basic alumina using benzene eluent.

Aminomethylation of 2,8-Dimethyl-5,6-dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazines (IIIe-h). A. The corresponding ethoxymethyldiakylamine (1.5 mmole) was added to a solution of 2,8-dimethyl-5,6-dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazine (Ib, 1 mmole) in benzene (10 ml). The reaction mixture was refluxed for 1-3 h until the starting material had disappeared on TLC. The evaporated reaction mixture was washed with acetone, the crystals filtered off, and the residue evaporated and then chromatographed on a basic alumina column using benzene eluent.

B. 1-(Piperidinomethyl)-1H-1,2,3-benzotriazole (0.42 mmole) was added to a solution of 2,8-dimethyl-5,6-dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazine (Ib, 0.5 mmole) in methylene chloride (10 ml). The reaction mixture was refluxed for 17-20 h and the solvent evaporated *in vacuo*. The residue was chromatographed on a 35/70 silica gel column using acetone eluent. Two fractions were separated. Fraction I contained compound IIIh and an unidentified reaction product and fraction

II contained IIIe. Acetone was added to fraction I, the crystals of IIIh were filtered off, and the residue chromatographed twice on a silica gel column using hexane-ethyl acetate eluent (4:1).

Aminomethylation Products of 2,8-Dimethyldipyrrolo[1,2-a; 2′,1′-c]pyrazine (IVd-g)]. Ethoxymethylpiperidine (1.5 mmole) or ethoxymethylmorpholine (3 mmole) was added to a solution of 2,8-dimethyldipyrrolo[1,2-a; 2′,1′-c]pyrazine (IIb, 1 mmole) in benzene (10 ml). The reaction mixture was refluxed for 1 h until the starting material had disappeared on TLC. The evaporated reaction mixture of compound IVd was dissolved in benzene (1-1.5 ml) and water (5-6 ml) was added with heating until crystals began to appear on the walls of the flask. The solution was left for 1 h at room temperature until the precipitate had formed completely and the obtained crystals filtered off. The benzene solutions of compounds IVe, g and IVf, g were washed several times with water to remove excess reagent and its degradation products. The benzene layer was dried over 4Å molecular sieve and the solvent evaporated. The oily mixture of IVf, g was evaporated several times with acetone, upon which the oil crystallized.

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