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DIPYRROLO[1,2-a; 2′,1′-c]PYRAZINES. 2.* ELECTROPHILIC SUBSTITUTION IN DIPYRROLO[1,2-a; 2′,1′-c]PYRAZINES: PROTONATION, TRIFLUOROACETYLATION, ACETYLATION

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A number of alkyl-substituted dipyrrolo[1,2-a; 2′,1′-c]pyrazines have been synthesized and investigated to determine their behavior in reactions of protonation, trifluoroacetylation, and acetylation. The experimental results correlate well with the calculated data in most cases.

Dipyrrolo[1,2-a; 2′,1′-c]pyrazine, a heterocycle with two bridge nitrogen atoms, has received very little attention. Only a few studies have been published previously [2-4], describing the synthesis of a number of representatives of this heterocyclic system. No detailed studies have been made of the reactivity of dipyrrolo[1,2-a; 2′,1′-c]pyrazines; however, it has been shown that protonation and deuterium exchange of symmetrically substituted dipyrrolo[1,2-a; 2′,1′-c]pyrazines proceeds at position 3 or 8. If these positions are occupied, the protonation may proceed at position 1. For unsymmetrically substituted dipyrrolo[1,2-a; 2′,1′-c]pyrazines, protonation is observed at both α-positions (3 and 8).

In our earlier quantum-chemical study of the structure and reactivity of dipyrrolo[1,2-a; 2′,1′-c]pyrazines with a single or double bond between the $C_{(5)}$ and $C_{(6)}$ atoms [1], it was shown that the most reactive positions in electrophilic substitution are the free α-positions of the pyrrole rings. In the work reported here, in order to confirm the theoretical results, we synthesized a series of dipyrrolo[1,2-a; 2′,1′-c]pyrazines with methyl substituents in different positions on the pyrrole rings and investigated their behavior in reactions with various electrophiles.

A convenient method that we had developed previously for obtaining pyrrolo[1,2-a]pyrazines [5, 6] provides a starting point for the synthesis of dipyrrolo[1,2-a; 2′,1′-c]pyrazines with rather good yields, essentially in a single stage. Quaternary salts, obtained throughthe interaction of the pyrrolo[1,2-a]pyrazines I and II with bromoacetone, are cyclized to dipyrrolo[1,2-a; 2′,1′-c]pyrazines III and IV through the Chichibabin reaction.

In order to clarify the direction of protonation, we took ^{1}H NMR spectra of the dipyrrolo[1,2-a; 2′,1′-c]pyrazines IIIa,b and IVa,b in a mixture of CF_3COOH and $CDCl_3$. For compounds IIIb and IVb, which have only one free α-pyrrole position, we can expect a clean-cut reaction. And in fact, the proton attacks position 3, as indicated by the two-proton singlet observed at 4.8 ppm for the cation Vb and at 5.2 ppm for the cation VIb. Here, the multiplicity of the signals of the other protons remains the same as in the original compounds.

In compounds IIIa and IVa, both α-pyrrole positions are open for electrophilic attack. As shown by the quantum-chemical calculations, the heat of formation of the cation through attack of a proton at position 3 is lower than at position 8 [1]. And correspondingly, in the ^{1}H NMR spectra, we observe the formation of only one thermodynamically stable cation Va, or correspondingly VIa.

Thus, the protonation of the dipyrrolo[1,2-a; 2′,1′-c]pyrazines IVa,b and their 5,6-dihydro analogs IIIa,b in a CF_3COOH–$CDCl_3$ mixture proceeds unambiguously at position 3.

*For communication 1, see [1].

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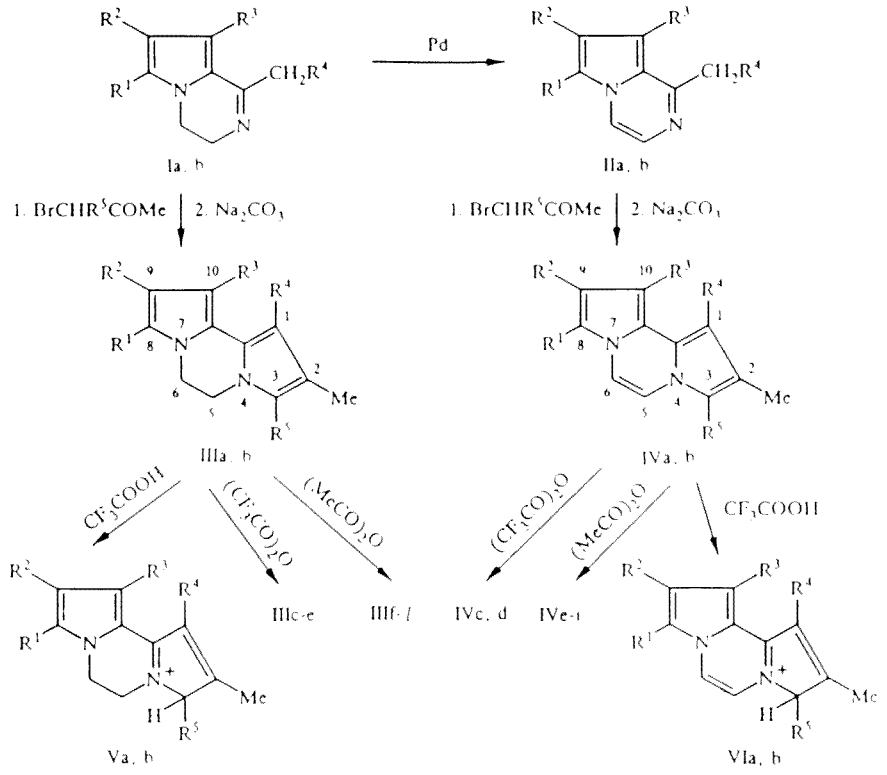

Ia R^1 – R^2 – R^3 – R^4 – H, IbR^1 – CH$_3$, R^2 – R^3 – R^4 – H; IIa R^1 – R^2 – R^3 – R^4 – H, IIbR^1 – CH$_3$, R^2 – – R^3 – R^4 – H; IIIa R^1 – R^2 – R^3 – R^4 – R^5 – H; IIIbR^1 – CH$_3$, R^2 – R^3 – R^4 – R^5 – H; IIIc R^1 – CF$_3$CO, R^2 – R^3 – R^4 – H, R^5 – CF$_3$CO, IIId R^1 – CH$_3$, R^2 – H, R^3 – CF$_3$CO, R^4 – H, R^5 – CF$_3$CO; IIIe R^1 – – CH$_3$, R^2 – CF$_3$CO, R^3 – R^4 – H, R^5 – CF$_3$CO, IIIf R^1 – R^2 – R^3 – R^4 – H, R^5 – CH$_3$CO, IIIg R^1 – – CH$_3$CO, R^2 – R^3 – R^4 – R^5 – H; IIIhR^1 – CH$_3$CO, R^2 – R^3 – R^4 – H, R^5 – CH$_3$CO; IIIi R^1 – CH$_3$, R^2 – R^3 – R^4 – H, R^5 – CH$_3$CO; IIIj R^1 – CH$_3$, R^2 – R^3 – H, R^4 – R^5 – CH$_3$CO; IIIk R^1 – CH$_3$, R^2 – H, R^3 – CH$_3$CO, R^4 – H, R^5 – CH$_3$CO; IIIl R^1 – CH$_3$, R^2 – CH$_3$CO, R^3 – R^4 – H, R^5 – CH$_3$CO, IVa R^1 – R^2 – R^3 – R^4 – R^5 – H; IVbR^1 – CH$_3$, R^2 – R^3 – R^4 – R^5 – H, IVc R^1 – CF$_3$CO, R^2 – R^3 – R^4 – H, R^5 – CF$_3$CO; IVdR^1 – CH$_3$, R^2 – H, R^3 – CF$_3$CO R^4 – H, R^5 – CF$_3$CO; IVe R^1 – R^2 – R^3 – R^4 – H,R^5 – CH$_3$CO, IVf R^1 – CH$_3$CO, R^2 – R^3 – R^4 – H, R^5 – CH$_3$CO; IVg R^1 – CH$_3$, R^2 – R^3 – R^4 – H,R^5 – CH$_3$CO, IVhR^1 – CH$_3$, R^2 – R^3 – H, R^4 – – CH$_3$CO, R^5 – H; IVi R^1 – CH$_3$, R^2 – H, R^3 – CH$_3$CO, R^4 – R^5 – H

In addition to the protonation of the dipyrrolo[1,2-a; 2′,1′-c]pyrazine derivatives IIIa,b and IVa,b, we investigated the trifluoroacetylation and acetylation of these compounds. The trifluoroacetyl cation is a rather strong electrophile. For example, the acylation of pyrrole with trifluoroacetic anhydride proceeds rapidly at 0°C [7]; and the trifluoroacetylation of indolizines containing even such strong electron-acceptor substituents as the nitro group will proceed in 5-10 min at 20°C, giving 3-trifluoroacetyl-6(8)-nitroindolizines with high yields [8]. In the case of the dipyrrolo[1,2-a; 2′,1′-c]pyrazines IIIa,b and IVa,b, the reaction proceeds in 1.5 h at room temperature, forming ditrifluoroacetyl derivatives.

The acylation of 2-methyl-5,6-dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazine (IIIa) and 2-methyldipyrrolo[1,2-a; 2′,1′-c]pyrazine (IVa) by trifluoroacetic anhydride gives 3,8-ditrifluoroacetyl-2-methyl-5,6-dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazine (IIIc) and 3,8-ditrifluoroacetyl-2-methyldipyrrolo[1,2-a; 2′,1′-c]pyrazine (IVc) with high yields. According to quantum-chemical calculations of compounds IIIa and IVa, the highest π-electron density in the HOMO is concentrated on the α-carbon atoms of the pyrrole rings [1]; this finding correlates well with the experimental results.

In compounds IIIa and IVa, both α-pyrrole positions are open for electrophilic attack. In the dipyrrolo[1,2-a; 2′,1′-c]pyrazines IIIb and IVb, in contrast, the α-position of one of the pyrrole rings is occupied by a methyl group, so that electrophilic substitution in this ring can proceed only at one of the remaining free positions 9 or 10. A calculation of the hypothetical molecule of 2,8-dimethyl-3-trifluoroacetyl-5,6-dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazine shows that the π-electron density in the HOMO of the $C_{(9)}$ and $C_{(10)}$ atoms is practically identical [1], thus making it equally probable that the second electrophilic attack will take place at either of these atoms. And in fact, in the trifluoroacetylation of 2,8-dimethyl-5,6-dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazine (IIIb), commensurate yields are obtained for the two ditrifluoroacetyl isomers, namely 3,9-ditrifluoroacetyl-2,8-dimethyl-5,6-dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazine (IIIe) and 3,10-ditrifluoroacetyl-2,8-dimethyl-

TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	T. mp., °C	PMR spectrum, δ, ppm (and J, Hz)	Yield, %
1	2	3	4	5
IIIa	$C_{11}H_{12}N_2$	Oil	2,10 (3H, s, 2-CH_3), 4,08 (2H, m, 5-CH_2), 4,14 (2H, m, 6-CH_2), 6,09 (1H, s, 1-H), 6,15 (1H, d. d, J_{910} = 3,6, J_{98} = 2,7, 9-H), 6,20 (1H, d. d, J_{109} = 3,6, J_{108} = 1,5, 10-H), 6,35 (1H, s, 3-H), 6,56 (1H, d. d, J_{89} = 2,7, J_{810} = 1-,5-,8-H)	35
IIIb	$C_{12}H_{14}N_2$	155	2,07 (3H, d. d, $J_{CH_3,1-H}$ = 0,9, $J_{CH_3,3-H}$ = 0,6, 2-CH_3), 2,22 (3H, d, J_{CH_3H} =0,9, 8-CH_3), 3,99 (2H, m, 6-CH_2), 4,05 (2H, m, 5-CH_2), 5,83 (1H, d. q, J_{910} = 3,4, J_{HCH_3} = 0,9, 9-H), 5,99 (1H, d. q, J_{13} = 1,6, J_{HCH_3} = 0,5, 1-H), 6,05 (1H, d, J_{109} = 3,4, 10-H), 6,34 (1H, d q, J_{31} = 1,7, J_{HCH_3} = 0,9, 3-H)	66
IIIc	$C_{15}H_{10}F_6N_2O_2$	135...136	2,44 (3H, d, J_{CH_3H} = 0,6, 2-CH_3), 4,83 (2H, m, 5-CH_2), 4,85 (2H, m, 6-CH_2), 6,51 (1H, d, J_{HCH_3} = 0,6, 1-H), 6,63 (1H, d, J_{109} = 4,5, 10-H), 7,31 (1H, m, J_{910} = 4,5, 9-H)	65
IIId	$C_{16}H_{12}F_6N_2O_2$	185	2,32 (3H, d, J_{CH_3H} = 0,9, 8-CH_3), 2,43 (3H, q, J_{CH_3H} = 1,9, 2-CH_3), 4,14 (2H, m, 6-CH_2), 4,78 (2H, m, 5-CH_2), 6,56 (1H, m, J_{HCH_3} = 0,9, 9-H), 7,46 (1H, m, 1-H)	53
IIIe	$C_{16}H_{12}F_6N_2O_2$	228...230	2,41 (3H, d, J_{CH_3H} = 0,9, 2-CH_3), 2,64 (3H, s, 8-CH_3), 4,14 (2H, m, 6-CH_2), 4,78 (2H, m, 5-CH_2), 6,37 (1H, d, J_{HCH_3} = 0,9, 1-H), 6,95 (1H, bs, 10-H)	35
IIIf	$C_{13}H_{14}N_2O$	121	2,43 (3H, s, 2-CH_3), 2,47 (3H, s, 3-CH_3CO), 4,18 (2H, t, 6-CH_2), 4,86 (2H, t, 5-CH_2), 6,18 (1H, s, 1-H), 6,24 (1H, d. d, J_{910} = 3,6, J_{98} = 2,8, 9-H), 6,43 (1H, d. d, J_{108} = 1,2, J_{109} = 3,6, 10-H), 6,72 (1H, d. d, J_{89} = 2,8, J_{810} = 1,2,8-H)	42
IIIg	$C_{13}H_{14}N_2O$	—	1,95 (3H, bs, 2-CH_3), 2,14 (3H, s, 8-CH_3CO), 4,2 (2H, t. d, 5-CH_2), 4,9 (2H, t, d, 6-CH_2), 6,26 (1H, d, J_{109} = 4,2, 10-H), 6,31 (1H, q, J_{HCH_3} = 0,6, 1-H), 6,50 (1H, q, J_{HCH_3} = 1,0, 3-H), 7,00 (1H, d, J_{910} = 4,2, 9-H)	5*
IIIh	$C_{15}H_{16}N_2O_2$	195	2,42 (3H, bs, 2-CH_3), 2,45 (3H, s, 3-CH_3CO), 2,47 (3H, s, 8-CH_3CO), 4,78 (4H, bs, 5,6-CH_2), 6,30 (1H, bs, 1-H), 6,40 (1H, d. 10-H), 7,00 (1H, d, 9-H)	41
IIIi	$C_{14}H_{16}N_2O$	184	2,27 (3H, s, 8-CH_3), 2,40 (3H, s, 2-CH_3), 2,44 (3H, s, 3-CH_3CO), 4,02 (2H, t, 6-CH_2), 4,84 (2H, t, 5-CH_2), 5,95 (1H, d, J_{910} = 3,0, 9-H), 6,12 (1H, s, 1-H), 6,34 (1H, d, J_{109} = 3,0, 10-H)	81 20† 35‡
IIIj	$C_{16}H_{18}N_2O_2$	121...123	2,29 (3H, s, 8-CH_3), 2,49 (3H, s, 2-CH_3), 2,51 (3H, s, 1-CH_3CO), 2,54 (3H, s, 3-CH_3CO), 4,06 (2H, t, 6-CH_2), 4,75 (2H, t, 5-CH_2), 5,99 (1H, d. d, J_{910} = 3,7, 9-H), 6,67 (1H, d, J_{109} = 3,7, 10-H)	13
IIIk	$C_{16}H_{18}N_2O_2$	164...165	2,28 (3H, d, J_{CH_3H} = 0,8, 8-CH_3), 2,43 (3H, s, 2-CH_3), 2,46 (3H, s, 3-CH_3CO), 2,47 (3H, s, 10-CH_3CO), 4,02 (2H, t, 6-CH_2), 4,83 (2H, t, 5-CH_2), 6,36 (1H, d, J_{HCH_3} = 0,8, 9-H), 7,40 (1H, s, 1-H)	4† 7‡
IIIl	$C_{16}H_{18}N_2O_2$	221...222	2,42 (3H, s, 9-CH_3CO), 2,43 (3H, s, 2-CH_3), 2,46 (3H, s, 3-CH_3CO), 2,59 (3H, s, 8-CH_3), 4,09 (2H, t, 6-CH_2), 4,87 (2H, t, 5-CH_2), 6,19 (1H, s, 1-H), 6,72 (1H, s, 10-H)	13

TABLE 1 (continued)

1	2	3	4	5
IVa	$C_{11}H_{10}N_2$	86	2,22 (3H, s, 2-CH3), 6,37 (1H, s, 1-H), 6,52 (1H, dd, J_{910} = 3,6, J_{98} = 2,7, 9-H), 6,48 (1H, d, J_{109} = 3,7, 10-H), 6,76 (1H, s, 3-H), 6,95 (1H, d, J_{56} = 5,9, 5-H), 6,97 (1H, dd, J_{89} = 2,7, J_{810} = 1,5, 8-H), 6,99 (1H, d, J_{65} = 5,9, 6-H)	47
IVb	$C_{12}H_{12}N_2$	145...146	2,23 (3H, bs, 2-CH_3), 2,39 (3H, bs, 3-CH_3), 6,21 (1H, dd), J_{910} = 3,6, J_{HCH3} = 0,9, 9-H), 6,28 (1H, s, 1-H), 6,34 (1H, d, J_{109} = 3,6, 10-H), 6,77 (1H, s, 3-H), 6,91 (1H, d, J_{56} = 6,1, 5-H), 7,02 (1H, d, J_{65} = 6,1, 6-H)	58
IVc	$C_{15}H_8F_6N_2O$	146...147	262 (3H, d, J_{CH3H} = 1,6, 2-CH_3), 6,83 (1H, d, J_{HCH3} = 1,6, 1-H), 6,94 (1H, dd, J_{109} = 4,8, 10-H), 7,66 (1H, dd, J_{910} = 4,8, 9-H), 8,95 (1H, d, J_{56} = 6,5, 5-H), 9,11 (1H, d, J_{65} = 6,5, 6-H)	86
IVd	$C_{16}H_{10}F_6N_2O_2$	196	2,51 (3H, s, 2-CH_3), 2,61 (3H, d, J_{CH3H} = 0,9, 8-CH_3), 7,01 (1H, s, 9-H), 7,36 (1H, d, J_{65} = 6,3, 6-H), 7,98 (1H, q, J_{HCH3} = 0,6, 1-H), 9,22 (1H, d, J_{56} = 6,3, 5-H)	98
IVe	$C_{13}H_{12}N_2O$	126...127	2,52 (3H, s, 3-CH_3CO), 2,54 (3H, d, J_{CH3H} = 0,5, 2-CH_3), 6,40 (1H, q, J_{HCH3} = 0,5, 1-H), 6,63 (1H, dd, J_{910} = 3,8, J_{98} = 2,7, 9-H), 6,68 (1H, d, d, d, J_{109} = 3,8, J_{108} = 1,4, J_{106} = 0,7, 10-H), 7,14 (1H, dd, J_{89} = 2,7, J_{810} = 1,4, 8-H), 7,21 (1H, dd, J_{65} = 6,3, J_{610} = 0,7, 6-H), 8,92 (1H, d, J_{56} = 6,3, 5-H)	61 38 †
IVf	$C_{15}H_{14}N_2O_2$	151...152	2,57 (3H, s, 3-CH3CO), 2,59 (3H, s, 8-CH_3CO), 2,61 (3H, d, J_{CH3H} = 0,6, 2-CH_3), 6,63 (1H, q, J_{HCH3} = 0,6, 1-H), 6,72 (1H, dd, J_{109} = 4,5, J_{106} = 0,6, 10-H), 7,37 (1H, d, J_{910} = 4,5, 9-H), 8,93 (1H, d, J_{56} = 6,5, 5-H), 9,10 (1H, dd, J_{65} = 6,5, J_{610} = 0,6, 6-H)	12
IVg	$C_{14}H_{14}N_2O$	162...163	2,44 (3H, d, 8-CH_3), 2,52 (3H, s, 3-CH_3CO), 2,54 (3H, d, 2-CH_3), 6,38 (2H, bs, 1,9-H), 6,62 (1H, d, 10-H), 7,08 (1H, d, J_{65} = 6,3, 6-H), 8,97 (1H, d, J_{56} = 6,3, 5-H)	82 52 †
IVh	$C_{14}H_{14}N_2O$	—	2,43 (3H, s, 8-CH_3), 2,44 (3H, s, 1-CH_3CO), 2,57 (3H, s, 2-CH_3), 6,39 (1H, d, J_{98} = 4,0, 9-H), 6,75 (1H, s, 3-H), 6,99 (1H, d, J_{65} = 6,0, 6-H), 7,10 (1H, d, J_{56} = 6,0, 5-H), 7,80 (1H, d, J_{109} = 4,0, 10-H)	9*
IVi	$C_{14}H_{14}N_2O$	—	2,29 (3H, s, 2-CH_3), 2,39 (3H, s, 8-CH_3), 2,52 (3H, s, 10-CH_3CO), 6,61 (1H, s, 9-H), 6,90 (1H, d, J_{56} = 6,0, 5-H), 6,97 (1H, s 3-H), 7,24 (1H, d, J_{65} = 6,0, 6-H), 7,81 (1H, s, 1-H)	6*
Va	—	—	2,29 (3H, d, J_{CH3H} = 1,1, 2-CH_3), 4,20 (2H, t, 6-CH_2), 4,48 (2H, t, 5-CH_2), 4,83 (2H, s, 3-CH_2), 6,60 (1H, dd, J_{910} = 4,3, J_{98} = 2,5, 9-H), 6,80 (1H, d, J_{HCH3} = 1,1, 1-H), 7,28 (1H, d, J_{109} = 4,3, 10-H), 7,35 (1H, d, J_{89} = 2,5, 8-H)	—
Vb	—	—	2,38 (3H, bs, 8-CH_3), 2,46 (3H, bs, 2-CH_3), 4,19 (2H, t, 6-CH_2), 4,37 (2H, t, 5-CH_2), 4,80 (2H, bs, 3-CH_2), 6,44 (1H, d, J_{910} = 4,4, 9-H), 6,76 (1H, bs, 1-H), 7,26 (1H, d, J_{109} = 4,4, 10-H)	—
VIa	—	—	2,45 (3H, d, J_{CH3H} = 1,5, 2-CH_3), 5,20 (2H, s, 3-CH_2), 7,06 (1H, m, J_{HCH3} = 1,5, 1-H), 7,29 (1H, dd, J_{910} = 4,5, J_{98} = 2,5, 9-H), 7,52 (1H, d, J_{65} = 5,8, 6-H), 7,58 (1H, m, J_{109} = 4,5, 10-H), 7,98 (1H, m, 8-H), 8,04 (1H, d, J_{56} = 5,8, 5-H)	—
VIb	—	—	2,49 (3H, d, J_{CH3H} = 0,8, 2-CH_3), 2,71 (3H, bs, 8-CH_3), 5,23 (2H, s, 3-CH_2), 7,06 (1H, bs, 1-H), 7,17 (1H, d, J_{910} = 4,2, 9-H), 7,57 (1H, d, J_{65} = 5,8, 6-H), 7,60 (1H, d, J_{109} = 4,2, 10-H), 7,84 (1H, d, J_{56} = 5,8, 5-H)	—

*Compounds IIIg, IVh, and IVi could not be isolated in individual form. Yields were calculated on the basis of mixture component ratios as indicated by PMR spectra.

†Obtained by method B.

‡Obtained by method C.

5,6-dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazine (IIId). In the molecule of 2,8-dimethyl-3-trifluoroacetyldipyrrolo[1,2-a; 2′,1′-c]pyrazine, in contrast to its 5,6-dihydro analog, the preferred site of electrophilic attack is position 10 [1]. This evidently explains the fact that the trifluoroacetylation of 2,8-dimethyldipyrrolo[1,2-a; 2′,1′-c]pyrazine (IVb) yields only one product, 3,10-ditrifluoroacetyl-2,8-dimethyldipyrrolo[1,2-a; 2′,1′-c]pyrazine (IVd), in almost quantitative yield.

TABLE 2. Elemental Analysis of Synthesized Compounds

Compound	Found, %			Calculated, %		
	C	H	N	C	H	N
IIIb	77,57	7,73	15,26	77,42	7,53	15,05
IIIc	49,19	2,75	7,36	49,45	2,75	7,59
IIId	49,26	3,06	7,17	50,79	3,17	7,41
IIIe	50,05	3,07	6,97	50,79	3,17	7,41
IIIf	72,80	6,90	12,64	72,89	6,54	13,08
IIIi	73,57	7,05	12,80	73,68	7,02	12,28
IVa	78,10	6,03	17,27	77,65	5,88	16,47
IVb	78,06	6,56	15,60	78,26	6,52	15,22
IVc	50,02	2,36	7,46	49,72	2,21	7,73
IVd	51,26	2,59	7,83	51,06	2,66	7,45
IVg	73,26	5,89	11,79	74,34	6,19	12,39

It is known that the acetyl cation is a weaker electrophile than the trifluoroacetyl cation; therefore, acetylation of the dipyrrolo[1,2-a; 2′,1′-c]pyrazines IIIa,b and IVa,b proceeds only when the reaction mixture is refluxed in toluene for several hours; the reaction yields mainly the 3-monoacetyl derivatives. Thus, in the acylation of compounds IIIb, IVa, and IVb by acetic anhydride, only the 3-monoacetyl derivative is formed: From compound IIIb, 3-acetyl-2,8-dimethyl-5,6-dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazine (IIIi) (81%); from compound IVa, 3-acetyl-2-methyldipyrrolo[1,2-a; 2′,1′-c]pyrazine (IVe) (61%); from the dipyrrolopyrazine IVb, 3-acetyl-2,8-dimethyldipyrrolo[1,2-a; 2′,1′-c]pyrazine (IVg) (82%).

In contrast to the dipyrrolopyrazines IIIb, IVa, and IVb, the 5,6-dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazine IIIa interacts with acetic anhydride to form a mixture of the 3- and 8-monoacetyl isomers. As expected, however, the main product is still 3-acetyl-2-methyl-5,6-dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazine (IIIf) (42%); the yield of 8-acetyl-2-methyl-5,6-dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazine (IIIg) is only 5%, this product being recovered only as a mixture with compound IIIf.

It has been reported that catalysis of acylation by anhydrous magnesium perchlorate increases the product yield [9]. In the case of the dipyrrolopyrazines, we do not observe any higher yields of 3-acetyldipyrrolo[1,2-a; 2′,1′-c]pyrazines, but only the formation of diacetyl derivatives or a change in the direction of electrophilic attack. The use of Anhydrone [magnesium perchlorate] in this reaction probably lowers its energy barrier and permits the appearance of products that are less thermodynamically favorable, even though the 3-monoacetyl derivative is still the principal product. Only in the acetylation of the dipyrrolo[1,2-a; 2′,1′-c]pyrazine IIIa in the presence of magnesium perchlorate did we fail to detect the 3-monoacetyl derivative; the only reaction product that was recovered was 3,8-diacetyl-2-methyl-5,6-dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazine (IIIh).

Acetylation of compound IVa in the presence of magnesium chlorate leads to a mixture of the 3-monoacetyl derivative IVe and the 3,8-diacetyl derivative IVf, with the former as the main reaction product, yield 38%; the yield of 3,8-diacetyl-2-methyldipyrrolo[1,2-a; 2′,1′-c]pyrazine (IVf) is 12%.

The main product from the acetylation of the dipyrrolopyrazine IIIb, the same as in the preceding case, is the 3-monoacetyl derivative IIIi. However, a mixture of diacylated products is also formed: 3,9-diacetyl- (IIIl, 13%), 3,10-diacetyl- (IIIk, 4%), and 1,3-diacetyl-2,8-dimethyl-5,6-dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazine (IIIj) (trace amounts).

Compounds IIIi (35%), IIIj (13%), and IIIk (7%) were also recovered when the reaction temperature was increased to 200°C.

The predominant product from the acetylation of 2,8-dimethyldipyrrolo[1,2-a; 2′,1′-c]pyrazine (IVb) is 3-acetyldipyrrolo[1,2-a; 2′,1′-c]pyrazine (IVg, 52%); but here also, a change of the direction of electrophilic attack is observed, with the formation of a mixture of two minor monoacetyl components 1-acetyl-2,8-dimethyldipyrrolo[1,2-a; 2′,1′-c]pyrazine (IVh) and 10-acetyl-2,8-dipyrrolo[1,2-a; 2′,1′-c]pyrazine (IVi), which could not be separated, owing to their very similar chromatographic mobilities. The total yield of the isomers IVh and IVi is 15%, and the ratio of isomers is 3:2 as determined from high-resolution PMR spectra.

EXPERIMENTAL

PMR spectra of compounds IIIb, IIId, IIIe, and IVd in CD_2Cl_2, spectra of compounds IIIa, IIIc, IIIf-*l*, IVa, IVc, and IVe-i in $CDCl_3$, and spectra of protonation* of compounds IIIa,b and IVa,b in a CF_3COOH–$CDCl_3$ mixture were taken in a Varian VXR-400 instrument, internal standard TMS. The course of the reaction was monitored by TLC on Silufol UV-254 plates. The yields, constants, and spectral characteristics of the compounds that were obtained are listed in Table 1.

Elemental analyses of the synthesized compounds for C, H, and N matched the calculated values (Table 2).

5,6-Dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazines (IIIa,b) and Dipyrrolo[1,2-a; 2′,1′-c]pyrazines (IVa,b). To a solution of 20 mmoles of a 3,4-dihydropyrrolo[1,2-a]pyrazine (Ia,b) or pyrrolo[1,2-a]pyrazine (IIa,b), in acetone, 22 mmoles of bromoacetone were added. The reaction mixture was left for one day at room temperature, the precipitated salt was dissolved in hot water, and a saturated sodium carbonate solution was added. After one day at approximately 20°C, the crystalline compounds IIIb, IVa, and IVb were filtered off and recrystallized from 2-propanol. Compound IIIa was extracted with chloroform, the solvent was evaporated, and the residue was chromatographed in a column with 40/100 mμ silica gel in a 4:1 hexane–ethyl acetate system.

Ditrifluoroacetyl Derivatives of 5,6-Dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazine (IIIc-e) and Dipyrrolo[1,2-a; 2′,1′-c]pyrazine (IVc,d). To a solution of 1 mmole of a 5,6-dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazine IIIa,b or dipyrrolo[1,2-a; 2′,1′-c]pyrazine IVa,b in 5 ml of toluene, 22 ml of trifluoroacetic anhydride was added. The reaction mixture was held for 1.5 h at room temperature, after which the solvent and excess anhydride were evaporated. The mixture of compounds IIId and IIIe were separated in a column with Silperl in a 5:1 benzene–hexane system; compounds IIIc and IVc were separated in a column with 40/100 μm silica gel in a hexane–ethyl acetate system with a gradient from 4:1 to 1:1; compound IVd was separated in a column with 5/40 μm silica gel in a 1:2 benzene–ethyl acetate system.

Acetyl Derivatives of 5,6-Dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazine (IIIf-*l*) and Dipyrrolo[1,2-a; 2′,1′-c]pyrazine (IVe-i). **A**. To a solution of 1 mmole of the 5,6-dihydrodipyrrolo[1,2-a; 2′,1′-c]pyrazine IIIa,b or the dipyrrolo[1,2-a; 2′,1′-c]pyrazine IVa,b in 10 ml of toluene, 2.3 mmoles of acetic anhydride was added. The reaction mixture was refluxed for 7-24 h until the original reactant had disappeared as determined by TLC. The solvent and the excess anhydride were removed under vacuum. Compounds IVe and IVg were crystallized from heptane; compound IIIi was separated in a column with Silperl in a hexane–ethyl acetate system with a gradient from 6:1 to 1:1; the mixture of compounds IIIf and IIIg was separated in a column with 40/100 μm silica gel in a 4:1 hexane–ethyl acetate system.

B. To a solution of 1 mmole of the 5,6-dihydrodipyrrolopyrazine IIIa,b or the dipyrrolopyrazine IVa,b and 23 mmoles of acetic anhydride in 10 ml of toluene, 0.2 mmole of magnesium perchlorate was added. The mixture was refluxed for 1-5 h. The solvent and excess anhydride were removed under vacuum. Compound IIIh was chromatographed on 100/250 μm silica gel in ethyl acetate. A mixture of compounds IIIi, IIIj, IIIk, and III*l* was separated in a column with 40/100 μm silica gel in a hexane–ethyl acetate system with a gradient from 6:1 to 1:1; the mixture of compounds IVe and IVf was separated in a 1:1 benzene–hexane system, then 1:4 acetone–hexane; the mixture of compounds IVg, IVh, and IVi was separated in a 1:1 benzene–hexane system, then 1:4 ethyl acetate–hexane.

C. A solution of 1 mmole of compound IIIb in 23 mmoles of acetic anhydride and 5 ml of toluene was heated for 35-40 h in a sealed ampul at 200°C, after which the solvent was taken off; the mixture of compounds IIIi, IIIj, and IIIk was separated in a column with 100/250 μm silica gel in a hexane–ethyl acetate system with a gradient from 6:1 to 1:1.

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REFERENCES

1. V. I. Terenin, K. V. Karapetyan, E. L. Ruchkina, V. M. Mamaev, and Yu. G. Bundel', Khim. Geterotsikl. Soedin., No. 11, 1559 (1995).
2. V. Boekelheide and K. Fahrenholtz, J. Am. Chem. Soc., **83**, 458 (1961).
3. R. Buchan, M. Fraser, and P. V. S. Kong Thoo Lin, Heterocycles, **28**, 857 (1989).
4. U. Burger, Tetrahedron, **39**, 2065 (1983).

*As in Russian original; possibly intended to refer to compounds Va,b and VIa,b — Translator.

5. A. M. Likhosherstov, V. P. Peresada, V. G. Vinokurov, and A. P. Skoldinov, Zh. Org. Khim., **22**, 2610 (1986).
6. V. I. Terenin, E. V. Kabanova, and Yu. G. Bundel', Khim. Geterotsikl. Soedin., No. 6, 763 (1991).
7. W. Cooper, J. Org. Chem., **23**, 1382 (1958).
8. E. V. Babaev, S. I. Bobrovskii, and Yu. G. Bundel', Khim. Geterotsikl. Soedin., No. 11, 1570 (1988).
9. G. N. Dorofeenko, A. P. Kucherenko, and N. V. Prokof'eva, Zh. Obshch. Khim., **33**, 586 (1963).