[Chem. Pharm. Bull. 23(11)2913—2917(1975)]

UDC 547.852.2'546.21.04 : 546.185.131-3.04

Synthesis of Pyrazine Derivatives. I. Reactions of 2,5-Dimethylpyrazine N-Oxides with Acid Chlorides*,[1]

Kobun Matsuura, Miyoko Inomata, Sumiko Oikawa, Kang Jin, and Takanobu Itai

Showa College of Pharmaceutical Sciences[2]

(Received May 12, 1975)

When N-oxides of 2,5-dimethylpyrazine and their 3,6-disubstituted (chlorine or alkoxy) derivatives were reacted with phosphorus oxychloride, various compounds substituted by chlorine on the nucleus and/or on the methyl group(s) were produced in low yields. Accordingly, a few kinds of other acid chlorides were examined to elevate the yields, but no one could improve the results. Chlorinated compounds thus obtained were converted to their corresponding alkoxy derivatives (methoxy, ethoxy or benzyloxy).

As 2,5-dimethylpyrazine 1,4-dioxide (I) can be obtained easily, *e.g.*, from ethyl acetoacetate, this study was undertaken to synthesize α-amino acids from I, by applying many reactions which have been discovered in the studies of aromatic amine oxides.[3]

The reactions of 2,5-dimethylpyrazine 1-oxide and the 1,4-dioxide (I) with phosphorus oxychloride have been reported already by Newbold and Spring,[4] by Baxter, Newbold, and Spring,[5,6] and by Blake and Sammes.[7] For instances, 2,5-dimethylpyrazine 1,4-dioxide (I) gave 3,6-dichloro-2,5-dimethylpyrazine (II) in 18% yield, and 3-chloro-2,5-dimethylpyrazine 1-oxide did the same compound in 33%. 2,5-Dimethylpyrazine 1-oxide was converted to 3-chloro-2,5-dimethylpyrazine in 85% yield. Simultaneously, compound (II) and 3-ethoxy-2,5-dimethylpyrazine 1-oxide produced the corresponding chloromethyl derivatives.

In order to produce starting meterials for synthesis of α-amino acids, as stated above, we reexamined the previous reports, which results will be described.

As shown in Chart 1, when compound (I) was heated with an excess amount of phosphorus oxychloride at 160° and the products were purified by an alumina column, 3,6-dichloro-2,5-dimethylpyrazine (II), 3-chloro-2,5-dimethylpyrazine 1-oxide (III) and 5-chloromethyl-2-methylpyrazine 1-oxide (IV) were isolated in 6%, 5% and 9% yields, respectively. In addition to these products, small amounts of 6-chloro-5-chloromethyl-2-methylpyrazine (V) and 2,5-bis(chloromethyl)pyrazine (VI) were identified by means of gas chromatography.

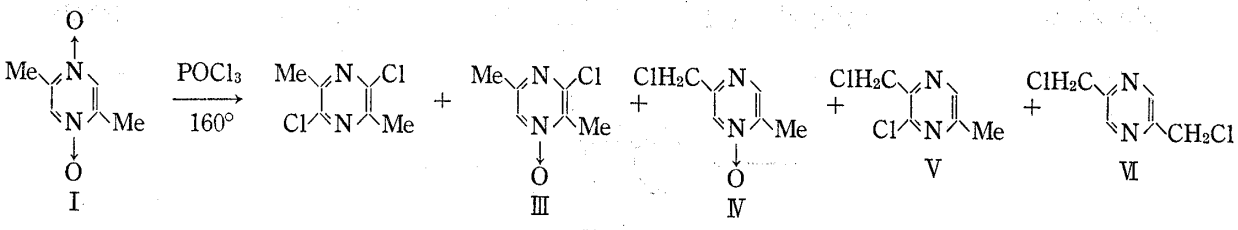

Chart 1

* Dedicated to the memory of Prof. Eiji Ochiai.

1) Presented at the 95th Annual Meeting of Pharmaceutical Society of Japan, Nishinomiya, April, 1975.

2) Location: *5-1-8, Tsurumaki, Setagaya, Tokyo, 154, Japan.*

3) E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Co., Amsterdam, 1967; A.R. Katritzky and J.M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press, London and New York, 1971.

4) G.T. Newbold and F.S. Spring, *J. Chem. Soc.*, **1947**, 1183.

5) G.T. Newbold and F.S. Spring, *J. Chem. Soc.*, **1947**, 1183.

6) R.A. Baxter, G.T. Newbold, and F.S. Spring, *J. Chem. Soc.*, **1948**, 1859.

7) K.W. Blake and P.G. Sammes, *J. Chem. Soc.*, (*C*), **1970**, 1070.

Subsequently, other acid chlorides such as *p*-tosyl chloride,[8] methane sulfonyl chloride or a mixture of phosphorus oxychloride and concentrated sulfuric acid were examined, but these did not give good results.

Blake and Sammes[7] have already reported briefly the N-oxidation of II with pertrifluoroacetic acid. As described in the Experimental of this report, we reexamined the reaction at various conditions, and could obtain 3,6-dichloro-2,5-dimethylpyrazine 1,4-dioxide (VII) and its mono-N-oxide in yields 69% and 16%, respectively. When VII was reacted with sodium alkoxides,[7] the corresponding 3,6-dialkoxy-2,5-dimethylpyrazine N-oxides (IX) were produced in good yields. In some cases, 5-alkoxy-1-hydroxy-3,6-dimethylpyrazin-2(1H)-one 4-oxides (X) were isolated as the by-products.

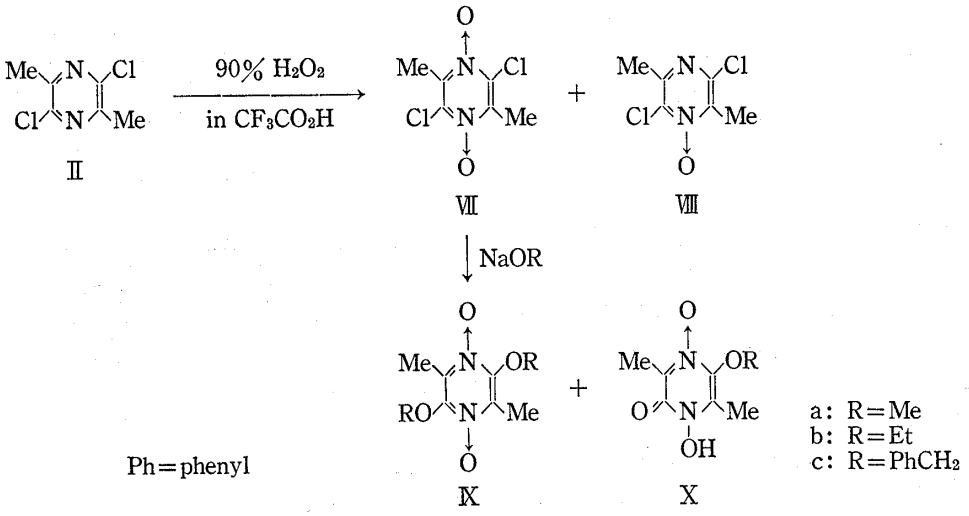

Chart 2

On reacting VII with an excess of phosphorus oxychloride at 170°, 3,6-dichloro-2,5-bis-(chloromethyl)pyrazine (XI) and 3,6-dichloro-5-chloromethyl-2-methylpyrazine 1-oxide (XII) were produced in yields 29% and 11%, respectively. Furthermore, VIII and II were obtained as the result of deoxygenation on heating. VIII was converted similarly to 3,6-dichloro-2-chloromethyl-5-methylpyrazine (XIII) and II.

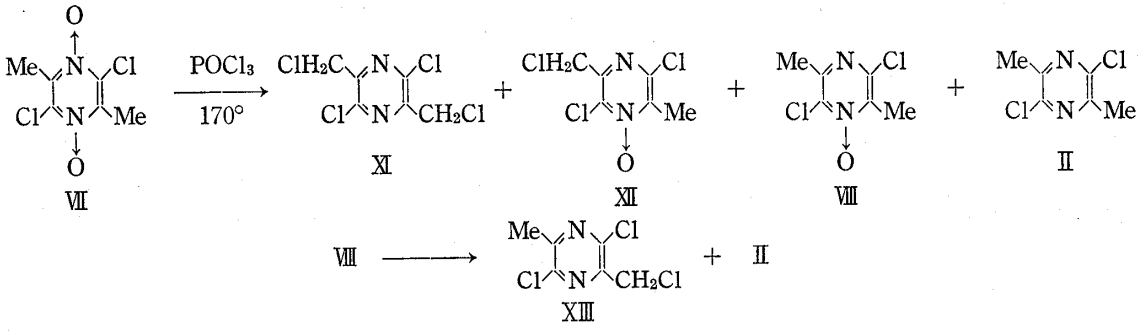

Chart 3

As the substitutes for phosphorus oxychloride, *p*-tosyl chloride, which changed α-picoline 1-oxide specifically to 2-chloromethylpyridine,[8] methanesulfonyl chloride, and a mixture of phosphorus oxychloride and concentrated sulfuric acid or trifluoroacetic acid were used in the reaction, but no good result was obtained.

The reaction of 3,6-dimethoxy- or -diethoxy-2,5-dimethylpyrazine 1,4-dioxide (IXa, b) with phosphorus oxychloride in a similar condition as before, afforded solely 3,6-dimethoxy-

8) E. Matsumura, *J. Chem. Soc. Japan*, **74**, 364 (1953); *idem*, *ibid.*, **82**, 616 (1961).

or -diethoxy-2,5-bis(chloromethyl)pyrazine (XIVa, b) in yields 11.7% and 26% together with resinous substances, respectively.

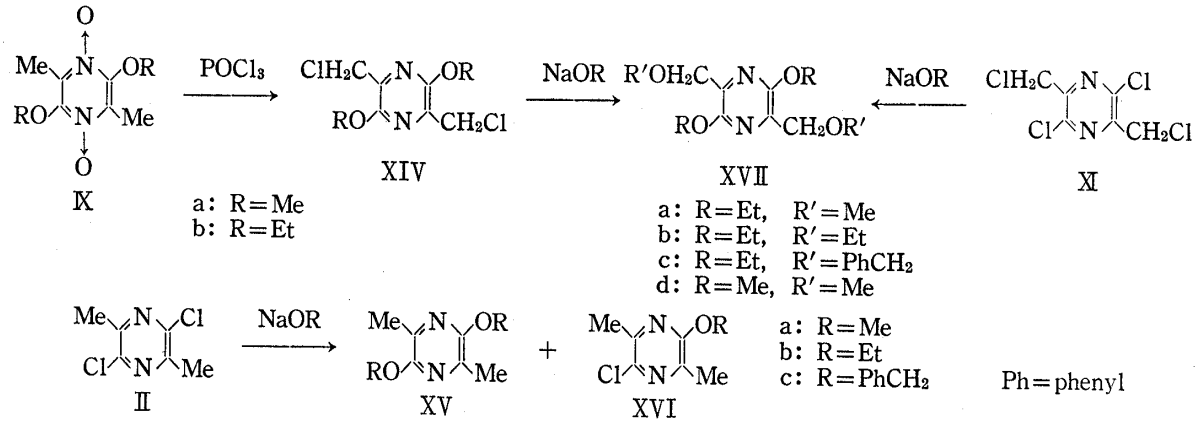

Chart 4

Reaction of a chlorine atom on pyrazine ring with alkoxides has already been reported by Baxter, Newbold and Spring[6]; Hirschberg and Spoerri[9]; and Kokorudz and Landon.[10] In fact, the first chlorine of II was replaced easily by alkoxide ions. However, it was found that the second one could only be substituted by heating the mixtures at 160—200°.

As previously reported, 3,6-dialkoxy-2,5-bis(chloromethyl)pyrazine (XIVa, b) were reacted with sodium alkoxides at room temperatures or under slight warming. However, the yields of 3,6-dialkoxy-2,5-bis(alkoxymethyl)pyrazine (XVIIa, b, c, d) were very low. Besides, a structure-unknown substance was produced at reactions of XIVb as the main product. Further study is now under progress.

Expecting to synthesize II more easily than by the method starting from ethyl acetoacetate, a reaction of alanine anhydride with phosphorus oxychloride[7] was re-investigated. As described in the Experimental, it was never achieved to improve the yields, in spite of all efforts made.

Experimental

Unless otherwise stated, infrared (IR) spectra were taken on KBr-tablets, and NMR spectra were measured in $CDCl_3$ using Varian 60 MHz apparatus, with tetramethyl silane (TMS) as internal reference. Melting points were determined on Yanagimoto micro-melting point apparatus and uncorrected. All organic extracts were dried with Na_2SO_4 or $CaCl_2$ before evaporation. Gas chromatograms were taken with Hitachi-063 gas chromatograph apparatus: Column filled SE-30, 1 m long, gas N_2, flow rate 30 ml/min, at 150°. Identities were confirmed by IR, nuclear magnetic resonance (NMR), and gas chromatography.

2,5-Dimethylpyrazine 1,4-Dioxide (I)——2,5-Dimethylpyrazine-3,6-dicarboxylic acid (XXII) was prepared according to the report of Iida, *et al.*[11] with some simplification. Yields from ethyl acetoacetate were about 60%. XXII was decarboxylated by heating in quinoline with copper powder. I was prepared by oxidation with 30% H_2O_2–maleic anhydride in CH_2Cl_2 in *ca.* 85%. Using trifluoroacetic acid as the substitute for maleic anhydride, the yield was 57%. Reacting 30% H_2O_2–conc. H_2SO_4 at a room temperature for 22 hr then at 60° for 2 hr, I was solely produced in yield 52%.

Reactions of 2,5-Dimethylpyrazine 1,4-Dioxide (I) with Acid Chlorides——A) $POCl_3$: A solution of I (3.0 g) in $POCl_3$ (20 ml) was refluxed in an oil-bath at 160° for 6 hr, the excess of $POCl_3$ was distilled partially *in vacuo*, and the residue was poured on ice. After making the solution alkaline with sodium hydroxide, the solution was extracted with $CHCl_3$. The residue obtained was separated through an alumina column. From benzene eluates, II mp 73°, 0.24 g (6%) and oil (14%), which was found as a mixture of V and VI by gas chromatography, were isolated. From $CHCl_3$ eluates, III mp 115—116°, 0.18 g (5%) and IV mp 89°, 0.3 g (9%) were isolated. Recovery was 38%. IV NMR ($CDCl_3$) δ: 8.38 (1H, s, C_6–H), 8.30 (1H, s, C_3–H), 4.57 (2H, s, CH_2Cl), 2.47 (3H, s, Me). UV λ_{max}^{EtOH} mμ (ε): 205 (6800), 227 (14700), 270 (10900). t_R 342 sec.

9) A. Hirschberg and R.P. Spoerri, *J. Org. Chem.*, **26**, 2356 (1956).
10) H. Gainer, M. Kokorudz, and W.K. Langon, *J. Org. Chem.*, **26**, 2360 (1961).
11) H. Iida, K. Hayashida, M. Yamada, K. Takahashi, and K. Yamada, *Synth. Commun.* 3, 225 (1973).

Anal. Calcd. for $C_6H_7ON_2Cl$: C, 45.43, H, 4.42, N, 17.67. Found: C, 45.99, H, 4.46, N, 17.72. V NMR ($CDCl_3$) δ: 8.32 (1H, s, C_5–H), 4.73 (2H, s, CH_2Cl), 2.58 (3H, s, Me). t_R 102 sec. VI NMR ($CDCl_3$) δ: 4.62 (4H, s, CH_2Cl). t_R 174 sec.

B) *p*-Tosyl Chloride: A benzene solution of I (1.4 g) and *p*-tosyl chloride (3.8 g) was allowed to stand at a room temperature for 24 hr, no change was observed. Distilling off the benzene, the mixture was dissolved in $CHCl_3$ and refluxed for 10 hr, but no reaction occurred. After evaporation, the residue was heated in a bath at 120°, and distilled *in vacuo*. The distillate bp_4 28—55°, 0.375 g. By gas chromatography, it was found that 3-chloro-2,5-dimethylpyrazine, II, and V were included with a ratio 2: 1: 2.

3,6-Dichloro-2,5-dimethylpyrazine 1,4-Dioxide (VII) and the 1-Oxide (VIII)——A solution of II (1.76 g) in trifluoroacetic acid (25 ml) and 90% H_2O_2 (2.3 ml) was refluxed for 1 hr and concentrated *in vacuo*. The residue was diluted with water, made alkaline with sodium carbonate, and extracted with $CHCl_3$. After evaporating, the residue was recrystallized with benzene–CCl_4. VII mp 248° (decomp), 0.98 g (47%). The residue from the mother liquid was dissolved in benzene, and passed through alumina column, VIII was obtained. mp 122°, 0.3 g (16%). From EtOH-eluates, VII 0.46 g (22%). Total amount of VII 1.44 g (69%). VII NMR ($CDCl_3$) δ: 2.72 (6H, s, Me). UV λ_{max}^{EtOH} mμ (ε): 214 (10800), 251 (21200), 311 (14800). VIII NMR ($CDCl_3$) δ: 2.60 (6H, s, Me). UV λ_{max}^{EtOH} mμ (ε): 219 (11900), 239 (15900), 275 (7500), 313 (2500), 319 (2700), 324 (2700). t_R 288 sec.

When amounts of H_2O_2 were increased stepwise to 4, 6, 8, or 10-moles for 1 mole of II, yields of VII were not improved, and VIII was produced rather more. The increase of trifluoroacetic acid improved a little the yields of VII. It was unnecessary to heat more that 1 hr. Addition of trifluoromethane sulfonic was unnecessary to heat more than 1 hr. Addition of CF_3SO_3H or 90% H_2O_2–H_2SO_4–AcOH gave solely VIII in yields *ca.* 70%.

3,6-Dimethoxy-2,5-dimethylpyrazine 1,4-Dioxide (IXa) and 1-Hydroxy-5-methoxy-3,6-dimethylpyrazin-2(1H)-one 4-Oxide (Xa)——To a solution of sodium methoxide prepared by dissolving Na (0.3 g) in abs, MeOH (6 ml), VII was added and allowed to stand at a room temperature for 30 min. After distilling off the solvent and adding water, the aq. solution was extracted with $CHCl_3$. The evaporated residue was recrystallized with hexane. IXa mp 170—171° (decomp.), 1.57 g (81.8%). NMR ($CDCl_3$) δ: 4.16 (6H, s, OMe), 2.50 (6H, s, Me). UV λ_{max}^{EtOH} mμ (ε): 205 (16400), 243 (26000), 302 (19600). *Anal.* Calcd. for $C_8H_{12}O_4N_2$: C, 48.00, H, 6.00, N, 14.00. Found: C, 47.59; H, 5.95, N, 13.84.

The extracted aq. solution was made acidic and extracted with $CHCl_3$. The residue was recrystallized with benzene–hexane. Xa mp 195—197° (decomp.), 0.1 g (5.6%). NMR ($CDCl_3$) δ: 5.73 (3H, s, OMe), 3.96 (1H, s, OH), 2.60 (3H, s, Me), 2.46 (3H, s, Me). UV λ_{max}^{EtOH} mμ (ε): 235 (21950), 282 (5580), 352 (5580).

3,6-Diethoxy-2,5-dimethylpyrazine 1,4-Dioxide (IXb) and 1-Hydroxy-5-ethoxy-3,6-dimethylpyrazin-2(1H)-one 4-Oxide (Xb)——IXb NMR δ: 4.50 (4H, q, J=7 cps, OEt), 2.50 (6H, s, Me), 1.44 (6H, t, J= 7 cps, OEt). UV λ_{max}^{EtOH} mμ (ε): 206 (15050), 244 (25540), 302 (17330), Xb NMR ($CDCl_3$) δ: 4.28 (2H, q, J= 7 cps, OEt), 3.17 (1H, s, OH), 2.52 (3H, s, Me), 2.44 (3H, s, Me), 1.40 (3H, t, J=7 cps, OEt). UV λ_{max}^{EtOH} mμ (ε): 229 (24800), 282 (8000), 356 (6800).

3,6-Dibenzyloxy-2,5-dimethylpyrazine 1,4-Dioxide (IXc)——To a suspension of sodium benzyloxide prepared by addition of 50% NaH in oil (0.6 g) in dried benzene (10 ml) and $C_6H_5CH_2OH$ (0.3 g), VII (1.04 g) was added. After a vigorous reaction subsided (2 hr), water was added, and the solution was extracted with $CHCl_3$. The evaporated residue was recrystallized from hexane. IXc mp 125—127°, 0.43 g (25%). NMR ($CDCl_3$) δ: 7.36 (10H, s, C_6H_5), 4.48 (4H, s, OCH_2), 2.26 (6H, s, Me). UV λ_{max}^{EtOH} mμ (ε): 206 (31680), 249 (25340), 303 (15840). The extracted aq. solution was made acid with HCl and extracted $CHCl_3$. Recrystallized from benzene, Xc mp 163—165°, 0.87 g (66.4%). NMR ($CDCl_3$) δ: 7.40 (5H, s, C_6H_5), 6.73 (1H, s, OH), 5.26 (2H, s, OCH_2), 2.50 (3H, s, Me), 2.24 (3H, s, Me). UV λ_{max}^{EtOH} mμ (ε): 231 (23580), 283 (6810), 356 (6810). *Anal.* Calcd. for $C_{13}H_{14}O_4N_2$: C, 59.54, H, 5.34, N, 10.69. Found: C, 58.95; H, 5.31; N, 10.65.

Reactions of 3,6-Dichloro-2,5-dimethylpyrazine 1,4-Dioxide (VII) with Acid Chlorides——A) $POCl_3$: A solution of VII (1.04 g) in $POCl_3$ (5 ml) was refluxed in a bath at 120° for 2 hr. After distilling off the excess of $POCl_3$ partially, and pouring the residue onto ice, it was extracted with $CHCl_3$. The evaporated residue was dissolved in hexane and chromatographed on alumina column. From hexane eluates, XI mp 65—67°, 0.35 g (29%), XIII mp 45—47° and II were isolated. From $CHCl_3$ and MeOH eluates, XII 0.12 g (11%) and a mixture 0.29 g were separated. The latter was purified to give VIII. XI NMR ($CDCl_3$) δ: 4.74 (4H, s, CH_2Cl). t_R 442 sec. XII NMR ($CDCl_3$) δ: 4.93 (2H, s, CH_2Cl), 2.68 (3H, s, Me). UV λ_{max}^{EtOH} mμ (ε): 222 (16270), 243 (17400), 272 (7910). t_R 660 sec. *Anal.* Calcd. for $C_6H_5ON_2Cl_3$: C, 31.65; H, 2.20; N, 12.31. Found: C, 32.86; H, 2.30; N, 12.18. XIII NMR ($CDCl_3$) δ: 4.72 (2H, s, CH_2Cl), 2.68 (3H, s, Me). UV λ_{max}^{EtOH} mμ (ε): 225 (10900), 296 (8600). t_R 180 sec. *Anal.* Calcd. for $C_6H_5N_2Cl_3$: C, 34.04, H, 2.36; N, 13.24. Found: C, 34.07; H, 2.33; N, 13.38.

B) $POCl_3$–H_2SO_4: A solution of VII (1.04 g) in $POCl_3$ (5 ml) and conc. H_2SO_4 (1 ml) was refluxed at 160° for 2 hr, and treated as before. On examining the evaporated residue by gas chromatography, it consisted of VII and a small amount of XIII with an unknown substance. By alumina column chromatography, VII mp 221°, 0.1 g and the unknown substance mp 141—143°, 0.24 g were isolated.

Reaction of 3,6-Dimethoxy-2,5-dimethylpyrazine 1,4-Dioxide (IXa) with $POCl_3$——A solution of IXa (1.09 g) in $POCl_3$ (5 ml) was heated in an oil bath at 140° for 1 hr, and treated as described in a reaction of

VII with $POCl_3$. The evaporated residue from $CHCl_3$ was purified by passing through alumina column. XIVa pale yellow needles, mp 117—118°, 0.15 g (11.7%). NMR ($CDCl_3$) δ: 4.63 (4H, s, CH_2Cl), 4.02 (6H, s, OMe). UV λ_{max}^{EtOH} mμ (ε): 234 (10620), 334 (10620). t_R 456 sec. *Anal.* Calcd. for $C_8H_{10}O_2N_2Cl_2$: C, 40.51; H, 4.22; N, 11.81. Found: C, 40.52; H, 4.13; N, 12.00.

Reaction of 3,6-Diethoxy-2,5-dimethylpyrazine 1,4-Dioxide (IXb) with $POCl_3$——A solution of IXb (0.77 g) in $POCl_3$ (6 ml) was heated in a bath at 120—130° for 2 hr, and treated as above. The evaporated residue from $CHCl_3$ extracts was brown needles, 0.52 g, which was purified by passing through alumina column and eluted with hexane and with $CHCl_3$. From these eluates, XIVb pale yellow needles mp 85°, 0.23 g (26%). Eluting with EtOH, a brown resinous substance. XIVb NMR ($CDCl_3$) δ: 4.63 (4H, s, CHCl), 4.40 (4H, q, J=7 cps, OEt), 1.40 (6H, t, J=7 cps, OEt). UV λ_{max}^{EtOH} mμ (ε): 235 (10300), 334 (9240). t_R 696 sec. *Anal.* Calcd. for $C_{10}H_{14}O_2N_2Cl_2$: C, 45.28; H, 5.28; N, 10.57. Found: C, 45.42, H, 5.30; N, 10.68.

Reaction of 3,6-Dichloro-2,5-dimethylpyrazine (II) with Sodium Alkoxides[5,12] 6-Chloro-3-methoxy-2,5-dimethylpyrazine (XVIa)——mp 59°, NMR ($CDCl_3$) δ: 2.96 (3H, s, OMe), 2.40 (3H, s, Me), 2.48 (3H, s, Me). UV λ_{max}^{EtOH} mμ (ε): 224 (10400), 303 (8700). t_R 78 sec. *Anal.* Calcd. for $C_7H_9ON_2$:Cl: C, 48.70; H, 5.22; N, 16.23. Found: C, 47.62; H, 5.15; N, 15.85.

3,6-Dimethoxy-2,5-dimethylpyrazine (XVa)——mp 65—67°, NMR ($CDCl_3$) δ: 3.88 (6H, s, OMe), 2.33 (6H, s, Me). UV λ_{max}^{EtOH} mμ (ε): 222 (9910), 317 (8900).

6-Chloro-3-ethoxy-2,5-dimethylpyrazine (XVIa)——mp 24°, NMR ($CDCl_3$) δ: 4.37 (2H, q, J=7 cps, OEt), 246 (3H, s, Me), 2.38 (3H, s, Me), 1.38 (3H, t, J=7 cps, OEt). UV λ_{max}^{EtOH} mμ (ε): 223 (10400), 303 (8400). t_R 108 sec.

3,6-Diethoxy-2,5-dimethylpyrazine (XVb)——mp 73—75°, NMR ($CDCl_3$) δ: 4.35 (4H, q, J=7 cps, OEt), 2.35 (6H, s, Me), 1.38 (6H, t, J=7 cps, OEt). UV λ_{max}^{EtOH} mμ (ε): 222 (10585), 3.19 (8820). t_R 108 sec.

3,6-Dibenzyloxy-2,5-dimethylpyrazine (XVc)——To a solution of sodium benzyloxide prepared by dissolving Na (0.45 g) in abs. $C_6H_5CH_2OH$ (23 g), II (1.76 g) was added and heated at 160—200° for 3.5 hr. On adding water to the mixture, fluorescent crystals, XVc mp 91—92°, 2.62 g (82%) were obtained. NMR ($CDCl_3$) δ: 7.38 (10H, s, C_6H_5–), 5.30 (4H, s, $OCH_2C_6H_5$), 2.36 (6H, s, Me). UV λ_{max}^{EtOH}mμ (ε): 211 (10900), 270 (2200), 315 (4600).

3,6-Diethoxy-2,5-bis(methoxymethyl)pyrazine (XVIIa)——To a solution of sodium methoxide prepared by dissolving Na (0.2 g) in abs. MeOH (5 ml), XIVb (0.16 g) was added and allowed to stand for 30 min. After evaporating and adding water, the aq. solution was extracted with $CHCl_3$. The residue was purified by passing through alumina column with benzene. XIIa mp 51—53°, 0.07 g (45%). NMR ($CDCl_3$) δ: 4.52 (4H, s, CH_2O), 4.40 (4H, q, J=7 cps, OEt), 3.48 (6H, s, OMe), 1.40 (6H, t, J=7 cps, OEt). UV λ_{max}^{EtOH} mμ (ε): 227 (11520), 324 (8450). *Anal.* Calcd. for $C_{12}H_{20}O_4N_2$: C, 56.25; H, 7.81; N, 10.94. Found: C, 56.02, H, 7.72; N, 10.95.

3,6-Diethoxy-2,5-bis(ethoxymethyl)pyrazine (XVIIb)——To a solution of sodium ethoxide prepared by dissolving Na (0.03 g) in abs. EtOH (5 ml), XIVb (0.14 g) was added and allowed to stand overnight. After treating as above. The evaporated residue was oil (0.13 g). This was passed through alumina column. White crystals. mp 139—140°, 0.08 g. The structure is unknown. XVIIb oil 0.01 g (6.7%). NMR ($CDCl_3$) δ: 4.56 (4H, s, CH_2O), 4.40 (4H, q. J=7 cps, OEt), 3.64 (4H, q, J=7 cps, CH_2OEt), 1.30 (12H, t, J=7 cps, OEt). t_R 912 sec, the extracted aq. solution was made acid with HCl and extracted with $CHCl_3$. From the extracts, a trace amount of resinous substance was obtained.

3,6-Diethoxy-2,5-bis(benzyloxymethyl)pyrazine (XVIIc)——To a solution of sodium benzyloxide prepared by dissolving Na (0.2 g) in abs. $C_6H_5CH_2OH$ (10 ml) XIVb (0.18 g) was reacted at a room temperature for 2 hr, and treated as before. XVIIc oil, 0.05 g (18%). NMR ($CDCl_3$) δ: 7.32 (10H, s, C_6H_5–), 4.64 (4H, s, CH_2O), 4.60 (4H, s, $CH_2C_6H_5$), 4.38 (4H, q, J=7 cps, OEt), 1.36 (6H, t, J=7 cps, OEt).

3,6-Dimethoxy-2,5-bis(methoxymethyl)pyrazine (XVIId)——To a solution of sodium methoxide prepared by dissolving Na (0.1 g) in abs. MeOH (5 ml), XIVa (0.1 g) was reacted at a room temperature for 1 hr, and treated as before. XVIId needles, mp 80—81°, 0.03 g (31%). NMR ($CDCl_3$) δ: 4.54 (4H, s, CH_2O), 4.00 (6H, s, OMe), 3.46 (6H, s, CH_2OMe). UV λ_{max}^{EtOH} mμ (ε): 224 (7300), 322 (5245). *ts* 396 sec.

3,6-Dichloro-2,5-dimethylpyrazine (II) from Alanine Anhydride (XVIII)——As yields of II from XVIII were poor according to previous papers,[7,13] the reaction conditions were examined. The shorter the reaction time was, the more 5-chloro-3,6-dimethylpyrazin-2(1H)-one (XIX) was produced. The longer the time was, the more 3-chloro-2,5-dimethylpyrazine (XX) was obtained. Adding PCl_5 in $POCl_3$, yields of II was improved a little, accompanying more XXI. A reaction of XX with $POCl_3$ afforded solely XXI. Many attempts to improve the yields have resulted entirely in failure.

Acknowledgement The authors express their thanks to Mr. A. Nara, Kowa Co. Ltd., for elemental analysis.

12) G. Karmas and P.E. Spoerri, *J. Am. Chem. Soc.*, **79**, 680 (1957).
13) R.A. Baxter and F.S. Spring, *J. Chem. Soc.*, **1947**, 1179.