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Studies on Pyrazine Derivatives. I. Synthesis of Pyrazinoylmorpholine and Related Compounds[1]

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For the evaluation of biological activities, 4-pyrazinoylmorpholine (II) and many new compounds have been synthesized from the N-oxide of II. The reactions of 2-(4-morpholinocarbonyl)pyrazine 4-oxide (IV) with halogenation reagents were examined, and the main product was proved to be 6-chloro-2-(4-morpholinocarbonyl)pyrazine (VII) by correlating the product to the known 2-amino-6-chloropyrazine (XIV).

In 1965, it was first reported that 3,5-dimethylpyrazole is fifty-four times more potent orally as a hypoglycemic agent than tolbutamide in glucose-injected, fasted intact rats.[3] Since then, numerous papers concerning its ability to depress the level of blood sugar and also plasma free fatty acids have appeared. Subsequent studies on the metabolism of 3,5-dimethylpyrazole revealed that the active metabolite was 5-methylpyrazole-3-carboxylic acid.[4,5] In order to find orally active hypoglycemic substances having a different mode of action from those of sulfonylureas and biguanides, the authors have synthesized a number of compounds related to pyrazinamide derivatives.

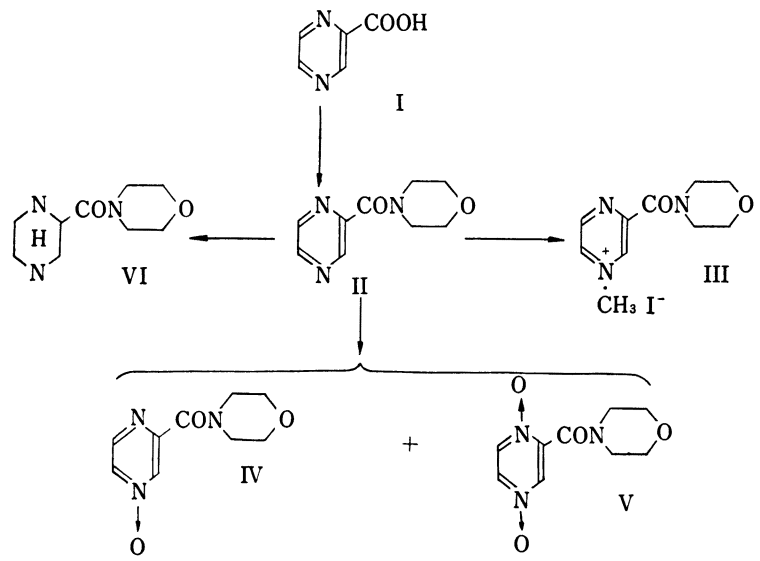

Chart 1

1) A part of this work was presented at The 2nd Symposium on Heterocyclic Chemistry (Japan), Nagasaki, November, 1969.
2) Location: *Minamifunaboricho, Edogawa-ku, Tokyo.*
3) G.C. Gerritsen and W.E. Dulin, *Diabetes*, **14**, 507 (1965).
4) D.L. Smith, A.A. Forist, and W.E. Dulin, *J. Med. Chem.*, **8**, 350 (1965).
5) G.C. Gerritsen and W.E. Dulin, *J. Pharmacol. Exp. Therap.*, **150**, 491 (1965).

4-Pyrazinoylmorpholine (II) was obtained from pyrazinoic acid by several methods as a model compound. Its methiodide, N-oxides, and hydrogenated piperazinocarbonylmorpholine (VI) were further synthesized from II as shown in Chart 1. In N-oxidation of II, besides the main product (IV) small amount of di-N-oxide (V), the structure of which was confirmed by means of ultraviolet and infrared spectrometry and the analytical values, was obtained. The N-O function in IV was expected to be at the position 4 which was precisely determined by alternative synthesis of IX. The details of structure-proof of IV will be reported in the forthcoming article.

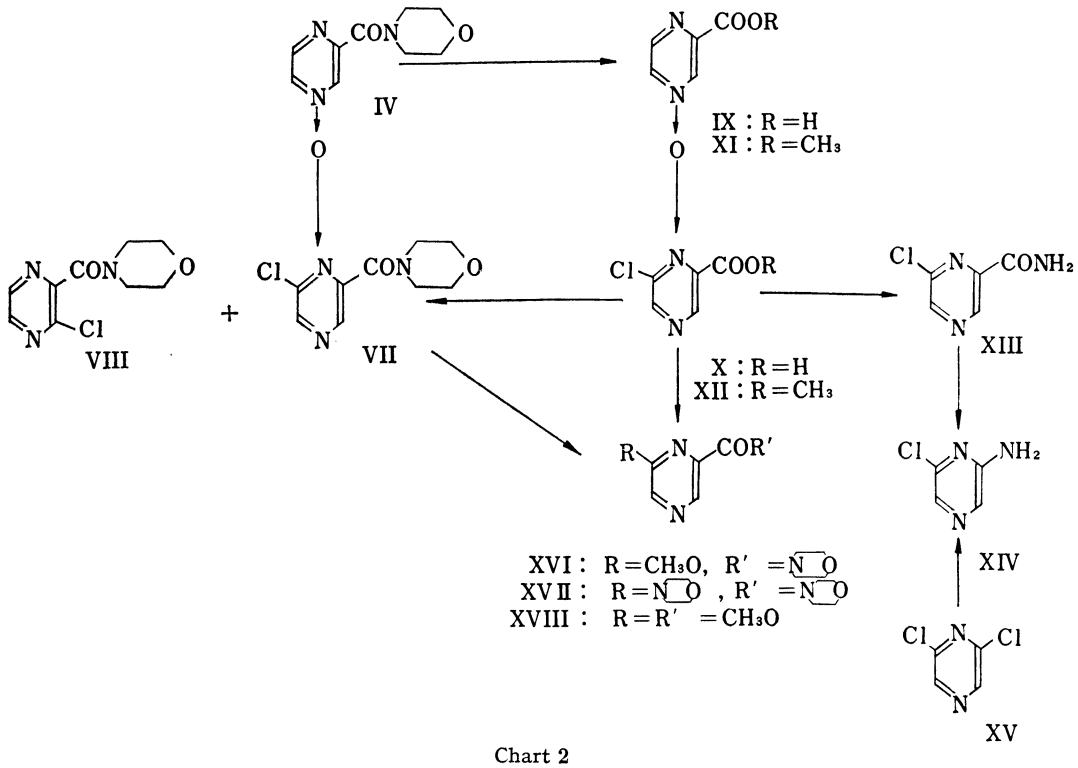

Chart 2

Treatment of IV with phosphoryl chloride or thionyl chloride gave a mono-chloro compound as the main product (VII) along with small amount of a by-product (VIII). Reaction of pyrazinoic acid 4-oxide (IX) with phosphoryl chloride, followed by morpholine amide formation gave the chloro compound which was obtained above as the main prodnt (VII). The ester (XII) of the acid (X) was also obtained from ester N-oxide (XI) by reaction with phosphoryl chloride. The position of chloro group in VII, X ,and XII was confirmed by converting XII to the known 2-amino-6-chloropyrazine (XIV).[6-8] The above by-product (VIII)[6-8] was proved to be 3-chloro derivative (VIII) by alternative synthesis, which will be reported in a subsequent paper.

By refluxing with methanolic hydrogen chloride or sulfuric acid for a few minutes, chlorocarboxylic acid (X) afforded the ester (XII) in reasonable yield. In contrast, by longer

6) L. Bernardi, G. Palamidessi, A. Leone, and G. Larini, *Gazz. Chim. Ital.*, **91**, 1431 (1961); *Chem. Abstr.*, **57**, 2223e (1962).
7) D. Pitré, S. Boveri, and E.B. Grabitz, *Chem. Ber.*, **100**, 555 (1967).
8) F.G. McDonald and R.C. Ellingson, *J. Am. Chem. Soc.*, **69**, 1034 (1947).

refluxing a part of XII was further converted to methoxy derivative (XVIII)[9] which was isolated and identified with the authentic sample.

From the amide (VII), the carboxylic acid (X), and the ester (XII), a number of new compounds such as XVI, XVII, and XVIII were derived for the evaluation of their biological activity. Furthermore, the analogous substances (XXa—d) as (XVII) were synthesized from compound (X). Physical data of these new substances are given in Table I.

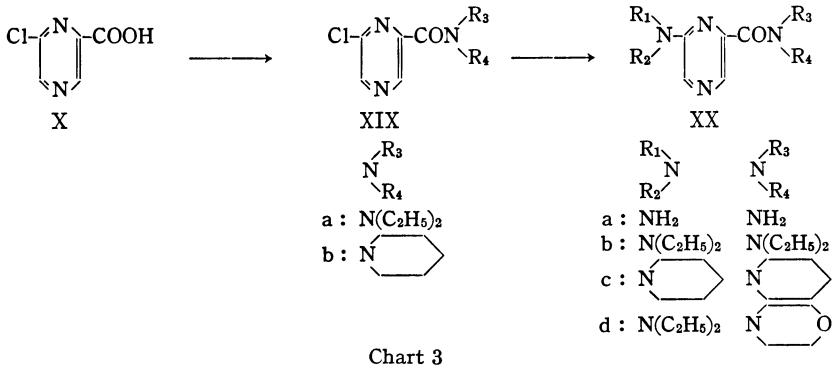

Chart 3

TABLE I. Pyrazinoylmorpholine and Its Derivatives

Compound		mp bp	IR $\nu_{C=O}$	Calculated C	H	N	Found C	H	N
II	bp	126 —129 (0.1 mmHg)	1631	55.95	5.74	21.75	55.70	5.77	21.84
	mp	54 — 55.5							
III		196 —197 (decomp.)	1644 1623	35.83	4.21	12.54	36.01	4.06	12.49
IV		148 —149 (decomp.)	1636	51.68	5.30	20.09	51.50	5.68	20.24
V		210 —213 (decomp.)	1635	47.99	4.92	18.66	48.54	5.18	19.06
VI[a]		258.5—260 (decomp.)	1658	39.66	7.03	15.42	39.56	7.13	15.17
VII		92 — 93	1634	57.48	4.42	18.45 15.57[b]	47.50	4.67	18.92 15.43[b]
VIII		106.5—108	1645	47.48	4.42	18.45 15.57[b]	47.90	4.86	18.68 15.76[b]
X		158 —159	1730	37.81	1.90	17.66 22.36[b]	38.09	2.40	17.70 22.04[b]
XI		166.5—167.5	1722	46.67	3.92	18.18	46.52	3.68	18.18
XII	bp	108 —109 (5 mmHg)	1733	41.76	2.92	16.24	41.84	3.14	15.89
	mp	43.5— 44.5							
XVI		109.5—110	1638	53.80	5.87	18.83	54.30	5.86	18.48
XVII		106 —107.5 (decomp.)	1630	56.10	6.52	20.13	55.80	6.74	20.34
XVIII	bp	112 (6 mmHg)	1722	49.98	4.80	16.63	50.19	4.81	16.67
	mp	74.5— 75.5							
XIXa	bp	125 —127 (3—4 mmHg)	(1640)	50.58	5.66	19.66	50.47	5.96	19.12
XIXb	bp	115 —120 (0.02 mmHg)	(1640)	53.22	5.36	18.62	53.07	5.18	18.34
XXa	mp	203 —204.5	1708	43.48	4.38	40.57	43.62	4.51	40.36
XXb	bp	125 —127 (0.01 mmHg)	(1630)	62.37	8.86	22.38	62.17	8.38	23.15
XXc	bp	165 —170 (0.03 mmHg)	(1635)	65.66	8.08	20.42	65.75	8.00	20.53
XXd	mp	87 — 88.5	1627	59.07	7.63	21.19	58.93	7.41	21.09

a) 2 HCl, *b*) the value for Cl

9) It seems reasonable that this reaction involves nucleophilic attack of pyrazine ring by methanol, as the protonation of ring nitrogen increases the electron-withdrawing power of nitrogen atom like other azaheterocycles. See, for instance, H. Gershon, *J. Org. Chem.*, **27**, 3507 (1962); J.H. Hill and J.G. Kraus, *J. Org. Chem.*, **29**, 1642 (1964); C.K. Banks, *J. Am. Chem. Soc.*, **66**, 1127 (1944).

On the other hand, in the case of 6-chloropicolinic acid no methanolysis occurs by refluxing with methanolic hydrogen chloride. M.P. Cava and N.K. Bhattacharyya, *J. Org. Chem.*, **23**, 1287 (1958).

Hypoglycemic Activity

Normal male rats weighing 150—200 g were employed. The test compounds (5 mg/kg) were dissolved in water or propyleneglycol for intraperitoneal administration; controls received an equal volume of vehicle. Blood samples (0.05 ml×2) obtained from tail veins 1,2,3 and 4 hr after dosing were assayed for blood glucose (% of reducing effect against value before administration) using the Somogyi–Nelson method. Serum NEFA levels were determined according to the Novak method.

Among these compounds 6-substituted pyrazinoic acid derivatives, especially (XVII) and (XVIII), showed the highest activity. Detailed studies of the pharmacology of the substituted pyrazine derivatives will be reported elsewhere.[10]

Experimental[11]

All melting points are uncorrected. Thin-layer chromatography was performed using 20×5 cm precoated silica gel. Ultraviolet spectra were measured with a Hitachi Recording Spectrophotometer EPS-2U, and infrared spectra were taken on Hitachi EPI-2, EPI-S2 and EPI-G2 spectrophotometers. The JEOLCO Model LNM 4H-100 high resolution nuclear magnetic resonance (NMR) spectrometer was used for measurements of NMR spectra, and chemical shifts showed in ppm from TMS as a standard signal. Gas chromatographic works were done with a Hitachi Perkin–Elmer Model 53K.

4-Pyrazinolymorpholine (II)——To a solution of dry morpholine (450 g) in absolute benzene (1.5 liters) was slowly added a solution of pyrazinoyl chloride prepared from pyrazinoic acid (149 g) in benzene (600 ml) with stirring. After the reaction mixture was allowed to stand at room temperature overnight, the precipitate was filtered off and the filtrate was concentrated *in vacuo*. The resulting brown oily residue was dissolved in chloroform (2.5 liters) and the solution was washed with three portions of 2% sodium hydrogen carbonate solufion (each 300 ml) which was saturated with sodium chloride. The liquid obtained from the chloroform layer was distilled under reduced pressure to give 4-pyrazinoylmorpholine as yellow-brown viscous oil (175 g, 75.4%), bp 133—140° (0.02—0.03 mmHg), which crystallized to form prisms, mp 52.5—54°.

For the purpose of further purification, this product was dissolved in water (2 liters), decolorized with active charcoal, and concentrated *in vacuo* to a small volume which was extracted twice with chloroform (each 200 ml), the chloroform layer was dried over anhydrous sodium sulfate. After evaporation of the solvent, petroleum ether was added to the oily residue to afford pyrazinoyl morpholine (II) as colorless fine powder (141.7 g, 60.8%), mp 53.5—55.5°. Recrystallization from ether afforded (II) as colorless prisms, mp 54—55.5°. UV $\lambda_{max}^{H_2O}$ mμ (log ε): 270 (3.90), 301 shoulder (2.99).

4-Methyl-2-(4-morpholinocarbonyl)pyrazinium Iodide (III)——This compound, mp 196—197° (decomp.), was obtained from 4-pyrazinoylmorpholine and methyl iodide.

2-(4-Morpholinocarbonyl)pyrazine 4-Oxide (IV)——A mixture of 4-pyrazinoylmorpholine (9.65 g), glacial acetic acid (41.5 ml) and 30% hydrogen peroxide (11.4 ml) was heated at 60° for 60 hr. To this solution cold water (40 ml) was added, and acetic acid and excess hydrogen peroxide were evaporated under reduced pressure, and this procedure was repeated several times. The residual crude mono-N-oxide contained appreciable amounts of di-N-oxide checked by thin-layer chromatography. This material was dissolved in chloroform and chromatographed over silica gel (150 g). Elution with chloroform–ethanol (9:1) (750 ml) gave the crude pyrazine 4-oxide (IV), mp 138—144° which was recrystallized from methanol to form colorless prisms, mp 148—149° (decomp). IR ν_{max}^{KBr} cm^{-1}: 1323 (ν_{N-O}). UV $\lambda_{max}^{H_2O}$ mμ (log ε): 224 (4.08), 268.5 (4.01). TLC chloroform–ethanol (9:1), *Rf* 0.77.

Further elution with chloroform–ethanol (9:1) afforded 2-(4-morpholinocarbonyl)pyrazine di-N-oxide (V), which was recrystallized from ethanol to give colorless prisms, mp 210—213° (decomp.). Yield, 113 mg. UV $\lambda_{max}^{H_2O}$ mμ (log ε): 232.5 (3.93), 311 (4.15). IR ν_{max}^{KBr} cm^{-1}: 1228 (ν_{N-O}). TLC chloroform–ethanol (9:1), *Rf* 0.23.

4-(2-Piperazinocarbonyl)morpholine (VI) Dihydrochloride——The reaction was carried out using the technique of Felder, *et al.*,[12] for pyrazinamide.

10) These experiments were kindly carried out by Dr. Shigeta of Osaka University. *cf.*, Y. Shigeta and N. Oji, *Tônyobyo*, **13**, 115 (1970).

11) Thanks are due to Mr. T. Nakatsuka for his technical assistance, Messrs. I. Ito and K. Tomita for NMR spectral measurements, Mr. B. Kurihara for Mass spectral measurements, and Mr. K. Shimazaki, Miss K. Takahashi for elemental analyses.

12) E. Felder, S. Maffei, S. Pietra, and D. Pitré, *Chimia*, **13**, 263 (1959); *Chem. Abstr.*, **54**, 7712^g (1960).

A solution of 2-(4-morpholinocarbonyl)pyrazine (II) (1.93 g) in ethanol (25 ml) to which 10% palladium on charcoal (4.5 g) was added, is treated at atmospheric pressure and about 50° with hydrogen. The reaction was stopped when hydrogen (about 900 ml) had been absorbed. After removal of the catalyst by filtration, the filtrate was evaporated to leave a colorless oily residue which was taken up in 30% hydrochloric acid (5 ml). Evaporation of water *in vacuo* and recrystallization of the residue from aqueous ethanol afforded 4-(2-piperazinocarbonyl)morpholine (VI) dihydrochloride (1.53 g, 56%), mp 258.4—260° (decomp.) as colorless fine powder.

6-Chloro-2-(4-morpholinocarbonyl)pyrazine (VII)——Method A: A solution of the N-oxide (IV) (9 g) in thionyl chloride (35 ml) was heated under reflux for 1.25 hr. Excess thionyl chloride was removed *in vacuo*, the residue was poured onto ice and the cold solution was neutralized with 10% potassium carbonate solution. The product was extracted with chloroform, and the extract was dried (Na_2SO_4) and concentrated to dryness *in vacuo*. The residue was taken up in a small volume of methanol and a undissolved starting material (0.5 g) was filtered off. The filtrate was concentrated *in vacuo* and the residue was distilled under reduced pressure to give 6-chloro-2-(4-morpholinocarbonyl)pyrazine (VII) as viscous oil (4 g, 40.4%), bp 120—140° (0.03 mmHg), which crystallized on standing. Gas–liquid chromatography using a 1% XE-60 column at 185° revealed that this crude (VII) is contaminated with small amounts of 2-(4-morpholinocarbonyl) pyrazine (II), 3-chloro-2-(4-morpholinocarbonyl)pyrazine (VIII) and an unknown compound.

Pure 6-chloro-2-(4-morpholinocarbonyl)pyrazine (VII) was obtained after recrystallization from iso propyl alcohol as colorless prisms, mp 92—93°.

Method B: A suspension of 2-(4-morpholinocarbonyl)pyrazine 4-oxide (2.5 g) in phosphoryl chloride (21.5 g) was heated with vigorous stirring and the exothermic reaction occured at about 50°. After 5 min two-thirds of phosphoryl chloride was removed *in vacuo*. The dark residue was poured onto chopped ice with vigorous stirring. After the decomposition of the excess reagent was complete, the solution was neutrallized with 10% potassium carbonate solution and extracted with chloroform. The crude product from chloroform layer was distilled under reduced pressure collecting the fraction, bp 128—134° (0.035 mmHg), 1.92 g (70.5%). This product was proved to contain significant amount of 3-chloro-2-(4-morpholinocarbonyl) pyrazine (VIII) checking by gas–liquid chromatography, which was isolated by silica gel column chromatography and identified with the authentic sample (VIII)[13] by mixed melting point determination and comparison of IR, NMR and UV spectra.

Method C: A suspension of 6-chloro-2-pyrazinoic acid (X) (10.5 g) in thionyl chloride (46 ml) and dry benzene (80 ml) was heated under reflux with vigorous stirring for 2.5 hr. After evaporation of the solvent the residue was dissolved in dry benzene (60 ml). This solution was added dropwise to a solution of dry morpholine (20.4 g) in dry benzene (75 ml) with stirring and the mixture was allowed to stand overnight. The resulting precipitate was filtered off, and the filtrate was evaporated to dryness *in vacuo* to give crude product (11.9 g). A small volume of water was added to this material, and the solid was crushed to powder, filtered and recrystallized from isopropyl alcohol to form colorless needles (6.90 g, 50.5%), mp 93—94°, which was shown to be free from 3-chloro-2-(4-morpholinocarbonyl)pyrazine (VIII) by using TLC (benzene–ethanol 9:1) and GLC (1% XE-60 column, at 180°).

Acid Hydrolysis of 2-(4-Morpholinocarbonyl)pyrazine 4-Oxide (IV) to 2-Pyrazinoic Acid 4-Oxide (IX)——A solution of the N-oxide (IV) (87.5 mg) in 18% hydrochloric acid (4 ml) was heated under reflux for 8 hr. After evaporation of the solvent *in vacuo* the resulting solid was washed with ethanol and collected by filtration. The crude product (20 mg, 34.2%), mp 182—183° (decomp.), was recrystallized from water (active charcoal) to afford 2-pyrazinoic acid 4-oxide (IX), mp 188—188.5° (decomp.) which was identified with an authentic sample (IX)[14] by mixed melting point and comparison of IR spectra.

6-Chloro-2-pyrazinoic Acid (X)——To phosphoryl chloride (18.5 ml) 2-pyrazinoic acid 4-oxide (2.5 g) was added and the suspension was heated gradually with stirring until exothermic reaction, which occurs at about 50°, subsided. The solution was refluxed for further 15 min and two-thirds of phosphoryl chloride was removed *in vacuo*. The dark residue was cooled and poured cautiously on chopped ice with vigorous stirring and the solution was allowed to stand at room temperature overnight. The product was extracted with chloroform, and the extract was washed with a small portion of water and dried over sodium sulfate. Evaporation of the solvent and recrystallization of the residue (1.5 g, 48%) from water afforded a pure sample, mp 154—155°.

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13) The synthesis of VIII will be mentioned in a subsequent paper. mp 106.5—108°. UV λ_{max}^{MeOH} mμ (log ε): 278 (3.83). NMR δ ppm ($CDCl_3$): 8.52, 8.44 (2H, AB quartet, J=2.7 Hz).

14) The authentic sample (IX) prepared by an unambiguous route had mp 188—188.5° (decomp.), which will be reported in the following paper. H. Foks and J. Sawlewicz [*Acta Polon. Pharm.*, **21**, 429 (1964); *Chem. Abstr.*, **62**, 7754^f (1965)] reported that the mp of 2-pyrazinoic acid 4-oxide (IX) which was prepared from 2-pyrazinecarboxamide 4-oxide is 212—213°. However, the authors obtained 2-pyrazinoic acid 4-oxide (IX), mp 188—188.5° (decomp.), according to a similar reaction described by Foks and Sawlewicz.

2-Carbomethoxypyrazine 4-Oxide (XI)——A suspension of finely powdered 2-pyrazinoic acid 4-oxide (IX) [50 g, mp 188° (decomp.)] in 10% methanolic hydrogen chloride (380 ml) was refluxed for 40 min. The solution was cooled and the crystalline mass was filtered to give light brown crystals (45 g, 81.7%), mp 165.5—167.5°. For analysis, the compound was recrystallized from methanol to give colorless needles, mp 166.5—167.5°.

Foks and Sawlewicz[11] reported the mp of this compound as 172—173°.

Methyl 6-Chloro-2-pyrazinecarboxylate (XII)——Method A: A suspension of 6-chloro-2-pyrazinoic acid (0.79 g) in 12% methanolic hydrogen chloride (4 ml) was refluxed for 5 min. The resulting faint yellow solution was evaporated *in vacuo* (below 40°) and the residue was dissolved in cold water (5 ml). It was neutralized with sodium hydrogen carbonate and extracted with chloroform. Evaporation of the solvent afforded the crude chloropyrazine (XII) (0.722 g, 84.5%), mp 32—36°. Gas–liquid chromatography of the material using a 5% PEG–succinate column at 120° revealed that it had a purity of 93% and methyl 6-methoxy-2-pyrazinecarboxylate (XVIII) was a contaminant. Recrystallization from cyclohexane afforded pure methyl 6-chloro-2-pyrazinecarboxylate (0.46 g, 53.3%) as colorless needles, mp 41—42°, which was checked by gas–liquid chromatography. After several recrystallization from cyclohexane, this compound showed the mp of 42.5—44.5°. UV $\lambda_{max}^{H_2O}$ mμ (log ε): 219 (4.02), 285 (4.02).

Method B: A suspension of 2-carbomethoxypyrazine 4-oxide (XI) (19.7 g) in phosphoryl chloride (120 ml) was gradually heated with vigorous stirring until the exothermic reaction, which occurs at about 80°, subsided. Heating under reflux was continued for additional 10 min. The resulting dark mixture was poured cautiously on chopped ice with vigorous stirring. After decomposition was complete, the solution was extracted with chloroform and the chloroform layer was dried and evaporated *in vacuo*. The residue was distilled under reduced pressure to give a liquid (19.9 g, 97%), bp 115° (10 mmHg) which crystallized on standing. Recrystallization from cyclohexane gave XII as colorless needles (10.49 g, 51%), mp 41—42.5°.

6-Chloro-2-pyrazinecarboxamide (XIII)——A suspension of methyl 6-chloro-2-pyrazinecarboxylate (XII) (0.44 g) in 28% ammonium hydroxide solution was stirred at room temperature. Yellow needles separated out within 10 min. After standing at room temperature overnight the reaction mixture was chilled and the precipitate was collected and the product (0.37 g, 92%), mp 168—169°, was recrystallized from water to afford 6-chloro-2-pyrazinecarboxamide (XIII) (0.3 g, 74.6%) as light yellowish prisms, mp 171—172.5°.[15]

2-Amino-6-chloropyrazine (XIV)——This aminopyrazine (XIV) was obtained from 6-chloro-2-pyrazinecarboxamide (XIII) (7.1 g) prepared from methyl 6-chloro-2-pyrazinecarboxylate (XII) as described by Bernardi, *et al.*[6] The crude aminopyrazine (XIV) (3.4 g, 58.5%), mp 144—180°, was chromatographed on silica gel with chloroform–acetone (1:1). Elution with acetone afforded the aminopyrazine (XIV) (0.88 g) as slight yellowish prisms, mp 152—154°, undepressed on admixture with an authentic sample of 2-amino-6-chloropyrazine (XIV), mp 152—154°, prepared by the method of Bernardi, *et al.*[6] This 2-amino-6-chloropyrazine (XIV) was identified also by comparing its infrared spectrum (KBr) with that of an authentic sample.

6-Methoxy-2-(4-morpholinocarbonyl)pyrazine (XVI)——Method A: To morpholine (0.907 g) methyl 6-methoxy-2-pyrazinecarboxylate (XVIII) (0.35 g) was added and the solution was refluxed for 30 min. After evaporation of the excess morpholine *in vacuo* (below 60°) the dark brown residue was dissolved in chloroform and the solution was decolorized with active charcoal, evaporated to dryness *in vacuo* affording 470 mg of a crude product. It was dissolved in chloroform and chromatographed on a silica gel column. Elution with chloroform furnished 254 mg of 6-methoxy-2-(4-morpholinocarbonyl)pyrazine (XVI). Recrystallization from isopropyl alcohol afforded XVI as colorless prisms, mp 109—110.5°. UV λ_{max}^{MeOH} mμ (log ε): 219.3 (4.04), 290.8 (3.82).

Method B: To a cold solution of sodium methoxide prepared from sodium (0.45 g) and absolute methanol (20 ml) was added a solution of 6-chloro-2-(4-morpholinocarbonyl)pyrazine (VII) (3.3 g) in absolute methanol (36 ml) with stirring and cooling. The solution was kept at room temperature for 6 hr. The resulting precipitate was filtered off and the solution was concentrated *in vacuo* to give a crude product which was dissolved in water (5 ml) and the solution was extracted with chloroform. The crude product (2.4 g, 74.2%) from the chloroform layer was chromatographed on a silica gel column (20 g). The eluate from chloroform was recrystallized from isopropyl alcohol to afford 6-methoxy-2-(4-morpholinocarbonyl)pyrazine (XVI) as colorless prisms, mp 109.5—110°.

6-(4′-Morpholino)-2-(4-morpholinocarbonyl)pyrazine (XVII)——A solution of methyl 6-chloro-2-pyrazinecarboxylate (XII) (6.3 g) in dry morpholine (40 ml) was heated under reflux for 7.5 hr. After the solution was chilled, the precipitated morpholine hydrochloride was filtered off and washed with benzene. The combined filtrate and washing were (combined and) concentrated *in vacuo* and the residue was dissolved in benzene and filtered. After evaporation of the solvent the residue (9.57 g, 86%) was dissolved in chloroform (60 ml), washed with saturated sodium chloride solution, and the chloroform layer was dried and evaporated *in vacuo*. The crude product was then recrystallized from ether to afford 6-(4′-

15) The mp of this compound was reported at 176° by M. Asai [*Yakugaku Zasshi*, **81**, 1475 (1961)]. Bernardi, *et al.*, gave the mp of 175—176° [L. Bernardi, G. Palamidessi, A. Leone, and G. Larini, *Gazz. Chim. Ital.*, **91**, 1431 (1961); *Chem. Abstr.*, **57**, 2223^e (1962)].

morpholino)-2-(4-morpholinocarbonyl)pyrazine (XVII) (6.17 g, 55.4%) as colorless plates, mp 105.5—107°. After several recrystallization from ether this compound (XVII) had mp 106—107.5°. UV $\lambda_{max}^{H_2O}$ mμ (log ε): 261.5 (4.16) 349 (3.72).

Method B: A solution of 6-chloro-2-(4-morpholinocarbonyl)pyrazine (VII) (15 g) and morpholine (45.6 g) in benzene (100 ml) was heated at 70° for 48 hr. The precipitated morpholine hydrochloride was removed by filtration. The excess morpholine and benzene was evaporated *in vacuo* and a small amount of petroleum ether was added to the residue to afford a crystalline solid (17.0 g, 93.3%), mp 103—104°. Recrystallization from isopropyl alcohol gave light yellow prisms (14.8 g, 82%), mp 106—107.5°.

Methyl 6-Methoxy-2-pyrazinecarboxylate (XVIII)——Method A: To a cold solution of sodium methoxide prepared from sodium (0.88 g) and absolute methanol (20 ml) was added methyl 6-chloro-2-pyrazinecarboxylate (XII) (5.0 g) with stirring and cooling. The precipitation of sodium chloride had occured immediately. The solution was kept at room temperature for 1 hr and then ether (20 ml) was added. The resulting precipitate was filtered off, washed with ether and the combined solution was concentrated to dryness *in vacuo* yielded a crude product which was dissolved in ether (50 ml) and the solution was filtered to remove the trace of insoluble material. The crude product obtained as above was distilled under reduced pressure and the distillate was crystallized to furnish the methoxypyrazine (XVIII) as colorless needles (2.19 g), mp 74.5—75.5°, bp 82° (3 mmHg). UV $\lambda_{max}^{H_2O}$ mμ (log ε): 226 (3.86), 296 (3.86).

Method B: A solution of 6-chloro-2-pyrazinoic acid (X) (15.8 g) in methanol (100 ml) and sulfuric acid (9 ml) was heated under reflux for 3 hr. After addition of water (50 ml) the solution was made slightly basic with sodium carbonate and extracted with chloroform. The chloroform was evaporated *in vacuo* and the oily residue was dissolved in ether, filtered, concentrated *in vacuo* to afford a mixture of methyl 6-chloro-2-pyrazinecarboxylate (XII) and methyl 6-methoxy-2-pyrazinecarboxylate (XVIII) as a solid (10.5 g). The mixture was recrystallized from cyclohexane (active charcoal) and then petroleum ether to yield methyl 6-methoxy-2-pyrazinecarboxylate (XVIII) (1.76 g) as light yellow needles, mp 73—74°, which was identified with an authentic sample of (XVIII) prepared by Method A by mixed melting point determination and the comparison of IR and NMR spectra.

6-Chloro-N,N′-disubstituted Pyrazinamides (XIX-a,b)——These products were prepared by treating 6-chloro-2-pyrazinoyl chloride in benzene with corresponding amines as described in method B of above 6-chloro-2-(4-morpholinocarbonyl)pyrazine (VII). The yields were as follows: XIX-a, bp 125—127° (3—4 mmHg), 71.3%, UV λ_{max}^{MeOH} mμ (log ε): 281.5 (4.03); XIX-b, bp 115—120° (0.02 mmHg), 44.6%, UV λ_{max}^{MeOH} mμ: 281.5.

Methyl 6-Amino-2-pyrazinecarboxamide (XX-a)——A suspension of methyl 6-chloro-2-pyrazinecarboxylate (XII) (5.0 g) in liquid ammonia (about 80 ml) in an autoclave (100 ml) was heated at 80° for 14 hr. After evaporation of ammonia the residue was washed with water, collected by filtration and recrystallized from water to afford (XX-a) as prisms (2.1 g, 50.2%). Further recrystallization from methanol gave light yellow needles, mp 203—204.5°. UV $\lambda_{max}^{H_2O}$ mμ (log ε): 245 (3.96), 335 (3.76).

N,N,N′,N′-Tetraethyl-6-amino-2-pyrazinecarboxamide (XX-b)——A mixture of 6-chloro-N,N-diethylpyrazinamide (3.8 g) and diethylamine (40 ml) was heated in an autoclave (100 ml) at 75—83° for 100 hr. After evaporation of excess diethylamine *in vacuo* the oily residue was dissolved in chloroform (300 ml), washed with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was distilled under reduced pressure to afford a colorless liquid (3.56 g, 79.8%), bp 135—137° (0.03 mmHg). This liquid was further purified by silica gel chromatography and redistillation to give (XX-b), bp 125—127° (0.01 mmHg). UV λ_{max}^{MeOH} mμ (log ε): 263 (4.21), 357 (3.46).

6-Piperidino-2-piperidinocarbonylpyrazine (XX-c)——A solution of 6-chloro-2-piperidinocarbonylpyrazine (XIV-b) (1.5 g) in piperidine (4.5 g) and benzene (15 ml) was heated at 70° for 48 hr. The solution was chilled and the precipitate was filtered off. After evaporation of excess piperidine and benzene the residue was purified by silica gel chromatography and distilled under reduced pressure to give (XX-c) (1.45 g, 80.3%) as colorless liquid, bp 165—170° (0.03 mmHg). UV λ_{max}^{MeOH} mμ (log ε): 265 (4.23).

6-Diethylamino-2-(4-morpholinocarbonyl)pyrazine (XX-d)——A solution of 6-chloro-2-(4-morpholinocarbonyl)pyrazine (VII) (1.0 g) in diethylamine (15 ml) was heated in an autoclave at 80° for 100 hr. The solution was chilled and the precipitated diethylamine hydrochloride was removed by filtration, and the filtrate was concentrated *in vacuo* to dryness. The residue was recrystallized from ether to afford (XX-d) as light yellow prisms (0.65 g, 60%), mp 84.5—86.5°. An analytical sample had mp 87.5—88.5°.

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