THE 5-SUBSTITUTED DERIVATIVES OF 2-PYRAZINECARBOXAMIDE

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Various procedures for the preparation of 5-chloro-2-pyrazinecarboxamide (*III*) have been studied particularly with the use of pyrazinecarboxamide as the starting compound.

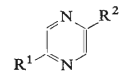
During our investigations on tuberculostatic properties of 5-alkoxy-2-pyrazinecarboxamides[1], we have been particularly interested in the preparation of 5-halo-substituted amides of pyrazinecarboxylic acids. A special attention has been paid to the synthesis of 5-chloro-2-pyrazinecarboxamide (*III*) because of some discrepancies in the literature. The amide *III* was obtained by Assai[2] along with a small amount of 6-chloro-2-pyrazinecarboxamide. On the other hand, the latter 6-chloro isomer was claimed by Bernardi and coworkers[3] as the sole product of the same reaction. In our hands, however, the principal product was represented by the compound *III*. In the present paper, we wish to report additional procedures for the preparation of 5-chloro-2-pyrazinecarboxamide (*III*) and some related reactions.

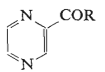
Treatment of pyrazinecarboxamide (*I*) with hydrogen peroxide[2] gave a mixture of the 1- and 4-oxide. We have now shown by means of paper chromatography that the 4-oxide highly predominated. An authentic specimen of 2-pyrazinecarboxylic acid 1-oxide was obtained by oxidation of 2-methylpyrazine 1-oxide (prepared in turn according to Gumprecht and coworkers[4]). Infrared spectra of the 4-oxide *XI* and of the isomeric mixture (enriched by the 1-oxide by extraction of the crude pyrazinecarboxamide N-oxide with butanol) were compared with those (in nujol) of picolinic amide N-oxide, ν(CO) at 1680 cm^{-1}, and nicotinic amide N-oxide, ν(CO) at 1890 cm^{-1}. It may be seen that the ν(CO) value is lower when the CO group is in the neighbourhood of the polar N→O group. This observation is in accordance with the reported data of 2- and 3-acetylpyridine 1-oxides, ν(CO) 1691 cm^{-1} and 1707 cm^{-1}, resp. [5] The ν(CO) value of the 4-oxide *XI* is 1684 cm^{-1} while that of the 1-oxide is lower 1670 cm^{-1}. The 4-oxide *XI* was also prepared (along with the amide *I* as the principal product) from 2-cyanopyrazine by the action of hydrogen peroxide in an alkaline medium.

The 4-oxide *XI* was treated with phosphorus oxychloride and the resulting 5-chloro-2-cyanopyrazine (*II*) hydrolysed to the amide *III* either with 37% hydrochloric acid[2] or with hydrogen peroxide in an alkaline medium. An additional compound, namely, the isomeric 6-chloro-2-pyrazinecarboxamide was isolated from the reaction mixture resulting after hydrolysis with hydrochloric acid. The direct conversion of the amide *I* into the nitrile *II* was effected by the action of phosphorus oxychloride and then bromine[6]; replacement of bromine by chlorine did not lead to the required nitrile *II*. An exclusive formation of the amide *III* was effected by a procedure analogous to the reported[7] synthesis of 6-hydroxy-2-pyrazinecarboxamide. The methyl ester *XII* was acetoxylated with acetic anhydride and the product hydrolysed to give methyl 5-hydroxy-2-pyrazinecarboxylate (*IV*). By the action of phosphorus oxychloride, compound *IV* was converted into the 5-chloro derivatives *V*, the ammonolysis of which led to the amide *III*. Compound *V* was obtained also by chlorination of the methyl ester *XII* with phosphorus oxychloride. Another preparation of the amide *III* started from 2-pyrazinecarboxylic acid 4-oxide (*XIV*). Compound *XIV* was treated with thionyl chloride and the resulting chloride of 5-chloro-2-pyrazinecarboxylic acid (*VI*) subjected to ammonolysis under the formation of the amide *III*. Hydrolysis of the chloride *VI* gave the acid *VII*.

5-Bromo-2-pyrazinecarboxamide (*IX*) was synthesized from the ethyl ester *XIII* analogously to the preparation of the chloro derivative *III*. The attempted preparation of 5-iodo-2-pyrazinecarboxamide from the amide *III* by the action of sodium iodide or hydriodic acid failed. The treatment with hydriodic acid was accompanied by reduction of the pyrazine nucleus under the formation of 5-chloro-2-piperazinecarboxamide. The amide *III*, prepared by various methods, was heated with sodium methoxide to afford 5-methoxy-2-pyrazinecarboxamide (*X*). The isomeric 3- and 6-methoxy-2-pyrazinecarboxamide were prepared from the corresponding chloro derivatives.

Position of the halo atom and the methoxy group in the pyrazinecarboxamide derivatives *III* and *X* was established by means of NMR spectra. In both cases, the signals of heteroaromatic protons are singlets (*III*, δ = 9·31, 9·16 p.p.m.; *X*, δ = 8·92,





I, R^1 = H, R^2 = $CONH_2$ *VI*, R^1 = Cl, R^2 = COCl *XI*, R = NH_2
II, R^1 = Cl, R^2 = CN *VII*, R^1 = Cl, R^2 = COOH *XII*, R = OCH_3
III, R^1 = Cl, R^2 = $CONH_2$ *VIII*, R^1 = Br, R^2 = $COOC_2H_5$ *XIII*, R = OC_2H_5
IV, R^1 = OH, R^2 = $COOCH_3$ *IX*, R^1 = Br, R^2 = $CONH_2$ *XIV*, R = OH
V, R^1 = Cl, R^2 = $COOCH_3$ *X*, R^1 = OCH_3, R^2 = $CONH_2$

8·69 p.p.m.), the line width at half-height being equal to 1 Hz. It may be seen that the interaction between both protons is very weak. Consequently, these hydrogen atoms are in *para* position to each other.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block) and are corrected. Analytical samples were dried over phosphorus pentoxide *in vacuo* for 24 hours. Infrared spectra were measured on a UR-10 (Zeiss Jena) spectrometer in nujol or in KBr pellets. Liquids were measured in the form of a film. NMR spectra were taken on a Tesla BS 487 B (80 MHz) spectrometer (hexadeuteriodimethyl sulfoxide as solvent; hexamethyldisiloxane as external standard; the chemical shifts were not recalculated in respect to tetramethylsilane).

Pyrazinecarboxamide N-Oxides

A. The N-oxides were prepared according to Kushner and coworkers[8] in a 50% yield, m.p. of the crude material 303—305°C (decomposition). The crude N-oxides were extracted with two 70 ml portions of butanol. The remaining solid was recrystallised from boiling water to afford the 4-oxide *XI*, m.p. 309—311°C (decomposition). Infrared spectrum: ν_{max} (nujol) 767, 960, 1 010, 1 086, 1 272, 1 312, 1 390, 1 597, 1 684 cm^{-1}. The butanolic extract was cooled down to afford a mixture of pyrazinecarboxamide 1- and 4-oxide, m.p. 297—303°C (decomposition). Infrared spectrum: ν_{max} (nujol) 767, 960, 1 010, 1 086, 1 110, 1 272, 1 312, 1 390, 1 597, 1 670, 1 684 cm^{-1}. The pure 4-oxide *XI* and the mixture of the 1- and 4-oxide were converted to the free acids with aqueous sodium hydroxide and the subsequent acidification with hydrochloric acid. The chromatography was performed on paper Whatman No 2 in butanol–formic acid–water (75 : 15 : 10). The spots were detected with ferrous sulfate (the 4-oxide *XI*, R_F 0·44) and bromophenol blue (the 1-oxide, R_F 0·54).

B. A mixture of 2-cyanopyrazine (8·5 g), water (125 ml), and 30% hydrogen peroxide (18 ml) was adjusted with 2M-NaOH to pH 9 and then heated for 3 hours at 70°C, the pH being maintained at 9. The reaction mixture was then cooled down to 43°C to deposit 1·3 g of the 4-oxide *XI*, m.p. 304—307°C (decomposition). Concentration of mother liquours afforded 4·1 g of the amide *I*, m.p. 192—193°C (R_F value 0·64 in the above solvent mixture).

5-Chloro-2-cyanopyrazine (*II*)

A. The title compound *II* was prepared in a 72% yield from the 4-oxide *XI* and phosphorus oxychloride according to Asai[2]. A sample of the crude *II* was purified by conversion to the amide *III* by hydrolysis with hydrochloric acid and the subsequent recovery of the nitrile *II* by dehydration with phosphorus oxychloride. Infrared spectrum (film): 891 (CH), 2 242 (CN) cm^{-1}.

B. A suspension of the amide *I* (60 g) and phosphorus oxychloride (240 g) was heated gradually to 90—95°C and then treated dropwise over 150 minutes with bromine (90 ml). After additional 20 minutes, the excess bromine and phosphorus oxychloride were distilled off at 130°C. The distillation residue was treated with ice and extracted with ether. Work-up of the extract afforded 13·5 g (50%) of the nitrile *II*, b.p. 58—60°C at 1 Torr.

Methyl 5-Hydroxy-2-pyrazinecarboxylate (*IV*)

A mixture of the methyl ester *XII* (31 g) and acetic anhydride (413 ml) was heated at 160°C for 30 hours and then evaporated under reduced pressure. The residue was treated with water (310 ml) and extracted with benzene. Evaporation of the extract afforded 28 g (90%) of methyl acetoxypyrazinecarboxylate which was heated with water (280 ml) until a solution was obtained.

The solution was filtered with active charcoal and the filtrate cooled (15°C) to deposit 7·3 g (26%) of the ester *IV*, m.p. 202—204°C. For $C_6H_6N_2O_3$ (154·1) calculated: 46·75% C, 3·92% H, 18·18% N; found: 46·49% C, 3·85% H, 18·25% N.

Methyl 5-Chloro-2-pyrazinecarboxylate (*V*)

A. A mixture of the methyl ester *XII* (5 g) and phosphorus oxychloride (40 ml) was refluxed for 3 hours, poured onto ice, and extracted with ether. The extract was evaporated and the residue distilled at 76—78°C/1 Torr to afford 3·3 g (59%) of the methyl ester *V*, m.p. 38—40°C (aqueous ethanol). For $C_6H_5ClN_2O_2$ (172·6) calculated: 41·77% C, 2·92% H, 16·23% N; found: 41·69% C, 2·97% H, 16·24% N.

B. A mixture of the methyl ester *IV* (5·2 g) and phosphorus oxychloride (53 ml) was heated at 120°C for 90 minutes, poured into ice, neutralised with sodium hydrogen carbonate, and extracted with ether. Distillation at 76—78°C/1 Torr afforded 3·2 g (58%) of the methyl ester *V*, m.p. 41—43°C.

5-Chloro-2-pyrazinecarboxamide (*III*)

A. Saponification of the nitrile *II* with 37% hydrochloric acid according to Asai[2] afforded a 65% yield of the amide *III*, m.p. 173·5—174°C (aqueous ethanol). The mother liquors (60 ml) were diluted with water (120 ml) and neutralised with sodium hydrogen carbonate to afford 2% of the isomeric 6-chloro-2-pyrazinecarboxamide, m.p. 175·5—177°C (aqueous ethanol).

B. A solution of 30% hydrogen peroxide (9 ml) in water (60 ml) was adjusted with 2M-NaOH to pH 9 and treated dropwise under stirring with the nitrile *II* (4·5 g). The emulsion was heated under stirring for 150 minutes at 55°C, cooled down, and the precipitate washed with water. Yield, 4 g (74%) of the amide *III*, m.p. 172—172·5° (aqueous ethanol). For $C_5H_4ClN_3O$ (157·5) calculated: 38·14% C, 2·55% H, 26·68% N; found: 38·22% C, 2·65% H, 26·79% N. Infrared spectrum (nujol): 1571, 1721 (CO), 3175, 3340 (NH) cm^{-1}. Ultraviolet spectrum (in ethanol): λ_{max} 224, 283 nm (ε 9000).

C. Gaseous ammonia was introduced over one hour onto a solution of the ester *V* (1·2 g) in ethanol (12 ml). Yield, 1·2 g (92%) of the amide *III*, m.p. 172—173°C (aqueous ethanol).

D. A mixture of the 4-oxide *XIV* (5 g) and thionyl chloride (20 ml) was refluxed until the solid dissolved (5½ hours). The thionyl chloride was distilled off and the residue poured into 27% aqueous ammonia (50 ml). Yield, 2·7 g (56%) of the amide *III*, m.p. 172—173·5°C (water and active charcoal).

5-Chloro-2-pyrazinecarboxylic Acid (*VII*)

A mixture of the 4-oxide *XIV* (5 g) and thionyl chloride (20 ml) was refluxed until the solid dissolved and then evaporated. The residue was treated with water and ice and the resulting precipitate collected with suction. After drying over phosphorus pentoxide, the precipitate was extracted with acetone. Yield, 2·5 g (45%) of the acid *VII*, m.p. 162·5—165°C (water). For $C_5H_3ClN_2O_2$ (158·5) calculated: 37·89% C, 1·90% H, 17·67% N; found: 37·60% C, 2·12% H, 17·63% N.

Ethyl 2-Pyrazinecarboxylate 4-Oxide (*XIII*)

A mixture of the 4-oxide *XIV* (15 g), ethanol (150 ml), and thionyl chloride (35 ml) was refluxed until the acid dissolved (3 hours) and the mixture evaporated to a small volume. Yield, 11 g (63%)

of compound *XIII*, m.p. 146—148°C (aqueous ethanol and active charcoal). For $C_7H_8N_2O_3$ (168·1) calculated: 50·01% C, 4·79% H, 16·65% N; found: 49·97% C, 4·97% H, 16·90% N.

Methyl 2-pyrazinecarboxylate 4-oxide (*XII*). This compound was obtained analogously. M.p. 168—170°C (reported[9], m.p. 172—173°C).

Ethyl 5-Bromo-2-pyrazinecarboxylate (*VIII*)

A mixture of compound *XIII* (3·4 g) and phosphorus oxybromide (15 g) was heated at 110°C for 15 minutes, poured onto ice, neutralised with sodium hydrogen carbonate, and extracted with ether. Yield, 1·9 g (42%) of the ester *VIII*, b.p. 69—73°C at 0·8 Torr. For $C_7H_7BrN_2O_2$ (231·0) calculated: 12·13% N; found: 11·93% N.

5-Bromo-2-pyrazinecarboxamide (*IX*)

A mixture of the ethyl ester *VIII* (1·3 g), ethanol (5 ml), and 27% aqueous ammonia (5 ml) was kept at room temperature for 3 hours to afford 0·7 g (64%) of the amide *IX*, m.p. 168·5—169·5°C (aqueous ethanol). For $C_5H_4BrN_3O$ (202·0) calculated: 29·73% C, 1·99% H, 20·80% N; found: 29·83% C, 2·03% H, 20·70% N. Infrared spectrum (nujol): 1594, 1695 (CO), 3435, 3445 (NH) cm^{-1}.

5-Chloro-2-piperazinecarboxamide Dihydro Iodide

A mixture of the amide *III* (2 g), hydroiodic acid (12 ml), and red phosphorus (0·5 g) was heated at 130°C for 90 minutes and concentrated. The solid was collected with suction and recrystallised from aqueous ethanol (active charcoal) to afford 1·4 g (36%) of the title dihydro iodide. For $C_5H_{12}ClI_2N_3O$ (419·4) calculated: 14·31% C, 2·86% H, 10·01% N; found: 14·59% C, 2·64% H, 9·98% N. Ultraviolet spectrum (ethanol): λ_{max} 224 nm (ε 40500).

5-Methoxy- and 6-Methoxy-2-pyrazinecarboxamide

Methanolic sodium methoxide (prepared from 0·035 gramatom of sodium and 30 ml of methanol) was treated with 0·01 mol of 5-chloro- or 6-chloro-2-pyrazinecarboxamide, the whole mixture refluxed for one hour, and the methanol evaporated. The residue was dissolved in water (25 ml) and the pH adjusted to 9. The recrystallisation was performed from aqueous ethanol.

5-Methoxy-2-pyrazinecarboxamide (X). M.p. 214—215°C; yield, 77%. For $C_6H_7N_3O_2$ (153·2) calculated: 47·03% C, 4·60% H, 27·43% N; found: 46·99% C, 4·62% H, 27·78% N. Infrared spectrum (KBr pellet): 1586, 1692 (CO), 3415 (NH) cm^{-1}. *6-Methoxy-2-pyrazinecarboxamide.* M.p. 235—235·5°C; yield, 59%. For $C_6H_7N_3O_2$ (153·2) calculated: 47·03% C, 4·60% H, 27·43% N; found: 47·14% C, 4·93% H, 27·41% N. Infrared spectrum (KBr pellet): 1596, 1676 (CO), 3438 (NH) cm^{-1}.

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