*Chemistry of Heterocyclic Compounds, Vol.35, No. 2, 1999*

# DIPYRROLO[1,2-*a*; 2',1'-*c*]PYRAZINES. 5*. AZO COUPLING OF 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 synthesized a series of previously unreported azo dyes via the azo coupling of alkyl substituted dipyrrolopyrazines with aryldiazonium chloride. For this type of substrate where one or both α-positions of the pyrrole rings of the molecules are not occupied by substituents, electrophilic attack was found to occur initially at carbon atom $C_{(3)}$.*

Arylazo derivatives of dipyrrolopyrazines can be formally considered as analogs of prodigiosines which are natural red-orange dye pigments having antibacterial and fungicidal activity. In this connection, the appearance of similar biological activity might be expected both for arylazo-substituted dipyrrolopyrazines and for their 5,6-dihydro analogs. We have studied the azo coupling of 2-methyl- and 2,8-dimethylaza-substituted dipyrrolopyrazines IIa,b and 5,6-dihydrodipyrrolopyrazines Ia,b, obtained previously [1-3] using aryldiazonium chloride. As known from literature sources [4, 5], pyrrolo[1,2-*b*]pyridazines and pyrrolo[1,2-*c*]pyrimidines enter into an azo coupling reaction to form substitution products at free α-carbon atom in 50-70% yields. Since the diazo component is quite a weak electrophile, the azo component must be quite reactive in electrophilic substitution reactions. Several substrates, e.g. pyrrolo[1,2-*a*]pyrazine do not undergo diazo coupling and appear to be stable to substitution by weakly electrophilic agents [6]. By contrast to pyrrolo[1,2-*a*]pyrazines, the bicyclic dipyrrolo-[1,2-*a*; 2',1'-*c*]pyrazine analogs readily take part in this type of reaction. Azo coupling of compounds Ia,b and IIa,b with aryldiazonium chloride salts occurs at room temperature to give the corresponding arylazo compounds in 41-92% yields.

A substitutent in the *para* position of the benzene ring of the diazo component was shown to affect the color of the final azo coupling products. In the series of arylazo derivatives III or IV change in color is observed from orange to violet in agreement with an increase of the extent of the conjugated chain in the given heterocyclic systems. The long wavelength UV absorption bands for compounds IIIa and IIIb are found in the general region of 488 and 492 nm respectively, whereas for compound IIIc an expected (and rather large) bathochromic shift of 73-77 nm is observed.

Azo coupling of dipyrrolopyrazines Ia, IIa with aryldiazonium chloride (where R = H or $OCH_3$) is carried out using a direct addition method whereas for the *para*-nitrophenyldiazonium chloride a reverse addition method can be used to increase the reaction product yield.

In the $^1$H NMR spectra of compounds IIIa-c characteristic signals for 9-H, 1-H, and 10-H are recorded in the region of 5.97-6.04, 6.26-6.38, and 6.38-6.53 ppm respectively. For compounds IIIa and IIIb with phenylazo- and *para*-methoxyphenylazo-substituents in position 3 of the pyrrole fragment, the proton signals for

* For communication 4 see [1]

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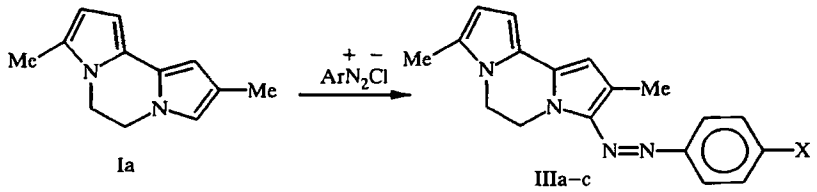
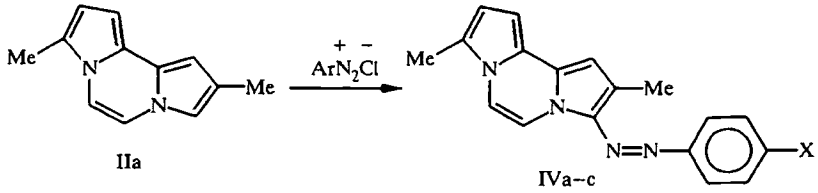
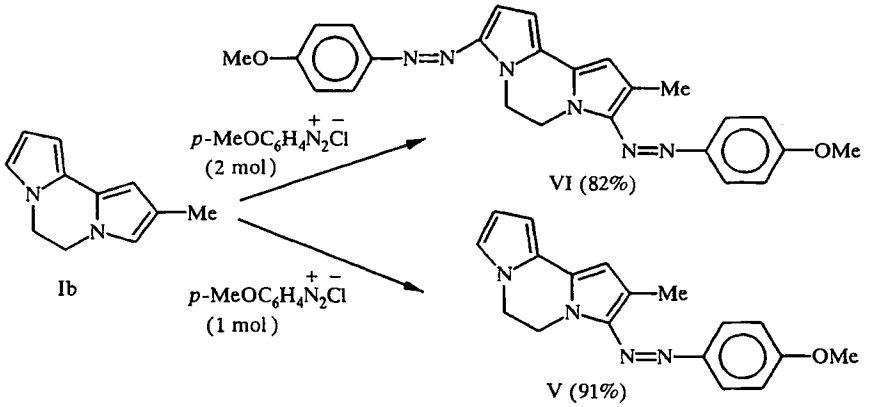
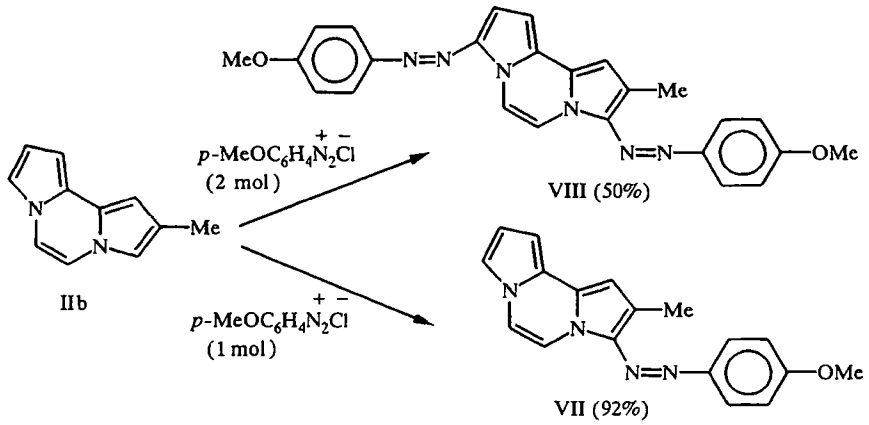



III–IVa X = H, b X = $OCH_3$, c X = $NO_2$

the pyrazine ring and the 10-H proton have a normal form and multiplicity. However, for 3-(*para*-nitrophenylazo)-5,6-dihydrodipyrrolopyrazine IIIc, the 10-H and 6-H proton signals appear as a broad singlet and the signals for the protons at position 5 of the pyrazine ring are non-equivalent and are found at 4.59 and 5.00 ppm.




For 2,8-dimethyl-3-arylazodipyrrolopyrazines IVa-c with a double bond between the $C_{(5)}$—$C_{(6)}$ carbon atoms, the high resolution PMR spectra show the following regularity: the protons on $C_{(5)}$ of the pyrazine ring appear as a broadened singlet whereas the protons at the neighboring $C_{(6)}$ atom are seen as a doublet with spin-spin coupling constant of 6.3 Hz.

TABLE 1. Properties of Synthesized Compounds

| Compound | Empirical formula | Found, % / Calculated, % | | | $M^+$ | mp, °C | Substrate/ reagent, mmol | Yield, % |
|---|---|---|---|---|---|---|---|---|
| | | C | H | N | | | | |
| IIIa* | $C_{18}H_{18}N_4$ | 74,84 / 74,50 | 6,36 / 6,20 | | 290 | 144...146 | 1:1 | 41 |
| IIIb* | $C_{19}H_{20}N_4O$ | 71,80 / 71,25 | 6,37 / 6,25 | 17,60 / 17,50 | 320 | 139...140 | 1:1 | 76 |
| IIIc* | $C_{18}H_{17}N_5O_2$ | 65,15 / 64,47 | 5,50 / 5,07 | | | 180...182 | 1:1 | 65 |
| IVa | $C_{18}H_{16}N_4$ | 74,72 / 75,00 | 5,59 / 5,55 | 19,53 / 19,40 | 288 | 145...147 | 1:1 | 73 |
| IVb | $C_{19}H_{18}N_4O$ | 71,56 / 71,69 | 5,60 / 5,66 | 17,56 / 17,61 | | 165...170 | 1:1 | 75 |
| IVc | $C_{18}H_{15}N_5O_2$ | | | | 333 | *2 | 1:1 | 72 |
| V | $C_{18}H_{18}N_4O$ | | | | 306 | 88...90 | 1:1 | 91 |
| VI | $C_{25}H_{24}N_6O_2$ | | | | 440 | 215 | 1:2 | 82 |
| VII | $C_{18}H_{16}N_4O$ | | | | 304 | 75...80 | 1:1 | 92 |
| VIII | $C_{25}H_{22}N_6O_2$ | 69,92 / 68,49 | 5,36 / 5,02 | 19,11 / 19,17 | 438 | 220...225 | 1:2 | 50 |

* UV Spectra, $\lambda_{max}$ (log ε): IIIa 488 (4.52), 295 (4.09); IIIb 492 (4.59), 300 (4.13), 235 (4.01); IIIc 565 (4.48), 384 (4.08), 304 (3.97), 268 nm (3.92).

*2 Compound IVc could not be isolated in the pure state.

When treating the 2-methyl-substituted substrates Ib and IIb (where both α-positions of the pyrrole rings of the molecules are free for electrophilic attack) with an equimolar amount of the aryldiazonium chloride the 3-arylazo substituted derivatives V and VII are formed in high yield. If the amount of reagent is increased twofold, the electrophilic attack produces 3,8-disubstituted derivatives VI and VIII.

Hence for azo coupling, in common with other electrophilic substitution reactions, in a series of alkyl-substituted dipyrrolopyrazines and their 5,6-dihydro analogs (in which one or both α-positions of the pyrrole rings in the molecules are not occupied by substituents) electrophilic attack is initially directed to the $C_{(3)}$ carbon atom.

## EXPERIMENTAL

PMR spectra for compounds III-VIII were recorded for $CDCl_3$ solutions on a Varian VXR-400 instrument with TMS as internal standard. Mass spectra for compounds IIIa,b, IVa,c, and V-VIII were measured on a Kratos MS-90 instrument with an ionization energy of 70 eV. UV spectra were taken on a Varian Cary 219 spectrophotometer using $CH_2Cl_2$. Monitoring of the reaction course was carried out by TLC on Silufol UV-254 plates.

Yields, parameters, and substrate reagent ratios for all of the synthesized compounds are given in Table 1 and PMR spectral data in Table 2.

2,8-Dimethyl-5,6-dihydrodipyrrolo[1,2-*a*; 2',1'-*c*]pyrazine (Ia), 2-methyl-5,6-dihydrodipyrrolo[1,2-*a*; 2',1'-*c*]pyrazine (Ib), 2,8-dimethyldipyrrolo[1,2-*a*; 2',1'-*c*]pyrazine (IIa), and 2-methyldipyrrolo[1,2-*a*; 2',1'-*c*]pyrazine (IIb) were prepared as in method [2].

**Arylazo Derivatives of 5,6-Dihydrodipyrrolo[1,2-*a*; 2',1'-*c*]pyrazines IIIa-c, V, VI, and Dipyrrolo-[1,2-*a*; 2',1'-*c*]pyrazines IVa-c, VII, VIII.** To solution of 5,6-dihydrodipyrrolo[1,2-*a*; 2',1'-*c*]pyrazine Ia,b or dipyrrolo[1,2-*a*; 2',1'-*c*]pyrazine IIa,b (1 mmol) in methanol (30 ml), solution of aryldiazonium chloride, which had been previously neutralized to pH ~6, prepared using the usual method, was gradually added at room temperature and with stirring. For preparation of compounds IIIc-IVc the method of reverse addition was used [7]. After the reaction had finished, the reaction mixture was left overnight and separated by one of the methods indicated below.

TABLE 2. PMR Spectral Characteristics for Synthesized Compounds (δ, ppm, *J*, Hz)

| Compound | Protons and substituents in the pyrrole rings | | | | | | Pyrazine ring protons |
|---|---|---|---|---|---|---|---|
| | 1-H | 2-R | 3-R | 8-R(H) | 9-H | 10-H | |
| IIIa | 6,29 br. s | 2,47 br. s (3H) | 7,27 m (1H, *p*-H)<br>7,43 m (2H, *m*-H)<br>7,75 m (2H, *o*-H) | 2,31 s (3H) | 6,00 d $J_{910}$ = 3,6 | 6,42 d $J_{109}$ = 3,6 | 4,80 m (2H, 5-$CH_2$)<br>4,10 m (2H, 6-$CH_2$) |
| IIIb | 6,26 br. s | 2,44 br. s (3H) | 3,86 s (*p*-$OCH_3$)<br>6,94 m (2H, *o*-H)<br>7,71 m (2H, *m*-H) | 2,28 s (3H) | 5,97 d $J_{910}$ = 3,6 | 6,38 d $J_{109}$ = 3,6 | 4,72 m (2H, 5-$CH_2$)<br>4,08 m (2H, 6-$CH_2$) |
| IIIc | 6,38 br. s | 2,47 br. s (3H) | 7,76 m (2H, *o*-H)<br>8,25 m (2H, *m*-H) | 2,32 d (3H) | 6,04 dq $J_{910}$ = 3,0<br>$J_{H,CH_3}$ = 0,9 | 6,54 br. s | 4,59 br.s (1H, 5-H)<br>5,00 br.s (1H, 5-H)<br>4,11 br.s (2H, 6-$CH_2$) |
| IVa | 6,54 s | 2,58 s (3H) | 7,28 m (1H, *p*-H)<br>7,44 m (2H, *m*-H)<br>7,79 m (2H, *o*-H) | 2,45 d (3H) | 6,41 dq $J_{910}$ = 3,7<br>$J_{H,CH_3}$ = 0,8 | 6,67 d $J_{109}$ = 3,7 | 8,80 br.s (1H, 5-H)<br>7,08 d (1H, 6-H)<br>$J_{65}$ = 6,3 |
| IVb | 6,52 q | 2,57 d (3H)<br>$J_{CH_3,H}$ = 0,6 | 3,87 s (*p*-$OCH_3$)<br>6,97 m (2H, o-H)<br>7,77 m (2H, *m*-H) | 2,45 d (3H)<br>$J_{CH_3,H}$ = 0,7 | 6,39 dq $J_{910}$ = 3,7<br>$J_{H,CH_3}$ = 0,7 | 6,64 d $J_{109}$ = 3,7 | 8,71 br.s (1H, 5-H)<br>7,07 d (1H, 6-H).<br>$J_{65}$ = 6,3 |
| IVc | 6,32 br. s | 2,69 br. s (3H) | 7,81 m (2H, *o*-H)<br>8,27 m (2H, *m*-H) | 2,50 s (3H) | 6,19 d $J_{910}$ = 3,5 | 6,35 d $J_{109}$ = 3,5 | 9,21 br.s (1H, 5-H)<br>7,21 d (1H, 6-H)<br>$J_{65}$ = 5,9 |
| V | 6,32 d, $J_{H,CH_3}$ = 0,86 | 2,44 br. s (3H) | 3,84 s (*p*-$OCH_3$)<br>6,94 m (2H, *o*-H)<br>7,72 m (2H, *m*-H) | 6,70 dd $J_{89}$ = 2,65<br>$J_{810}$ = 1,45 | 6,23 dd $J_{910}$ = 3,6<br>$J_{98}$ = 2,14 | 6,43 dd $J_{109}$ = 3,6<br>$J_{108}$ = 1,45 | 4,72 m (2H, 5-$CH_2$)<br>4,20 m (2H, 5-$CH_2$) |
| VI | 6,45 d, $J_{H,CH_3}$ = 0,92 | 2,46 br. s (3H) | 3,874 s (*p*-$OCH_3$)<br>6,97 m (2H, *o*-H)<br>7,79 m (2H, *m*-H) | 3,877 s (*p*-$OCH_3$)<br>6,97 m (2H, *o*-H)<br>7,79 m (2H, *m*-H) | 6,81 d $J_{910}$ = 4,2 | 6,59 d $J_{109}$ = 4,2 | 4,71 m (2H, 5-$CH_2$)<br>4,81 m (2H, 5-$CH_2$) |
| VII | 6,55 br. s | 2,57 br. s (3H) | 3,87 s (*p*-$OCH_3$)<br>6,97 m (2H, *o*-H)<br>7,78 m (2H, *m*-H) | 7,14 dd $J_{89}$ = 2,74<br>$J_{810}$ = 1,65 | 6,63 dd $J_{910}$ = 3,9<br>$J_{98}$ = 2,74 | 6,69 ddd $J_{109}$ = 3,9<br>$J_{108}$ = 1,65<br>$J_{106}$ = 0,67 | 8,65 br.s (1H, 5-H)<br>7,19 dd (1H, 6-H)<br>$J_{65}$ = 6,3 $J_{610}$ = 0,67 |
| VIII | 6,71 s | 2,61 s (3H) | 3,888 s (*p*-$OCH_3$)<br>7,01 m (2H, *o*-H)<br>7,84 m (2H, *m*-H) | 3,891 s (*p*-$OCH_3$)<br>7,01 m (2H, *o*-H)<br>7,84 m (2H, *m*-H) | 7,18 d $J_{910}$ = 4,25 | 6,85 d $J_{109}$ = 4,25 | 8,33 d (1H, 5-H)<br>8,80 d (1H, 6-H)<br>$J_{65}$ = 6,1 |

A. The reaction mixture was diluted by several times with water until the reaction product precipitated, the precipitate filtered, dissolved in benzene, and the mother liquor extracted several times with benzene and dried with 3 Å molecular sieve. The combined benzene solution was evaporated and chromatographed on a silica gel column, eluting with benzene (for compound IIIa) or by crystallizing from methanol (for compound IVc).

B. The reaction mixture was evaporated and then chromatographed on a silica gel column, eluting with benzene.

C. The reaction mixture was evaporated, extracted several times with portions of hot benzene, the inorganic residue filtered off, and evaporated.

Compounds IIIa, IVc were prepared by method A, compounds IIIb,c by method B, and compounds IVa,b and V-VIII by method C.

The work was carried out with the financial support of the RFFR (grant No. 96-03-32157a).

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