Studies on pyrazines. Part 34.[1] Synthetic approach, stability and tautomerism of 2,6-dihydroxypyrazines

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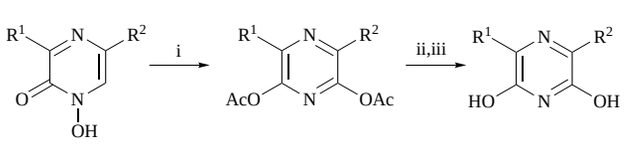
Demethylation of 2,6-dimethoxy-3,5-diphenylpyrazine with iodotrimethylsilane gives the corresponding 2,6-dihydroxy- and 2-hydroxy-6-methoxy-pyrazines, whilst the 3-methyl-5-phenyl analogue affords only monohydroxy compounds. In contrast, 2,6-dimethoxy-3,5-dimethylpyrazine decomposes completely under the demethylation conditions. Hydrolysis of 2,6-diacetoxypyrazines succeeds only in the formation of 2,6-dihydroxy-3,5-diphenylpyrazine. The stability of 2,6-dihydroxypyrazines is discussed on the basis of observations made in the synthetic approach. In addition, it has been established, on the basis of UV spectral analysis, that the 2-hydroxy-6-methoxypyrazines obtained in our work exist predominantly in the hydroxypyrazine form rather than as 1,2-dihydropyrazin-2-ones.

The stability and tautomerism of 2,6-dihydroxypyrazines have a particular interest for us. To our best knowledge, 2,6-dihydroxy-3,5-diphenylpyrazine[2] is the only known compound in this class, various efforts to prepare both the parent[3] and other alkyl or aryl derivatives[2,4] having been unsuccessful. The preparative failures are probably the result of the 2,6-dihydroxypyrazines having reduced stability. Previous reports[5–7] from our laboratory and others have described that the stability of related compounds, 2,5-dihydroxypyrazines, is strongly affected by the presence of other substituents; *i.e.* 3,6-dimethyl or 3,6-diphenyl derivatives were isolated with little difficulty, whilst the parent and monomethyl or phenyl pyrazines have resisted synthesis. Such a substituent effect is likely also to characterize the stability of 2,6-dihydroxypyrazines. One of our specific interests in this area is the tautomerism of 2,6-dihydroxypyrazines and 2-hydroxy-6-methoxypyrazines. In general, hydroxypyrazines in solution exist as their keto tautomers, namely 1,2-dihydropyrazin-2-ones.[8] A predominant tautomer of 2,6-dihydroxy-3,5-diphenylpyrazine was claimed to be the 6-hydroxy-1,2-dihydropyrazin-2-one[2] by comparison of its UV spectrum with that of 2,6-dimethoxy-3,5-diphenylpyrazine. Conversely, 2-chloro-6-hydroxy-3,5-diphenylpyrazine was shown to exist in the hydroxy form.[2] We are currently engaged in a program aimed at the synthesis of 3-methyl-5-phenyl- and 3,5-dimethyl-substituted 2,6-dihydroxypyrazines and 2-hydroxy-6-methoxypyrazines to elucidate their unusual properties.

The earlier synthesis of 2,6-dihydroxy-3,5-diphenylpyrazine **1a**[2] involves treatment of 1-hydroxy-3,5-diphenyl-1,2-dihydropyrazin-2-one **2a** with acetic anhydride–acetic acid followed by hydrolysis of the resulting 2,6-diacetoxypyrazine **3a** (Scheme 1).

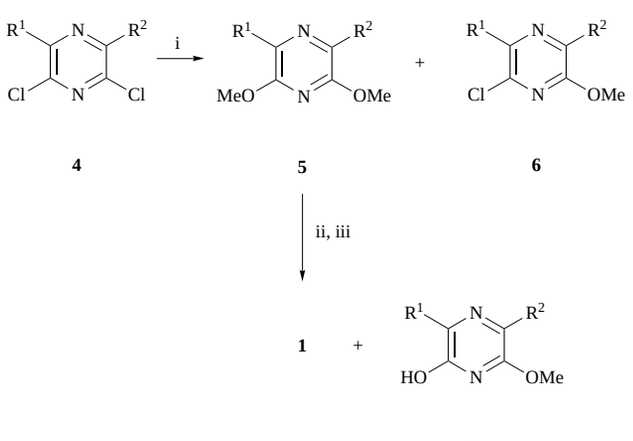


2 **3** **1**

1, 2, 3 **a** $R^1 = R^2$ = Ph
b R^1 = Ph, R^2 = Me
c $R^1 = R^2$ = Me

Scheme 1 *Reagents and conditions*: i, Ac_2O, AcOH; ii, $KHCO_3$, MeOH; iii, HCl, room temp.

This procedure, however, was shown to be of no use for the preparation of 2,6-dihydroxypyrazines possessing a 3- or 5-methyl group since the methyl substituent of **2** is acetylated to produce 2-acetoxy-3- or -5-acetoxymethylpyrazines.[2] Since, earlier, we had synthesized 3,6-disubstituted 2,5-dihydroxypyrazines by demethylation of 2,5-dimethoxypyrazines with iodotrimethylsilane,[6] we attempted to synthesize 2,6-dihydroxypyrazine **1a** in a similar way (Scheme 2). 2,6-Dichloro-3,5-



4 **5** **6**

1 + **7**

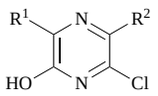
1, 4, 5, 6, 7 **a** $R^1 = R^2$ = Ph
b R^1 = Ph, R^2 = Me
c $R^1 = R^2$ = Me

Scheme 2 *Reagents and conditions*: i, NaOMe, MeOH; ii, Me_3SiI, MeCN; iii, H_2O, room temp.

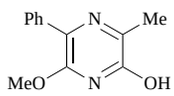
diphenylpyrazine **4a** was conveniently prepared together with a minor by-product, 2-chloro-6-hydroxypyrazine **8a**, by treatment of 1-hydroxy-1,2-dihydropyrazin-2-one **2a** with phosphoryl chloride at elevated temperature in a sealed reaction vessel. Reaction of **4a** with refluxing methanolic sodium methoxide gave dimethoxypyrazine **5a** and 2-chloro-6-methoxypyrazine **6a**.[4] Treatment of **5a** with iodotrimethylsilane in refluxing acetonitrile for 6 h, gave the desired 2,6-dihydroxypyrazine **1a** (39%) and partly dealkylated 2-hydroxy-6-methoxypyrazine **7a** (30%); 20% of the starting material was also recovered.

Our success in preparing dihydroxypyrazine **1a** prompted us to examine the synthesis of the 3-methyl-5-phenyl **1b** and 3,5-

dimethyl derivatives **1c**. Unlike dichloropyrazine **4a**, preparation of the 3-methyl-5-phenyl derivative **4b** was somewhat troublesome, *e.g.* 2-chloro-6-hydroxy-3-methyl-5-phenylpyrazine **8b**, prepared by controlled chlorination of readily acces-



8 **a** $R^1 = R^2 = Ph$
b $R^1 = Ph$, $R^2 = Me$



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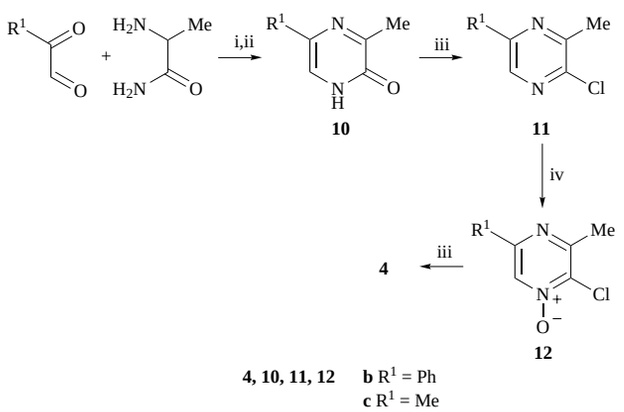
sible 1-hydroxy-5-methyl-3-phenyl-1,2-dihydropyrazin-2-one **2b**,[2] failed to undergo further chlorination with phosphoryl chloride at 175–185 °C and with recovery of only 25% of the starting material. However, the required dichloropyrazine **4b** was successfully synthesized by the reaction sequence shown in Scheme 3. Since the structure of 2-chloropyrazine 1-oxide **12b**



10 **11** **12** **4**

4, 10, 11, 12 **b** $R^1 = Ph$
c $R^1 = Me$

Scheme 3 *Reagents and conditions*: i, NaOH, MeOH, H_2O, −30 °C to room temp.; ii, HCl, room temp.; iii, $POCl_3$; iv, $K_2S_2O_8$, H_2SO_4, 10 °C to room temp.

was confirmed by X-ray analysis (Fig. 1), the possible formation of other isomers, arising from condensation and *N*-oxidation processes, was excluded. Reaction of **12b** with phosphoryl chloride at reflux smoothly proceeded to form, without chlorination of the side chain, the dichloropyrazine **4b** in excellent yield. Similarly, the formation of 2,6-dichloro-3,5-dimethylpyrazine **4c** was effected; identification of the intermediate chloropyrazine **11c** was established by comparison with the alternative, possible isomer, 2-chloro-3,6-dimethylpyrazine, which was unequivocally synthesized from 3,6-dimethylpiperazine-2,5-dione.[9]

Methoxylation of dichloropyrazine **4b** with methanolic sodium methoxide at reflux for 3.5 h gave 2,6-dimethoxypyrazine **5b**[4] in low yield (*ca.* 14%) together with the monomethoxylated products, 2-chloro-6-methoxypyrazine **6b** (79%) and 2-chloro-6-methoxy-3-methyl-5-phenylpyrazine (7%). The best yield of **5b** (85%) was obtained by heating the same reagents in a sealed tube at 126–127 °C for 18 h, although **6b** (3%) was still a contaminant. Separation of **5b** and **6b**, by recrystallization or Kugelrohr distillation proved difficult, whilst three cycles of HPLC development were necessary. Similarly, reaction of 2,6-dichloro-3,5-dimethylpyrazine **4c** with refluxing methanolic sodium methoxide for 6 h afforded mostly the monosubstituted product **6c** (68%), with little of the desired dimethoxy compound **5c** (5%). Interestingly, the desired substitution proceeded well in a system consisting of a crown ether and potassium methoxide to give the dimethoxypyrazine **5c** (78%) with little **6c** (9%). This procedure, however, failed to improve the yields of **5a** and **5b**.

Demethylation of dimethoxypyrazine **5b** with iodotrimethylsilane took longer than that of **5a**; *i.e.* even after 48 h under

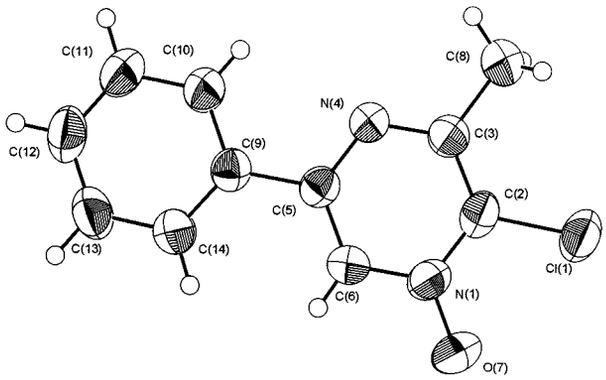
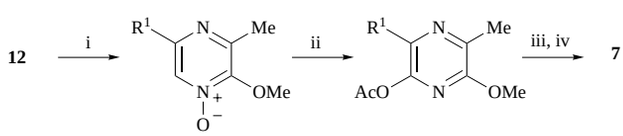


Fig. 1 X-Ray structure of compound **12b**

reflux, 44% of unchanged dimethoxypyrazine **5b** was still recovered; although two monohydroxy products **7b** and **9** were also obtained (*ca.* 20% each), the fully dealkylated product **1b** was absent. Under identical conditions, there was a 68% recovery of dimethoxypyrazine **5c**, none of the desired product being obtained. A comparison of the amounts of dimethoxypyrazines **5** recovered, suggests that the ability of the methoxy group to undergo cleavage decreases in the order: **5a** > **5b** > **5c**; this too is the order for the stability of the dealkylated products as judged by the product yields. Replacing iodotrimethylsilane with boron tribromide–methyl sulfide complex, a useful reagent for ether cleavage, failed to effect the necessary demethylation and gave almost quantitative recovery of the dimethoxypyrazine **5b**. To establish the structure of 2-hydroxy-6-methoxypyrazine **7b**, the compound was unambiguously synthesized as shown in Scheme 4; in this deoxidative acetoxylation led to



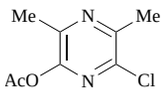
13 **14**

7, 12, 13, 14 **b** $R^1 = Ph$
c $R^1 = Me$

Scheme 4 *Reagents and conditions*: i, NaOMe, MeOH; ii, Ac_2O; iii, $NaHCO_3$, MeOH; iv, HCl, room temp.

formation of acetoxymethylpyrazines as well as the desired 2-acetoxy-6-methoxypyrazines **14**. An attempt to synthesize **7b** by treatment of 2-chloro-6-hydroxypyrazine **8b** with methanolic sodium methoxide in a sealed vessel at 126–127 °C gave recovery of starting material.

Taken together, the results for the various attempts to demethylate compound **5** suggest that the reaction conditions needed for ether cleavage are so severe as to result in decomposition, to a varying degree, of the initially formed 2,6-dihydroxypyrazines or other monohydroxypyrazines. Accordingly, we explored a synthetic method for the preparation of dihydroxypyrazine **1** under much milder conditions, namely deacetylation of 2,6-diacetoxypyrazines **3b** and **3c**; a successful hydrolysis of 2-acetoxy-6-methoxypyrazine **14c** had given 2-hydroxy-6-methoxypyrazine **7c** (Scheme 4), a compound not accessible by treating dimethoxypyrazine **5b** with iodotrimethylsilane. Although this procedure led to the preparation of **1a**, a drawback to it was the difficulty in preparing methyl substituted diacetoxypyrazines. A variety of synthetic approaches to **3** failed, *e.g.* by treating 2-acetoxy-6-chloro-3,5-dimethylpyrazine **15**, itself prepared by deoxidative acetoxylation of 2-chloropyrazine 1-oxides **12c**, with silver acetate or potassium acetate–crown ether. Consequently, compounds **3** were obtained, although in low yield (4–10%), by treating 1-hydroxy-1,2-dihydropyrazin-2-ones **2** with refluxing acetic anhydride–



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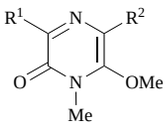

16 **a** $R^1 = R^2 = Ph$
b $R^1 = Ph$, $R^2 = Me$
c $R^1 = R^2 = Me$

acetic acid (Scheme 1). In addition to diacetoxypyrazine **3b**, 2-acetoxy-5-acetoxymethyl-3-phenylpyrazine and 2-acetoxy-5-methyl-3-phenylpyrazine were generated in modest yields. Formation of the latter compound was quite unexpected, in that it occurred as a result of deacetylation of the initially formed 1-acetoxy-1,2-dihydropyrazin-2-one, and subsequent acetylation of the resulting 1,2-dihydropyrazin-2-one, rather than by formation and successive deoxygenation of 2-acetoxypyrazine 1-oxide.

When diacetoxypyrazine **3b** was treated with potassium hydrogencarbonate in methanol at room temperature, it was completely consumed after 5 h, with the solution becoming dark greenish brown. As expected, the reaction yielded only tarry material upon work-up, the dihydroxypyrazine **1b** being neither isolated nor detected. On attempted deacetoxylation of **3c** under identical conditions, no product was detected nor starting material recovered, although the reaction mixture remained colourless. An attempt to hydrolyse **3c** with acidic ion-resin failed completely. In conclusion, since the 2,6-dihydroxypyrazines **1b** and **1c** could not be prepared, it is clear that the 2,6-dihydroxy isomer is far less stable than the 2,5-dihydroxy isomer, neither the dimethyl or methyl, phenyl substitutents having an effect on the stabilization. Since 2,5-dihydroxy-3,6-dimethylpyrazine decomposed even when carbon dioxide bubbled through an aqueous suspension,[7] it is likely that the instability described is a result of extreme susceptibility to acid or base.

A convenient method for the elucidation of hydroxypyrazine–pyrazinone tautomerism is by UV spectral analysis. For the purposes of comparison in studying 2,6-dihydroxy- and 2-hydroxy-6-methoxypyrazines, 2,6-dimethoxypyrazine **5** was needed as a proton-fixed tautomer, whilst 1-methyl-6-hydroxy-1,2-dihydropyrazin-2-one **16** was needed as the alternative type of structure. Treatment of 2-hydroxy-6-methoxypyrazine **7a** with ethereal diazomethane, however, afforded not the *N*-methylpyrazinone **16a** but only dimethoxypyrazine **5a** (24%), together with starting material **7a**. Similarly, compounds **16b** and **16c** were not accessible by treating the corresponding hydroxypyrazines **7** with diazomethane although a good deal of the starting material was consumed. Difficulties in preparing compounds **16** had been expected from the earlier lack of success in synthesizing **16a**,[2] *i.e.* 6-chloro-1-methyl-3,5-diphenyl-1,2-dihydropyrazin-2-one underwent facile displacement of the halogen with methoxide but further hydrolysis with hydrochloric acid upon work-up furnished 2-hydroxy-1-methyl-1,2-dihydropyrazin-2-one.

As shown in Table 1, the UV spectra of 2-hydroxy-6-methoxypyrazines **7** and **9** are closely similar to those of 2,6-dimethoxypyrazines **5**. Despite lack of the other pair of compounds **16** for comparison, it can, nevertheless, be concluded that in ethanol the hydroxy tautomers predominate: the spectra of proton-fixed tautomers **16** would be quite different from those of **5** as illustrated by published spectral data for *O*- and *N*-methylated derivatives of 2-chloro-6-hydroxypyrazines.[2] This conclusion is further supported by the spectra of **7b** and **9** which show absorption with almost identical maxima; this only occurs for compounds existing together in the hydroxy form. The spectrum of 2,6-dihydroxypyrazine **1a** shows four maximal absorptions, in which the shortest wavelength band was missed in the former study, and the longest one which was the evidence cited for the compounds being in the keto form.[2] However, no absorption >400 nm has been observed for pyrazine compounds excepting 1,2-dihydropyrazine-2-thiones;[10] further, the longest wavelength band in the spectrum of *N*-methylpyrazinone **16a** should appear in the 360–380 nm region, estimated on the basis of the absorption maxima for compounds **7** and **9** and 2-chloro-6-hydroxypyrazine derivatives.[2] With time, the UV spectrum of **1a** altered, the bands converging at 247, 305 and 413 nm. In view of the similarity of the three shorter wavelength bands in the spectrum of **1a** to those of dimethoxypyrazine **5a**, it seems most likely that 2,6-dihydroxypyrazine **1a** initially exists in the hydroxy form, but is gradually transformed into another compound whose structure as yet remains unidentified.

Table 1 UV spectra of the hydroxypyrazines **1**, **7**, **9** and 2,6-dimethoxypyrazines **5** in ethanol

Compd.	λ_{max}/nm (ε)
1a	227.0 (21 000), 274.5 (18 600), 349.5 (18 600), 416.5 (6100)
5a	230.5 (24 500), 276.0 (20 300), 343.0 (23 000)
7a	228.5 (19 700), 275.5 (15 800), 346.5 (18 400)
5b	258.0 (22 500), 326.5 (26 500)
7b	257.5 (13 900), 328.0 (17 100)
9	258.5 (13 900), 327.5 (16 900)
5c	224.0 (14 900), 311.0 (14 900)
7c	222.0 (11 800), 312.5 (12 300)

Experimental

Melting points were determined using a Büchi 535 apparatus and are uncorrected. Boiling points were oven temperatures for Kugelrohr distillation and are uncorrected. UV spectra were recorded on a Shimadzu UV-2100 spectrometer. NMR spectra were obtained with a JEOL JNM EX270 (270 MHz ^{1}H, 67.8 MHz ^{13}C) instrument with solutions in $CDCl_3$, unless otherwise noted, containing Me_4Si as internal standard. *J* Values are given in Hz. Column chromatography and preparative HPLC separation were performed using Silica Gel 60 and 10 μm SiO_2 (2.2 × 30 cm), respectively. Drying refers to drying over $MgSO_4$. Evaporation refers to evaporation under reduced pressure.

3-Methyl-5-phenyl-1,2-dihydropyrazin-2-one 10b

This compound was prepared by the procedure of Jones,[11] as needles, yield 33%; mp 225–226 °C (decomp.) (EtOAc) (lit.,[11] 212–213 °C) (Found: C, 71.0; H, 5.4; N, 15.0. $C_{11}H_{10}N_2O$ requires C, 71.0; H, 5.4; N, 15.0%); δ_H 2.59 (3H, s), 7.34–7.46 (3H, m), 7.61 (1H, s) and 7.77–7.80 (2H, m); δ_C 20.6, 119.8, 125.1, 128.0, 128.9, 134.4, 135.8, 156.9 and 157.5.

2-Chloro-3-methyl-5-phenylpyrazine 11b

A mixture of the pyrazinone **10b** (4.66 g, 25 mmol) and phosphoryl chloride (33 cm^3) in a sealed tube was heated at 170–175 °C for 18 h. The mixture was concentrated under reduced pressure, and the residue was poured into ice–water and extracted with $CHCl_3$ (3 × 150 cm^3). The combined extracts were washed with aqueous $NaHCO_3$ and then water, dried and evaporated. The residue was sublimed at 75–80 °C/1–2 mmHg giving the chloropyrazine **11b** (4.70 g, 92%) as needles; mp 77 °C (EtOH) (lit.,[4] 74–75 °C) (Found: C, 64.3; H, 4.5; N, 13.7. $C_{11}H_9N_2Cl$ requires C, 64.6; H, 4.4; N, 13.7%); δ_H 2.73 (3H, s), 7.48–7.51 (3H, m), 7.97–8.00 (2H, m) and 8.62 (1H, s); δ_C 22.4, 126.9, 129.1, 129.9, 135.5, 138.2, 147.1, 150.3 and 152.2.

Preparation of the 2-chloropyrazine 1-oxides 12

2-Chloro-3-methyl-5-phenylpyrazine 1-oxide 12b. Potassium persulfate (2.34 g, 8.65 mmol) was added to a mixture of chloropyrazine **11b** (1.59 g, 7.8 mmol) in concentrated sulfuric acid (15 cm^3) at <10 °C, and the mixture was stirred at room temperature for 24 h. It was then poured into ice–water and extracted with $CHCl_3$ (3 × 50 cm^3). The combined extracts were washed with aqueous $NaHCO_3$ and then water, dried and evap-

orated. The residue was chromatographed on silica (60 g; hexane–EtOAc, 4:1) to give recovery of the starting chloropyrazine (1.01 g, 63%). The following fraction afforded the *N*-oxide **12b** (0.386 g, 23%) as pale yellow needles; mp 142.5–143 °C (EtOH) (lit.,[4] 153–154 °C) (Found: C, 60.0; H, 4.1; N, 12.7. $C_{11}H_9N_2OCl$ requires C, 59.9; H, 4.1; N, 12.7%); δ_H 2.75 (3H, s), 7.50–7.52 (3H, m), 7.90–7.94 (2H, m) and 8.55 (1H, s); δ_C 22.9, 126.7, 129.1, 129.3, 130.7, 134.1, 152.0 and 155.4.

The melting point of the isomeric *N*-oxide, 3-chloro-2-methyl-6-phenylpyrazine 1-oxide, was reported as 141–142 °C.[4]

X-Ray crystallography. Single-crystal X-ray diffraction experiment on **12b**, prepared by recrystallization (20% v/v EtOAc–hexane) was carried out on a MAC Science MXC3k four-circle diffractometer with graphite-monochromatized Mo-Kα radiation ($\lambda = 0.710\ 73$ Å) and a ω–2θ scan technique. The structure was solved by direct methods (SIR 92) and refined on F by the full-matrix least-squares method. All the non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms found from the difference Fourier syntheses were included in the final refinement with the isotropic thermal parameters. The final R indices were $R = 0.043$ and $R_w = 0.047$ (weighting scheme, $\omega = \exp(10\ \sin^2\ \theta/\lambda^2)/[\sigma^2(F) + 0.0001F^2]$. The calculations were carried out using a SUN SPARK 10 work station (Crystan-GM program system provided by MAC Science).

Crystal data and structure refinement for **12b**.—Empirical formula = $C_{11}H_9N_2OCl$, formula weight = 220.50, $T = 298$ K, triclinic, $P\bar{1}$, $a = 7.056(4)$ Å, $b = 7.170(8)$ Å, $c = 11.032(5)$ Å, $\alpha = 76.24(6)°$, $\beta = 83.48(4)°$, $\gamma = 72.16(6)°$, $V = 515.6(7)$ Å^3, $Z = 2$, $d_c = 1.417$ Mg m^{-3}, absorption coefficient = 0.340 mm^{-1}, crystal size = 0.35 × 0.20 × 0.20 mm, θ_{max} for data collected = 26.47°, index ranges = $-9 \leqslant h \leqslant 8$, $-9 \leqslant k \leqslant 0$, $-14 \leqslant l \leqslant 13$, reflections collected = 2627, independent reflections = 2331, refinement method = full-matrix least-squares on F, data/parameters = 1458/172, goodness of fit on $F = 1.586$, final R indices [$I > 3.00\sigma(I)$] R 0.043, R_w 0.047, largest diff. peak and hole = 0.25 and −0.25 e Å^{-3}.

2-Chloro-3,5-dimethylpyrazine 1-oxide 12c. A mixture of chloropyrazine **11c**[12] (2.00 g, 14.0 mmol) in concentrated sulfuric acid (14 cm^3) was treated with potassium persulfate (4.0 g, 15 mmol) in the above manner. Chloroform extracts were evaporated, and the residue was recrystallized to give the *N*-oxide **12c** (1.69 g, 76%) as small prisms; mp 82–85 °C (hexane) (Found: C, 45.6; H, 4.5; N, 17.6. $C_6H_7N_2OCl$ requires C, 45.4; H, 4.5; N, 17.7%); δ_H 2.48 (3H, s), 2.65 (s) and 8.24 (1H, s); δ_C 21.1, 22.6, 131.2, 152.6 and 155.0.

Preparation of the 2,6-dichloropyrazines 4

2,6-Dichloro-3,5-diphenylpyrazine 4a. A mixture of 1-hydroxy-1,2-dihydropyrazin-2-one **2a** (5.28 g, 20 mmol) and phosphoryl chloride (30 cm^3) in a sealed tube was heated at 160–170 °C (bath temperature) for 20 h. The mixture was concentrated under reduced pressure, and the residual oil was poured into ice–water to which ether (100 cm^3) was then added. Undissolved material was filtered off and the filtrate was extracted with ether (3 × 200 cm^3). The combined extracts were washed with water, dried and evaporated to give dichloropyrazine **4a** (3.65 g, 56%). The mother liquor and the above undissolved material were combined and extracted with $CHCl_3$ (3 × 100 cm^3). The extract was washed with aqueous Na_2CO_3, and then water, dried and evaporated. The residue was chromatographed on silica (45 g:hexane–EtOAc, 4:1) to give **4a** (0.350 g) from the first elution. The combined products were sublimed at 120–140 °C/1–3 mmHg to afford colourless crystals (3.62 g, 60%), mp 95–97 °C (lit.,[4] 100–101 °C); δ_H 7.49–7.51 (6H, m) and 7.86–7.90 (4H, m); δ_C 128.3, 129.6, 129.9, 135.2, 142.8 and 150.4.

The second fraction provided 2-chloro-6-hydroxypyrazine **8a** (0.171 g, 3%) as pale yellow needles, mp 249–250 °C (EtOH) (lit.,[2] 244–246 °C); δ_H[$(CD_3)_2SO$] 7.47–7.54 (6H, m), 7.78–7.81 (2H, m), 8.14–8.17 (2H, m) and 13.0 (1H, br s); δ_C[$(CD_3)_2SO$] 128.0, 128.1, 128.5, 128.6, 129.1, 129.2, 134.9, 136.3 and 155.5.

2,6-Dichloro-3-methyl-5-phenylpyrazine 4b. A mixture of 2-chloropyrazine 1-oxide **12b** (0.663 g, 3.0 mmol) in phosphoryl chloride (9 cm^3) was stirred and heated at 80 °C (bath temperature) for 30 min. After being cooled, the mixture was poured into ice–water, neutralized with $NaHCO_3$ and extracted with $CHCl_3$ (3 × 30 cm^3). The combined extracts were washed with water, dried and evaporated. Kugelrohr distillation at 140–150 °C/30 mmHg of the residue gave an oil (0.665 g, 93%), which crystallized with time, mp 59–60 °C (lit.,[4] 58–59 °C); δ_H 2.70 (3H, s), 7.48–7.50 (3H, m), 7.76–7.78 (2H, m); δ_C 21.4, 128.3, 129.4, 129.7, 135.4, 142.4, 144.7, 150.3 and 150.7.

2,6-Dichloro-3,5-dimethylpyrazine 4c. A mixture of the *N*-oxide **12c** (0.951 g, 6.0 mmol) in phosphoryl chloride (10 cm^3) was gently heated and stirred until complete dissolution and then refluxed for 1.5 h. After this, the solution was concentrated under reduced pressure and the residual oil was poured into ice–water. The resulting precipitate was filtered off, and the filtrate and washings were neutralized with $NaHCO_3$ and extracted with $CHCl_3$ (4 × 30 cm^3). The combined extracts were washed with water, dried and evaporated. The residue was purified by chromatography on silica (20 g; hexane–EtOAc, 2:1). The combined products were distilled to give an oil (0.869 g, 82%); bp 68 °C/40 mmHg; δ_H 2.60 (6H, s); δ_C 21.1, 143.7 and 149.9.

Preparation of the 2,6-dimethoxypyrazines 5

2,6-Dimethoxy-3,5-diphenylpyrazine 5a. A mixture of the dichloropyrazine **4a** (0.151 g, 0.50 mmol) in methanolic sodium methoxide, prepared from Na (0.058 g, 2.5 mmol) in dry MeOH (3 cm^3), was stirred and refluxed for 5 h. The solution was evaporated to dryness, and the residue was extracted with ether (3 × 30 cm^3). The combined extracts were dried and concentrated under reduced pressure. Chromatography of the residue on Florisil (hexane–EtOAc, 2:1) and, successively, HPLC (hexane–EtOAc 9:1) gave 2-chloro-6-methoxypyrazine **6a** (0.042 g, 29%) as needles; mp 79–80 °C (hexane) (lit.,[2] 95–96 °C); δ_H 4.12 (3H, s), 7.44–7.49 (6H, m), 7.84–7.88 (2H, m) and 8.12–8.15 (2H, m); δ_C 54.6, 128.1, 128.2, 128.7, 129.1, 129.5, 134.8, 136.6, 140.2, 140.5, 143.5 and 155.3.

The second fraction furnished the dimethoxypyrazine **5a** (0.097 g, 66%) as needles, mp 98–99 °C (MeOH) (lit.,[2] 98–99 °C); δ_H 4.10 (6H, s), 7.54–7.48 (6H, m) and 8.12–8.16 (4H, m); δ_C 53.8, 127.9, 128.1, 128.5, 132.2, 136.2 and 154.8.

2,6-Dimethoxy-3-methyl-5-phenylpyrazine 5b. A mixture of the dichloropyrazine **4b** (0.560 g, 2.34 mmol) and methanolic sodium methoxide, prepared from Na (0.567 g, 25 mmol) and dry MeOH (20 cm^3), in a sealed tube was heated at 126–127 °C (bath temperature) for 18 h, after which the mixture was concentrated under reduced pressure. The residue was diluted with water and the solution was extracted with EtOAc (3 × 50 cm^3). The combined extracts were washed with water, dried and evaporated. After chromatography of the residue on Florisil (hexane–EtOAc, 9:1), HPLC was performed using hexane–EtOAc (49:1); the development was repeated twice more. The less polar fraction was identified as the dimethoxypyrazine **5b** (0.457 g, 85%) and formed needles, mp 60–61 °C (MeOH) (Found: C, 68.1; H, 6.2; N, 12.2. $C_{13}H_{14}N_2O_2$ requires C, 67.8; H, 6.1; N, 12.2%); δ_H 2.45 (3H, s), 4.01 (6H, s), 7.29–7.35 (3H, m), 7.40–7.45 (2H, m) and 7.95–7.99 (2H, m); δ_C 17.9, 53.4, 53.6, 127.6, 128.0, 128.4, 131.2, 132.9, 136.4, 154.4 and 155.3.

The more polar fraction was 2-chloro-6-methoxypyrazine **6b** (0.014 g, 3%) and formed prisms, mp 79–80 °C (hexane) (lit.,[4] 81–82 °C); δ_H 2.51 (3H, s), 4.04 (3H, s), 7.40–7.46 (3H, m) and 7.70–7.74 (2H, m).

2,6-Dimethoxy-3,5-dimethylpyrazine 5c. A mixture of dichloropyrazine **4c** (0.354 g, 2.0 mmol) and dicyclohexano-18-crown-6 (1.864 g, 5.0 mmol) under argon was treated with 0.1 mol dm^{-3} potassium methoxide solution (MeOH–C_6H_6,

1:9) (50 cm^3, 5.0 mmol), added *via* a syringe. The mixture was stirred under reflux for 8 h and then evaporated. The residue was treated with water (80 cm^3) after which it was extracted with ether (4 × 30 cm^3). The extracts were worked up in the manner described above. Florisil chromatography (hexane–EtOAc, 3:1) of the residue and then HPLC (hexane–EtOAc, 9:1) gave 2-chloro-6-methoxypyrazine **6c** (0.031 g, 9%), bp 85–90 °C/45 mmHg, which crystallized with time; mp 54–55.5 °C (Found: C, 48.6; H, 5.3; N, 16.1. $C_7H_9N_2OCl$ requires C, 48.7; H, 5.3; N, 16.2%); δ_H 2.42 (3H, s), 2.51 (3H, s) and 3.96 (3H, s); δ_C 18.4, 20.5, 54.1, 141.0, 141.2, 141.3 and 156.1.

The dimethoxypyrazine **5c** (0.263 g, 78%) was obtained from the second fraction; bp 98–100 °C/46 mmHg, which crystallized with time; mp 76–77 °C (Found: C, 57.3; H, 7.3; N, 16.7. $C_8H_{12}N_2O_2$ requires C, 57.1; H, 7.2; N, 16.7%); δ_H 2.35 (6H, s) and 3.94 (3H, s); δ_C 17.5, 53.3, 131.2 and 154.8.

Demethylation of the dimethoxypyrazines 5

2,6-Dihydroxy-3,5-diphenylpyrazine 1a and 2-hydroxy-6-methoxy-3,5-diphenylpyrazine 7a. The dimethoxypyrazine **5a** (0.292 g, 1.0 mmol) under argon was treated with MeCN (4 cm^3) and iodotrimethylsilane (0.341 cm^3, 2.4 mmol), added *via* a syringe. The mixture was stirred and refluxed for 6 h after which it was diluted with water (0.72 cm^3) and stirred for 30 min. The precipitate was filtered off and identified as the 2,6-dihydroxypyrazine **1a** by spectral comparison with an authentic sample. The filtrate was concentrated under reduced pressure, and a small amount of EtOAc was added to the residue. After refrigeration overnight, a second crop as small orange coloured needles, was filtered off (total 0.103 g, 39%), mp 238 °C (decomp.) (nitromethane) [lit.,[2] 258–259 °C (decomp.)]; δ_H[$(CD_3)_2SO$] 7.33–7.36 (2H, m), 7.42–7.48 (4H, m) and 8.12–8.14 (4H, d); δ_C[$(CD_3)_2SO$] 127.2, 127.7, 127.9, 129.1, 136.5 and 154.5.

The above filtrate was treated with EtOAc after which it was washed with aqueous $NaHSO_3$, aqueous $NaHCO_3$ and brine, and then dried and evaporated. Florisil chromatography (hexane–EtOAc, 4:1) of the residue followed by HPLC (hexane–EtOAc, 4:1) afforded the starting dimethoxypyrazine **5a** (0.060 g, 21%). A second fraction provided 2-hydroxy-6-methoxypyrazine **7a** (0.084 g, 30%) as yellow prisms, mp 149–150 °C (hexane) (Found: C, 73.4; H, 5.1; N, 9.75. $C_{17}H_{14}N_2O_2$ requires C, 73.4; H, 5.1; N, 10.1%); δ_H 4.02 (3H, s), 6.58 (1H, br s), 7.34–7.49 (6H, m) and 8.10–8.18 (4H, m); δ_C 54.2, 128.1, 128.2, 128.3, 128.7, 130.4, 134.4, 135.8, 135.9, 152.4 and 154.8.

2-Hydroxy-6-methoxy-5-methyl-3-phenylpyrazine 7b and 2-hydroxy-6-methoxy-3-methyl-5-phenylpyrazine 9. A mixture of the dimethoxypyrazine **5b** (0.115 g, 0.50 mmol) in MeCN (2 cm^3) was treated with iodotrimethylsilane (0.36 cm^3, 2.5 mmol) as described above except that the reaction was run for 48 h. After being quenched with water, the mixture was evaporated and the residue was diluted with EtOAc. The resulting solution was washed with aqueous $NaHSO_3$, aqueous $NaHCO_3$ and brine and then dried and evaporated. The residue was purified by Florisil chromatography (hexane–EtOAc, 4:1) and then subjected to HPLC (hexane–EtOAc, 4:1) to afford starting material (0.050 g, 44%) as the first fraction. The second fraction gave the hydroxypyrazine **7b** (19 mg, 18%) as prisms, mp 191.5–192 °C (hexane–propan-2-ol) (Found: C, 66.75; H, 5.6; N, 12.9. $C_{12}H_{12}N_2O_2$ requires C, 66.65; H, 5.6; N, 12.95%); δ_H 2.46 (3H, s), 3.94 (3H, s), 7.33–7.46 (3H, m) and 8.00–8.01 (2H, m); δ_C 18.0, 53.9, 127.8, 128.2, 128.3, 129.2, 135.3, 136.1, 152.0 and 155.5.

The more polar portion furnished the alternative hydroxypyrazine **9** (24 mg, 22%) as small prisms; mp 126–127 °C (hexane) (Found: C, 66.6; H, 5.7; N, 12.8. $C_{12}H_{12}N_2O_2$ requires C, 66.65; H, 5.6; N, 12.95%); δ_H 2.44 (3H, s), 3.92 (3H, s), 6.94 (1H, br s), 7.33–7.44 (3H, m) and 7.92–7.94 (2H, m); δ_C 17.7, 53.9, 127.9, 128.1, 128.2, 128.6, 131.2, 136.0, 153.4 and 154.4.

Preparation of the 2-methoxypyrazine 1-oxides 13

2-Methoxy-3-methyl-5-phenylpyrazine 1-oxide 13b. A mixture of the chloropyrazine *N*-oxide **12b** (0.086 g, 0.39 mmol) in methanolic sodium methoxide, prepared from Na (0.057 g, 2.5 mmol) and dry MeOH (65 cm^3), was stirred and heated at 50–65 °C (bath temperature) for 2.5 h, and then concentrated under reduced pressure. Water was added to the residue, and the resulting solution was extracted with EtOAc (3 × 30 cm^3). The combined extracts were washed with water, dried and evaporated. The residue was subjected to chromatography on silica (14 g; hexane–EtOAc, 2:1) to give starting material (0.018 g, 21%) from the first fraction. The second fraction afforded **13b** (0.065 g, 77%) as needles, mp 142 °C (MeOH) (Found: C, 66.7; H, 5.6; N, 12.9. $C_{12}H_{12}N_2O_2$ requires C, 66.65; H, 5.6; N, 12.95%); δ_H 2.61 (3H, s), 4.18 (3H, s), 7.47–7.49 (2H, m), 7.86–7.89 (3H, m) and 8.39 (1H, s); δ_C 19.4, 59.7, 126.6, 129.1, 129.5, 130.1, 134.9, 149.6 and 152.3.

2-Methoxy-3,5-dimethylpyrazine 1-oxide 13c. A mixture of the chloropyrazine *N*-oxide **12c** (0.317 g, 2.0 mmol) in methanolic sodium methoxide, prepared from Na (0.064 g, 2.8 mmol) and dry MeOH (5 cm^3), was refluxed and stirred for 2.5 h, after which it was worked up as described above. Evaporation of the extracts gave a crude product, which was recrystallized to afford needles (0.207 g, 67%), mp 88–91 °C (hexane) (Found: C, 54.8; H, 6.6; N, 18.2. $C_7H_{10}N_2O_2$ requires C, 54.5; H, 6.5; N, 18.2%); δ_H 2.42 (3H, s), 2.51 (3H, s), 4.10 (3H, s) and 7.85 (1H, s); δ_C 19.0, 20.9, 59.3, 131.2, 149.0, 149.7 and 151.7.

Preparation of the 2-acetoxy-6-methoxypyrazines 14

2-Acetoxy-6-methoxy-5-methyl-3-phenylpyrazine 14b. A mixture of the *N*-oxide **13b** (0.059 g, 0.27 mmol) in Ac_2O (1.0 cm^3) was refluxed and stirred for 1 h, and then concentrated under reduced pressure. Water was added to the residue, and the resulting solution was neutralized with $NaHCO_3$ and extracted with EtOAc (3 × 20 cm^3). The combined extracts were washed with water, dried and evaporated. The residue was purified by chromatography on silica (6 g, hexane–EtOAc, 4:1) to give acetate **14b** (0.047 g, 67%) as powder, mp 66–67 °C (Found: C, 65.2; H, 5.5; N, 10.75. $C_{14}H_{14}N_2O_3$ requires C, 65.1; H, 5.5; N, 10.85%); δ_H 2.23 (3H, s), 2.53 (3H, s), 3.99 (3H, s), 7.36–7.46 (3H, m) and 7.70–7.74 (2H, m); δ_C 18.7, 21.1, 54.3, 128.3, 128.39, 128.44, 135.7, 136.5, 142.1, 147.2, 156.4 and 168.6.

2-Acetoxy-6-methoxy-3,5-dimethylpyrazine 14c. A mixture of the *N*-oxide **13c** (0.284 g, 1.8 mmol) in Ac_2O (3.2 cm^3) was stirred and heated at 120 °C (bath temperature) for 2 h, and then worked up as described above. Evaporation of extracts gave a crude product, which was purified by Florisil chromatography (hexane–EtOAc, 3:1) and successively HPLC (hexane–EtOAc, 5:1) to provide **14c** (0.178 g, 50%), which crystallized with time, bp 130–133 °C/53 mmHg, mp 56–57 °C (Found: C, 55.3; H, 6.2; N, 14.2. $C_9H_{12}N_2O_3$ requires C, 55.1; H, 6.2; N, 14.3%); δ_H 2.33 (3H, s), 2.36 (3H, s), 2.44 (3H, s) and 3.92 (3H, s); δ_C 17.6, 18.5, 20.8, 54.0, 134.9, 141.3, 147.8, 155.8 and 168.5.

The second fraction afforded 2-acetoxymethyl-5-methoxy-6-methylpyrazine (0.134 g, 38%), bp 100 °C/30 mmHg, which crystallized with time, mp 50.5–51 °C (Found: C, 55.1; H, 6.2; N, 14.25. $C_9H_{12}N_2O_3$ requires C, 55.1; H, 6.2; N, 14.3%); δ_H 2.11 (3H, s), 2.48 (3H, s), 3.98 (3H, s), 5.12 (2H, s) and 7.99 (1H, s); δ_C 19.2, 20.8, 53.7, 64.6, 137.6, 141.1, 144.4, 158.5 and 170.6.

2-Acetoxy-6-chloro-3,5-dimethylpyrazine 15. A mixture of the chloropyrazine *N*-oxide **12c** (0.476 g, 3.0 mmol) in Ac_2O (4.5 cm^3) was stirred and heated at 120 °C (bath temperature) for 2.5 h, and then evaporated. Water was added to the residue, after which the mixture was neutralized with Na_2CO_3 and extracted with EtOAc (3 × 10 cm^3). The combined extracts were washed with water, dried, evaporated and Kugelrohr distilled to give the acetoxypyrazine **15** (0.436 g, 72%), which crystallized with time as pale yellow prisms; bp 85 °C/32 mmHg, mp 38–41 °C (Found: C, 47.7; H, 4.5; N, 13.8. $C_8H_9N_2O_2Cl$ requires C,

47.9; H, 4.5; N, 14.0%); δ_H 2.37 (3H, s), 2.43 (3H, s) and 2.63 (3H, s); δ_C 18.4, 20.7, 21.3, 142.7, 144.6, 149.4, 150.1 and 168.1.

Hydrolysis of the acetoxypyrazines 14

2-Hydroxy-6-methoxy-5-methyl-3-phenylpyrazine 7b. A mixture of the acetoxypyrazine **14b** (0.014 g, 0.05 mmol) in MeOH (1 cm^3) containing $NaHCO_3$ (7 mg) was refluxed and stirred for 30 min. After being cooled, the mixture was acidified to pH 3 with 1 mol dm^{-3} hydrochloric acid and evaporated. Water was added to the residue, and the solution was extracted with $CHCl_3$ (3 × 5 cm^3). The combined extracts were washed with water, dried and evaporated to give the hydroxypyrazine **7b** (12 mg, 100%), which was identical with the compound obtained by demethylation of **5b** on the basis of spectral evidence.

2-Hydroxy-6-methoxy-3,5-dimethylpyrazine 7c. A mixture of the acetoxypyrazine **14c** (0.196 g, 1.0 mmol) in MeOH (20 cm^3) containing $NaHCO_3$ (0.134 g, 1.6 mmol) was stirred under reflux for 30 min, and worked up as described above. Evaporation of the extracts gave a crude product, which was recrystallized from hexane containing a trace of propan-2-ol to provide **7c** (0.136 g, 88%) as a powder, mp 165–168 °C (decomp.) (Found: C, 54.8; H, 6.6; N, 18.1. $C_7H_{10}N_2O_2$ requires C, 54.5; H, 6.5, N, 18.2%); δ_H 2.37 (3H, s), 2.41 (3H, s), 3.85 (3H, s) and 7.28 (1H, br s); δ_C 17.3, 17.6, 53.7, 129.2, 133.3, 152.9 and 155.0.

Preparation of the 2,6-diacetoxypyrazines 3

2,6-Diacetoxy-3-methyl-5-phenylpyrazine 3b. A mixture of 1-hydroxy-1,2-dihydropyrazin-2-one **2b** (2.026 g, 0.010 mol) in a mixture of Ac_2O (30 cm^3) and AcOH (6 cm^3) was refluxed and stirred for 2 h, and then evaporated. Water was added to the residue and the mixture was extracted with EtOAc (3 × 20 cm^3). The combined extracts were washed with aqueous $NaHCO_3$ and water, dried and evaporated. The residue was chromatographed on silica (100 g; hexane–EtOAc, 1:5) to provide the diacetate **3b** (0.121 g, 4%) as the least polar fraction; mp 106–106.5 °C (hexane–propan-2-ol, 7:1) (Found: C, 63.0; H, 4.9; N, 9.7. $C_{15}H_{14}N_2O_4$ requires C, 62.9; H, 4.9; N, 9.8%); δ_H 2.22 (3H, s), 2.39 (3H, s), 2.55 (3H, s), 7.43–7.49 (3H, m) and 7.77–7.81 (2H, m); δ_C 18.7, 20.8, 21.0, 128.6, 129.5, 134.8, 144.7, 145.1, 147.7, 149.1, 167.9 and 168.0.

The second polar fraction afforded 2-acetoxy-5-acetoxymethyl-3-phenylpyrazine (0.687 g, 24%), mp 187 °C (toluene) (lit.,[2] 186–187 °C); δ_H 2.18 (3H, s), 2.26 (3H, s), 5.34 (2H, s), 7.47–7.49 (3H, m), 7.81–7.85 (2H, m) and 8.40 (1H, s).

The most polar fraction gave 2-acetoxy-5-methyl-3-phenylpyrazine (0.685 g, 30%), mp 110–112 °C (hexane–propan-2-ol, 5:1) (Found: C, 68.5; H, 5.3; N, 12.2. $C_{13}H_{12}N_2O_2$ requires C, 68.4; H, 5.3; N, 12.3%); δ_H 2.38 (3H, s), 2.41 (3H, s), 7.08 (1H, s), 7.43–7.45 (3H, m) and 8.30–8.34 (2H, m); δ_C 17.8, 19.8, 122.5, 128.0, 129.0, 130.3, 130.8, 135.4, 149.4, 154.6 and 165.7.

2,6-Diacetoxy-3,5-dimethylpyrazine 3c. A mixture of the 1-hydroxy-1,2-dihydropyrazin-2-one **2c** (1.401 g, 0.010 mol) in a mixture of Ac_2O (2.5 cm^3) and AcOH (7 cm^3) was stirred and heated at 90 °C (bath temperature) for 12.5 h. The mixture was worked up in the above described manner to give the crude diacetoxypyrazine **3c** which was purified by chromatography on Florisil (hexane–EtOAc, 1:1) followed by HPLC (hexane–EtOAc 2:1) to afford pale yellow needles (0.230 g, 10%), mp 91.5–94.5 °C (hexane) (Found: C, 53.6; H, 5.4; N, 12.5. $C_{10}H_{12}N_2O_4$ requires C, 53.6; H, 5.4; N, 12.5%); δ_H 2.36 (6H, s) and 2.45 (6H, s); δ_C 18.4, 20.7, 144.4, 148.6 and 168.0.

Later fractions furnished a mixture of unidentified products.

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