On the Reaction of Phosphorus Oxychloride with Pyrazinecarboxamide 4-Oxide

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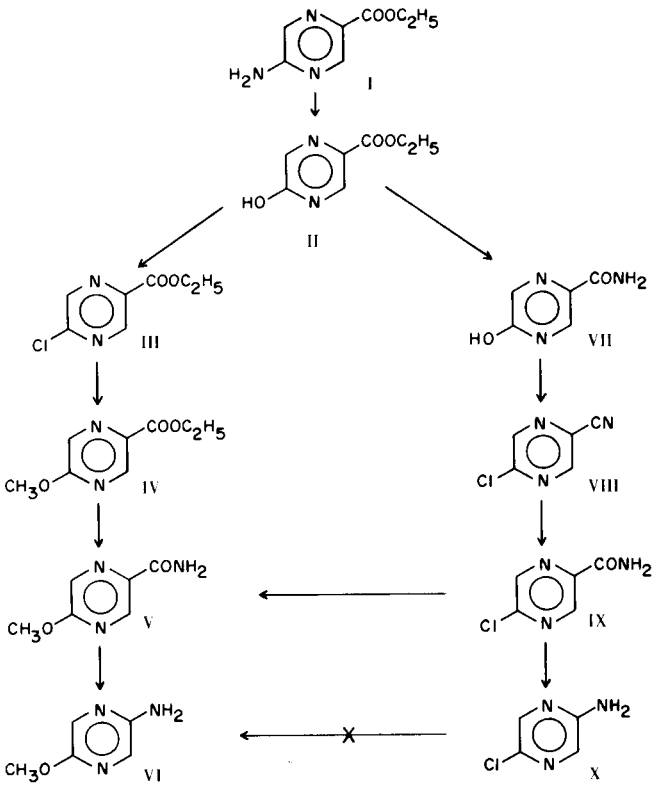
In a preceding paper (1) we reported that the reaction of phosphorus oxychloride with pyrazinecarboxamide 4-oxide essentially gives 2-cyano-6-chloropyrazine. The structure of the compound was established by transforming it into the corresponding 2-amino-6-methoxypyrazine (2), which resulted different from the known 2-amino-3-methoxy- and 2-amino-5-methoxypyrazine, previously described by us (2). On the contrary, in a recent paper (3), Nováček *et al.* claim, on the basis of pmr data (on the interpretation of which some critical comments will be made later) that the action of phosphorus oxychloride on pyrazinecarboxamide 4-oxide, in experimental conditions practically identical to those adopted by us, affords mainly 2-cyano-5-chloropyrazine, as previously stated but not proved by Asai (4). According to the above authors (3), also 2-cyano-6-chloropyrazine was obtained as a secondary product. From the mixture of the two cyanochloropyrazine isomers, Nováček *et al.* prepared the chloroamide derivatives and the methoxyamide derivatives of the main and of the secondary product, whose melting points are reported in Table I.

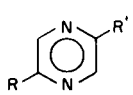
In order to resolve the question, we decided to synthesize unequivocally a series of pyrazines having the 2-5 substitution pattern and to compare their properties with those of the corresponding 2,6-disubstituted derivatives prepared by us (1,2) as well as with those of the supposed 2-5-disubstituted derivatives described by the Czech authors (3). With this in mind, starting from the known 2-carbethoxy-5-aminopyrazine (I) (5), a number of 2,5-disubstituted derivatives of pyrazine was obtained by us, as shown in the scheme. It is to be pointed out that 2-amino-5-chloropyrazine (X) and 2-amino-5-methoxypyrazine (VI), prepared according to the scheme, were identical with the compounds previously obtained by us by a different procedure (2,6).

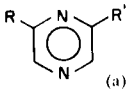
In Table I the melting and boiling points and in Table II the pmr spectral data of the compounds under examination are listed. The data reported in Table I show that the compounds synthesized by Nováček *et al.*, are the 2,6-disubstituted derivatives. As far as the pmr data are concerned, it is to be pointed out that the assignment of the relative positions of the substituents in the paper



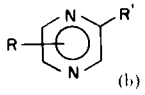
of Nováček *et al.* has been based on the wrong assumption that the interaction between the "para" hydrogen atoms is so weak that the corresponding signals appear as singlets, *i.e.* $J_{2,5}$ (or J para)≅0 Hz. Actually, it is known (7) that in the pyrazine ring the $J_{2,5}$ value is in the range 1.1-1.8 Hz, whereas the $J_{2,6}$ value is in the range 0-0.5 Hz. In fact, compounds V-X show well resolved doublets with J values in the range 1.1-1.5 Hz (Table II), corresponding to 2,5-disubstitution, whereas the J values of compounds XI-XV are about zero, indicating a 2,6-disubstitution. Thus, it is definitely established that reacting phosphorus oxychloride with pyrazinecarboxamide 4-oxide, 2-cyano-6-chloropyrazine is the main product, in agreement with our previsions results, and that also the derivatives prepared by Nováček *et al.* (with J≅0 Hz) are 2,6- and not 2,5-disubstituted pyrazines.

TABLE I





(a)



(b)

R	R	Compound	Melting Point	Compound	Melting or Boiling Point	Compound	Melting or Boiling Point
Cl	CN	VIII	47°	XIII	B.P. 59-61° (1 mm Hg)	XVI	B.P. 58-60° (1 mm Hg)
Cl	$CONH_2$	IX	205°	XIV	M.P. 175°	XVII	M.P. 174° (main compound)
CH_3O	$CONH_2$	V	235°				M.P. 215° (main compound)
				XI	M.P. 220°	XVIII	M.P. 235° (minor compound)

(a) Compounds prepared according to references 1 and 2. (b) Data from reference 3.

EXPERIMENTAL

Melting and boiling points are uncorrected. The pmr spectra were obtained in the solvents indicated, with TMS as internal reference, using a Varian A-60A (60 MHz) spectrometer. Chemical shifts are reported as δ values (ppm).

2-Carbethoxy-5-hydroxypyrazine (II).

To 30 ml. of concentrated sulfuric acid, 4.14 g. (0.06 mole) of sodium nitrite was added in small portions, with stirring and cooling with ice; the suspension was then heated at 50° to complete solution. A solution obtained by grinding in a mortar (at 0°) 7.5 g. (0.045 mole) of 2-carbethoxy-5-aminopyrazine (5) (I) in 45 ml. of concentrated sulfuric acid was added drop by drop, with stirring and cooling with ice. The solution was allowed to stand at room temperature and was then heated at 45° for 6-7 minutes. After cooling, the solution was poured in 300 ml. of crushed ice; the larger amount of acid was neutralized (at 0°) with 20% aqueous sodium hydroxide and the solution, still acid, was extracted several times with ethyl acetate. Evaporation of the solvent gave a solid of orange colour, which, after washing with a small amount of ethyl ether, gave 6 g. (80%) of II, m.p. 178°.

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.00; H, 4.79; N, 16.65. Found: C, 50.21; H, 4.86; N, 16.58.

2-Carbethoxy-5-chloropyrazine (III).

A mixture of 3 g. (0.018 mole) of 2-carbethoxy-5-hydroxypyrazine (II) and 30 ml. of phosphorus oxychloride was heated at 120° for 1.5 hours. After cooling, the mixture was poured into 150 g. of crushed ice and neutralized with a saturated solution of sodium carbonate. After extraction with ethyl ether, the organic layer was dried over anhydrous sodium sulfate and concentrated to give 2.7 g. (88%) of oily III.

Anal. Calcd. for $C_7H_7ClN_2O_2$: C, 45.00; H, 3.78; N, 15.01; Cl, 19.00. Found: C, 45.15; H, 3.83; N, 19.12; Cl, 14.83.

2-Carbethoxy-5-methoxypyrazine (IV).

To a solution of 2.7 g. (0.0145 mole) of 2-carbethoxy-5-chloropyrazine (III) in 25 ml. of anhydrous methanol a solution containing 0.516 g. (0.022 mole) of sodium in 12 ml. of anhydrous methanol was added. Initial separation of solid matter was observed. After boiling for 20 minutes, the solvent was evaporated and the solid residue was extracted with ethyl ether. Evaporation of the solvent gave 1 g. (40%) of IV, m.p. 85-87°.

Anal. Calcd. for $C_8H_{10}N_2O_3$: C, 52.79; H, 5.53; N, 15.48. Found: C, 53.05; H, 5.71; N, 15.22.

2-Carboxamido-5-methoxypyrazine (V).

(a) 2-Carbethoxy-5-methoxypyrazine (IV) (1 g., 0.0055 mole) was introduced into a 100 ml. steel bomb, containing 50 ml. of ethanol saturated with ammonia at -5°. The sample was allowed to stand overnight at room temperature; then the solution was evaporated under reduced pressure. The solid residue was washed with a small quantity of ethyl ether and 0.85 g. (100%) of V was obtained; m.p. 232-233°. After recrystallization from ethanol the m.p. was 234°.

Anal. Calcd. for $C_6H_7N_3O_2$: C, 47.05; H, 4.60; N, 27.43. Found: C, 47.18; H, 4.62; N, 27.27.

(b) To a solution of 0.87 g. (0.0055 mole) of 2-carboxamido-5-chloropyrazine (IX) in 30 ml. of anhydrous methanol, a solution of 0.3 g. (0.013 mole) of sodium in 2 ml. of anhydrous methanol was added. After boiling for 2 hours and evaporation of the solvent under reduced pressure, the residue was taken up with a small quantity of water, neutralized with 1 *N* hydrochloric acid, filtered and washed to neutrality; 0.8 g. (94%) of V was obtained, m.p. 232-233°.

Anal. Calcd. for $C_6H_7N_3O_2$: C, 47.05; H, 4.60; N, 27.43. Found: C, 47.25; H, 4.70; N, 27.35.

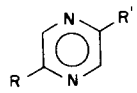
2-Carboxamido-5-hydroxypyrazine (VII).

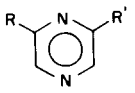
A sample of 3 g. (0.018 mole) of 2-carbethoxy-5-hydroxypyrazine (II) was introduced into a 100 ml. steel bomb containing 50 ml. of concentrated ammonium hydroxide, and heated at 100° for 3.5 hours. By evaporating the solvent under reduced pressure, 2.48 g. (100%) of VII was obtained as a pale yellow solid residue, m.p. 290-295° dec. After recrystallization from ethanol the m.p. was 295° dec.

Anal. Calcd. for $C_5H_5N_3O_2$: C, 43.23; H, 3.63; N, 30.24. Found: C, 43.41; H, 3.81; N, 30.33.

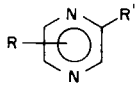
TABLE II

PMR Data (δ values: ppm; J values: Hz)





(a)



(b)

R	R	Compound	Solvent	δ aromatic protons	Δδ (J)	Compound	Solvent	δ aromatic protons	Δδ (J)	Compound	Solvent	δ aromatic protons	Δδ (J)
OCH_3	$CONH_2$	V	DMSO-d_6	8.71 8.21	0.50 (1.1)	XI	DMSO-d_6	8.73 8.48	0.25 (-)	XVIII (main compound)	DMSO-d_6	8.92 8.69	0.23 (-)
OCH_3	NH_2	VI	$CDCl_3$	7.67 7.45	0.22 (1.5)	XII	$CDCl_3$	7.49 7.44	0.05 (-)				
Cl	CN	VIII	DMSO-d_6	9.13 9.02	0.11 (1.4)	XIII	CCl_4	8.99 8.95	0.04 (-)				
Cl	$CONH_2$	IX	DMSO-d_6	8.99 8.84	0.15 (1.1)	XIV	DMSO-d_6	9.17 9.02	0.15 (-)	XVII	DMSO-d_6	9.31 9.16	0.15 (-)
Cl	NH_2	X	$CDCl_3$	7.91 7.66	0.25 (1.5)	XV	$CDCl_3$	7.80 7.76	0.04 (-)				

(a) Compounds prepared according to references 1 and 2. (b) Data from reference 3. The differences between the chemical shift values of compounds XI and XIV and those of compounds XVIII and XVII are due to the different referencing; however, the Δδ values are practically identical.

2-Cyano-5-chloropyrazine (VIII).

2-Carboxamido-5-hydroxypyrazine (VIII) (2.3 g., 0.0165 mole) was introduced into a 50 ml. round bottom flask equipped with a reflux condenser and a calcium chloride tube, together with 15 ml. of phosphorus oxychloride. The suspension was heated at 100° for 2 hours (after a few minutes the suspension became dark), cooled and poured in 100 g. of crushed ice. After 30 minutes, the suspension was extracted with ethyl ether and the organic layer, dried over anhydrous sodium sulfate and concentrated, gave a solid residue (1.7 g.), which, by sublimation, gave 1.65 g. (72%) of VIII as a white solid; m.p. 46-47°.

Anal. Calcd. for $C_5H_2ClN_3$: C, 43.03; H, 1.45; Cl, 25.40. Found: C, 43.12; H, 1.51; Cl, 25.50.

2-Carboxamido-5-chloropyrazine (IX).

A solution of 1.65 g. (0.012 mole) of 2-cyano-5-chloropyrazine (VIII) in 4 ml. of concentrated sulfuric acid was heated at 45° for one hour. Then the solution was poured in ice, neutralized with a saturated solution of sodium carbonate, and extracted with chloroform. The organic layer, dried over anhydrous sodium sulfate, and concentrated under reduced pressure, gave 1 g. (53%) of IX, m.p. 203-204°. After recrystallization from ethanol the m.p. did not change.

Anal. Calcd. for $C_5H_4ClN_3O$: C, 38.11; H, 2.55; Cl, 22.50. Found: C, 38.40; H, 2.71; Cl, 22.63.

2-Amino-5-chloropyrazine (X).

To a solution of potassium hypobromite, prepared at 0° by adding 1.6 ml. (0.031 mole) of bromine to 8.55 g. (0.152 mole) of potassium hydroxide in 80 ml. of water, 4 g. (0.025 mole) of 2-carboxamido-5-chloropyrazine (IX) was added. The mixture was heated at 80° for two hours, concentrated at a small volume under reduced pressure, acidified with 6 *N* hydrochloric acid, basified with 2 *N* sodium hydroxide after fifteen minutes, and finally extracted with chloroform. By evaporation of the chloroform 2.7 g. (83%) of X was obtained, m.p. 125°. After recrystallization from ethanol the m.p. is 130°.

Anal. Calcd. for $C_4H_4ClN_3$: C, 37.15; H 3.11. Found: C, 37.08; H, 3.23.

2-Amino-5-methoxypyrazine (VI).

The compound was prepared starting from 2.5 g. (0.016 mole) of 2-carboxamido-5-methoxypyrazine (V) with the procedure described for compound X. Compound VI (1.6 g., 78%) was obtained, m.p. 108-109°. After recrystallization from cyclohexane the m.p. is 111°.

Anal. Calcd. for $C_5H_7N_3O$: C, 48.08; H, 5.58. Found: C, 47.99; H, 5.63.

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