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[2.2](2,5)Pyrazinophanes: Synthesis and Molecular Structure

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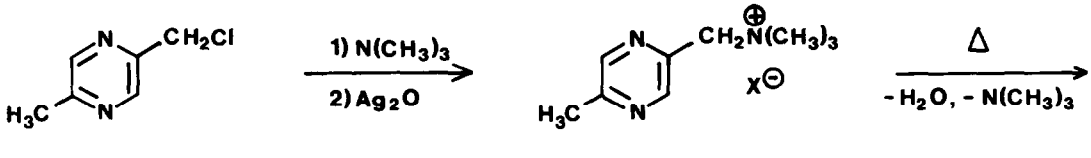
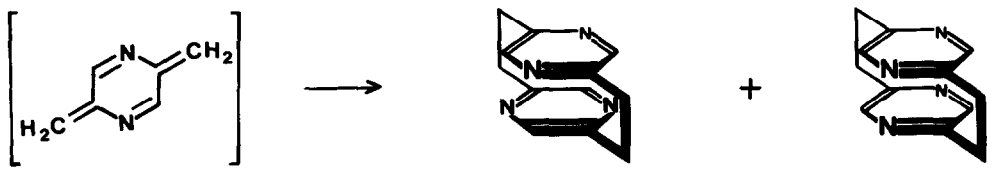
Abstract: The *pseudoortho* (**4a**) and the *pseudogeminal* [2.2](2,5)pyrazinophane (**4b**) have been synthesized via 1,6-Hofmann elimination of [(5-methyl-2-pyrazinyl)methyl]trimethylammonium hydroxide (**2b**) and dimerization of the generated 2,5-dihydro-2,5-bis(methylene)pyrazine (**3**). The molecular structures of both isomers, **4a** and **4b**, were determined by X-ray analysis.

In connection with studies of transannular interactions in heterocyclic [2.2]paracyclophanes[1] with π-electron deficient rings we were interested in the two isomeric [2.2](2,5)pyrazinophanes **4a** (*pseudoortho*) and **4b** (*pseudogeminal*). A direct synthetic approach leading to **4a** and **4b** is by dimerization of the intermediate 2,5-dihydro-2,5-bis(methylene)pyrazine (**3**), which can be formed from 2-chloromethyl-5-methylpyrazine (**1**)[2] as starting material. **1** obtained by reaction of 2,5-dimethylpyrazine with N-chloro succinimide (1:1 molar ratio, CCl_4, dibenzoyl peroxide, 24 h reflux, ≈ 50 % yield) was converted into the [(5-methyl-2-pyrazinyl)-methyl]trimethylammonium chloride **2a**[3] [ethyl acetate + nitromethane (2:1), $N(CH_3)_3$], colourless hygroscopic needles (dec. 223°C, 72 %), which in aqueous solution reacted with Ag_2O to give the ammonium hydroxide **2b**. Thermal decomposition of **2b** in boiling toluene in the presence of phenothiazine yielded via 1,6-Hofmann elimination and subsequent dimerization of the generated 2,5-dihydro-2,5-bis(methylene)pyrazine (**3**) the desired [2.2](2,5)pyrazinophanes **4a** (m.p. 255-256°C, 8.7 %) and **4b** (m.p. 297-298°C, 1.5 %).[4] As further products of this reaction bis(5-methyl-2-pyrazinyl)methyl ether (m.p. 66-67°C, 28 %)[5] and 1,2-bis(5-methyl-2-pyrazinyl)-ethylene (m.p. 211°C, 1 %)[6] were obtained.



1

2a: X = Cl
2b: X = OH



3 **4a** **4b**

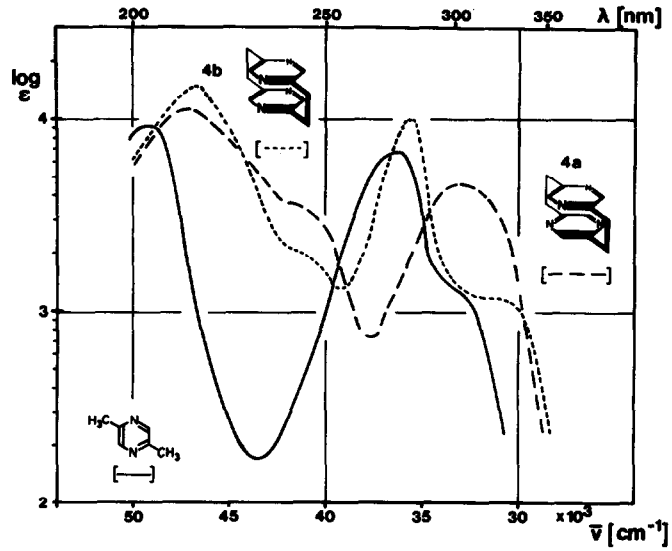


Fig. 1. Electron spectra of 2,5-dimethylpyrazine, **4a**, and **4b** in ethanol

A comparison of the electron spectra of **4a** and **4b** with that of the reference compound 2,5-dimethylpyrazine[7] (Fig. 1) shows as expected bathochromic shifts of the [2.2](2,5)pyrazinophane bands. Furthermore, the band pattern of **4b** closely resembles that of the reference compound. In case of the [2.2](2,5)pyridinophanes the electron spectra[8] of the *pseudoortho* and *pseudometa* isomers show a pronounced first band at 309 nm, whereas in those of the *pseudogeminal* and *pseudopara* isomers the first band appears only as a shoulder at 303 nm. Similar features are found in the electron spectra of **4a** and **4b**. The strong first absorption band (306 nm) of **4a** and the first band (shoulder at 320 nm) of **4b** may be taken as an indication that **4a** represents the *pseudoortho* and **4b** the *pseudogeminal* isomer. To obtain, however, clear evidence, the isomer assignment was proved by X-ray structure analysis.

4a crystallizes from ethyl acetate in orthorhombic prisms: Space group *Ccca* (No. 68 Int. Tables), $Z = 4$, $F(000) = 448$ (molecular symmetry in crystal D_2), $a = 1131.4$ (1), $b = 912.0$ (1), $c = 974.1$ (1) pm, $D_x = 1.403$ gcm^{-3}. Enraf-Nonius CAD-4 four circle diffractometer, graphite-monochromated Mo Kα radiation; Θ/2Θ scanning technique. 673 unique reflections measured $(\sin\Theta)/\lambda \leq 6.82$ nm^{-1}; 489 [$I \geq 1.96\,\sigma(I)$] used for structure solution and refinement. The structure was solved by analysis of a Patterson map. Full-matrix least squares refinement led to $R = 0.038$. **4b** crystallizes from ethyl acetate in monoclinic prisms: Space group $P2_1/n$ (No. 14 Int. Tables), $Z = 2$, $F(000) = 224$ (molecular symmetry in crystal C_i), $a = 726.3$ (2), $b = 912.0$ (2), $c = 773.3$ (2) pm, $\beta = 99.09$ (1) °, $D_x = 1.394$ gcm^{-3}. 1275 unique reflections $(\sin\Theta)/\lambda \leq 6.82$ nm^{-1}; 948 [$I \geq 1.96\,\sigma(I)$] observed. The structure was solved by conventional direct methods (Multan); full-matrix least squares refinement yielded $R = 0.051$.

Figures 2 and 3 show the molecular structures of **4a** and **4b** as top-views perpendicular to the least square planes of the four non-bridgehead atoms of the pyrazine rings and as side-views within these planes, together with bond lengths [pm] and angles [°][9] which are very similar to those of pyrazine: C-C 137.8, C-N 133.4 pm; C-N-C 115.1, C-C-N 122.4 °.[10] In **4a** and **4b** due to alkyl substitution at the bridgehead carbons the (CH_2)C-N and (H)C-N bond lengths are slightly different. As compared to the aromatic rings of [2.2]paracyclophane (interplanar angle $\alpha = 12.6$ °)[11] the boat-like deformation of the pyrazine rings in **4a** and **4b** is more pronounced . The interplanar angles α of **4a** [between the N(4), C(5), N(4i), C(5i) and the C(3), N(4), C(5i)

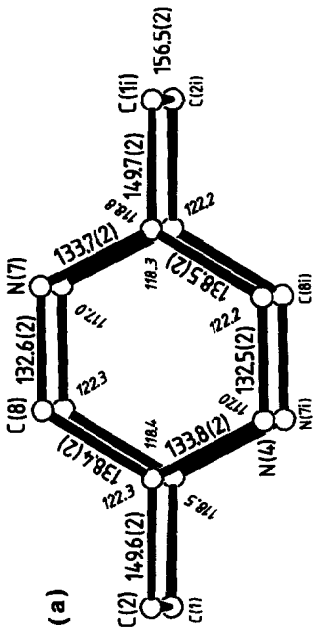


Fig. 3. Molecular structure of 4b: (a) Top-view with bond lengths [pm] and angles [°]; (b) side-view across pyrazine rings

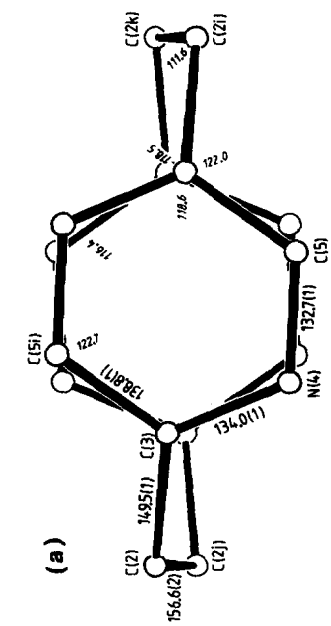


Fig. 2. Molecular structure of 4a: (a) Top-view with bond lengths [pm] and angles [°]; (b) side-view across pyrazine rings

planes] and of **4b** [between the N(4), C(5), N(7), C(8) and the C(3), N(4), C(8) planes] increase to ≈14.5 °. On the other hand, the angles β ≈ 8.1 - 9.4 ° [**4a**: between the C(3), N(4), C(5i) plane and the C(3)-C(2) vector; **4b**: between the C(3), N(4), C(8) plane and the C(3)-C(2) vector], are smaller than in [2.2]paracyclophane (11.2 °).[11] The "softer" pyrazine rings reduce the steric strain of the [2.2](2,5)pyrazinophane system mainly by deviation from planarity. The mean transannular distances with 306 and 308 pm are very similar to that in [2.2]paracyclophane (309 pm).[11] The twist of the pyrazine rings [angle between the C(2)-C(2i) and C(2j)-C(2k) axes ≈ 10 °] in the *pseudoortho* isomer **4a**, which leads to a slight reduction of the mean transannular distance, may be related to the intramolecular contacts between the H of the ring carbon and the *syn* H of the adjacent methylene substituent. Strain release of this mode is not possible in the *pseudogeminal* isomer **4b**. The pyrazine rings of **4b** show an ecliptic arrangement with the transannular N(4)---N(7i) (304 pm) distance being shorter than C(5)---C(8i) (314 pm).

1) H. A. Staab and W. K. Appel, *Liebigs Ann. Chem.* **1981**, 1065; H. A. Staab, H.-J. Hasselbach, and C. Krieger, *ibid.* **1986**, 751; F. A. Neugebauer and Hans Fischer, *Tetrahedron Lett.* **27**, 5367 (1986).

2) A. Hirschberg and P. E. Spoerri, *J. Org. Chem.* **26**, 2356 (1961). ^{1}H NMR (360 MHz, $CDCl_3$) δ = 2.58 (s; 3 H, CH_3), 4.69 (s; 2 H, CH_2), 8.43 (d, $^5J_{3,6}$ = 1.3 Hz; 6-H), 8.61 (d; 3-H); MS: *m/z* (%) = 142 (100, M^+).

3) Correct elemental analysis; ^{1}H NMR (360 MHz, [D_6]DMSO) δ = 2.56 (s; 3 H, 5-CH_3), 3.17 (s; 9 H, NCH_3), 4.76 (s; 2 H, CH_2), 8.67 (d, $^5J_{3,6}$ = 1.3 Hz; 6-H), 8.78 (d; 3-H).

4) Correct elemental analyses. **4a**: UV(ethanol): λ_{max} (lg ε) = 211 nm (4.09), 240 sh (3.62), 306 (3.70); ^{1}H NMR (360 MHz, $CDCl_3$) δ = 3.21 - 3.45 (AA'BB' m; 8 H, CH_2), 7.81 (s; 4 H, ArH); MS: *m/z* (%) = 213 (9, M^+ + 1), 212 (100, M^+). **4b**: UV(ethanol): λ_{max} (lg ε) = 212 nm (4.21), 282 (4.01), 320 sh (3.13); ^{1}H NMR (360 MHz, $CDCl_3$) δ = 3.32 - 3.45 (AA'BB' m; 8 H, CH_2), 7.73 (s; 4 H, ArH); MS: *m/z* (%) = 213 (9, M^+ + 1), 212 (100, M^+).

5) Correct elemental analysis; ^{1}H NMR (360 MHz, $CDCl_3$) δ = 2.57 (s; 6 H, CH_3), 4.78 (s; 4 H, CH_2), 8.41 (s; 2 H, 6-H), 8.62 (s; 2 H, 3-H); MS: *m/z* (%) = 230 (8, M^+).

6) Correct elemental analysis; ^{1}H NMR (360 MHz, $CDCl_3$) δ = 2.59 (s; 6 H, CH_3), 7.73 (s; 2 H, =CH), 8.46 (s; 2 H, 6-H), 8.55 (s; 2-H, 3-H); MS: *m/z* (%) = 212 (92, M^+).

7) 2,5-Dimethylpyrazine, UV(ethanol): λ_{max} (lg ε) = 203 nm (3.96), 277 (3.83), 300 sh (3.12).

8) A. K. Wisor and L. Czuchajowski, *J. Phys. Chem.* **90**, 1541 (1986).

9) Full details of the crystal structure investigation including the tables of atomic coordinates and of thermal parameters may be obtained from the Cambridge crystallographic Data Centre by quoting the name of the authors and the journal citation.

10) P. J. Wheatley, *Acta Crystallogr.* **10**, 182 (1957).

11) H. Hope, J. Bernstein, and K. N. Trueblood, *Acta Crystallogr. Sect B*, **28**, 1733 (1972).

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