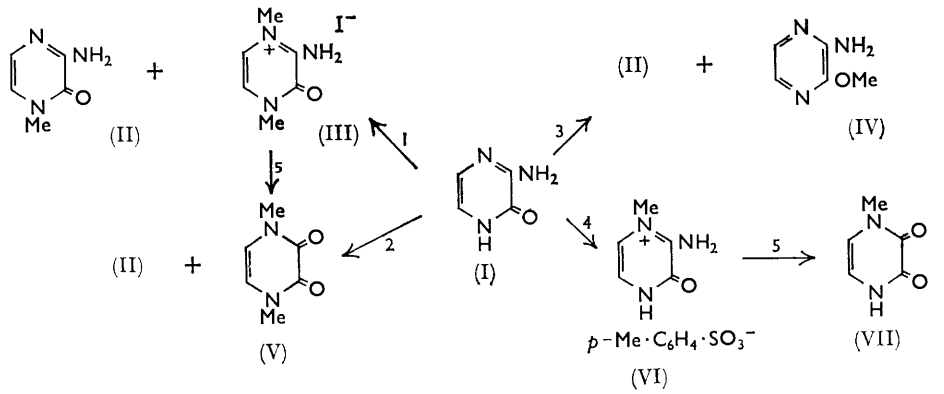
1241. *Pyrazines. Part II.*[1] *The Preparation and Reactions of 2,3-, 2,5-, and 2,6-Disubstituted Pyrazines*

By G. W. H. CHEESEMAN and E. S. G. TÖRZS

The reactions of 2-amino-3-hydroxy- and 2,3-dihydroxy-pyrazine with methylating reagents have been studied, and the nucleophilic displacement reactions of 2,6-disubstituted pyrazines with hydroxide and alkoxide ions investigated. One methoxyl group was displaced from 2,6-dimethoxypyrazine, and the benzyloxy-group from 2-benzyloxy-6-chloropyrazine, by mild treatment with aqueous ethanolic sodium hydroxide. Treatment of the latter compound with methanolic sodium methoxide resulted in the more usual displacement of chlorine.

THE present investigation was carried out partly as a result of our earlier interest in the reactions and tautomerism of 2- and 3-hydroxyquinoxalines [2] and partly because of the intrinsic interest of compounds such as 2-amino-3-hydroxy- and 2,3-dihydroxypyrazine which are isomeric with the important pyrimidines cytosine and uracil.

The reactions of 2-amino-3-hydroxypyrazine (I) with various methylating reagents were investigated. Treatment with methyl iodide and sodium methoxide gave the *N*-methyloxopyrazine (II), and when an excess of methyl iodide was used a mixture of compound (II) and the methiodide (III) was isolated. Reaction with methyl sulphate and alkali gave compound (II) and the *NN*-dimethyldioxopyrazine (V). The dimethyl



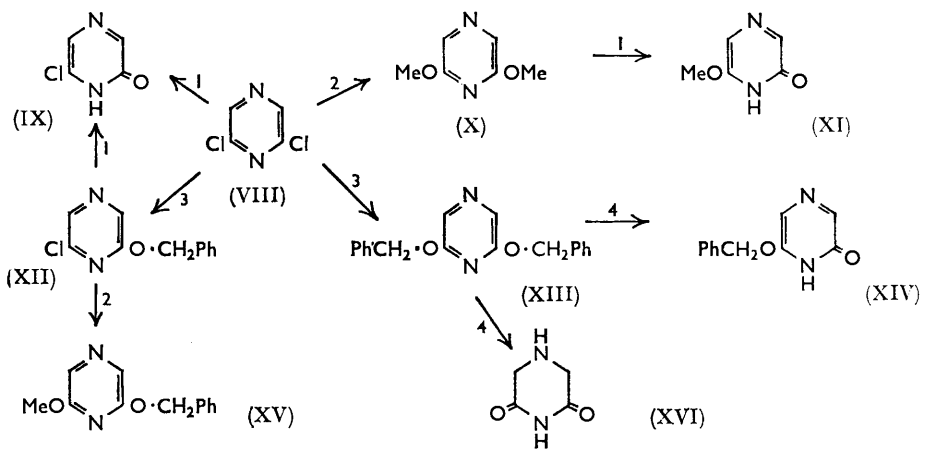
Reagents. 1, MeI–MeONa. 2, Me_2SO_4–NaOH. 3, CH_2N_2. 4, p-Me·C_6H_4·SO_3Me. 5, NaOH.

derivative was formed presumably as a result of hydrolysis of an intermediate quaternary salt, as it was also obtained by treatment of the methiodide (III) with aqueous sodium hydroxide. No product arising from a Dimroth-type rearrangement was isolated from this reaction. Reaction of 2-amino-3-hydroxypyrazine with ethereal diazomethane gave

[1] G. W. H. Cheeseman, *J.*, 1960, 242 is regarded as Part I.
[2] G. W. H. Cheeseman, *J.*, 1962, 1170, and earlier Papers.

the expected mixture of *N*- and *O*-methyl derivatives (II) and (IV) (see Table). With methyl toluene-*p*-sulphonate the quaternary salt (VI) was obtained, which on alkaline hydrolysis furnished the *N*-methyldioxopyrazine (VII). The latter compound was also isolated, in poor yield, from the reaction of compound (II) with nitrous acid. The corresponding reaction of 2-amino-3-hydroxypyrazine with nitrous acid gives 2,3-dihydroxypyrazine in good yield.[3] The dihydroxy-compound was converted into its *NN*-dimethyl derivative (V) by treatment with methyl sulphate and alkali, and gave, on reaction with excess of ethereal diazomethane, a mixture of its *NN*-, *ON*-, and *OO*-dimethyl derivatives (see Table). The reactions of 2-hydroxy-5-methoxy- and 2,5-dihydroxy-3,6-diphenylpyrazine with ethereal diazomethane were also carried out. The major product in each case was 2,5-dimethoxy-3,6-diphenylpyrazine. Careful chromatographic fractionation of the reaction mixtures revealed only minor amounts of *N*-methylated products (see Table). On heating 2,5-dimethoxy-3,6-diphenylpyrazine with methyl iodide at 150° for many hours, rearrangement to the isomeric *ON*-dimethyl pyrazine occurred.

2,6-Dichloropyrazine (VIII) is prepared conveniently either by reaction of 2-chloropyrazine with sulphuryl chloride [4] or by treatment of pyrazine 1,4-dioxide with phosphoryl chloride.[5] It was therefore employed as starting material for the preparation of various 2,6-disubstituted pyrazines. Reaction of 2,6-dichloropyrazine with excess of methanolic sodium methoxide gave 2,6-dimethoxypyrazine (X), but only one chlorine could be displaced by treatment with aqueous sodium hydroxide, presumably because of the resistance of the anion of (IX) to further nucleophilic attack. Reaction of 2,6-dimethoxypyrazine with sodium hydroxide gave 2-hydroxy-6-methoxypyrazine (XI). Stepwise displacement of the two chlorine atoms of 2,6-dichloropyrazine with the sodium salt of benzyl alcohol led to the preparation of 2-benzyloxy-6-chloropyrazine (XII) and 2,6-dibenzyloxypyrazine (XIII), respectively. The nucleophilic substitution reactions of 2-benzyloxy-6-chloropyrazine (XII) are of interest because 2-chloro-6-hydroxypyrazine (IX) was isolated from its reaction with aqueous ethanolic sodium hydroxide, and 2-benzyloxy-6-methoxypyrazine (XV) from its reaction with methanolic sodium methoxide. It is hoped to carry out a further study of these and related displacement reactions using chromatographic techniques.



Reagents. 1, NaOH. 2, MeONa. 3, $PhCH_2ONa$. 4, H_2—Pd/C.

Attempts to convert 2,6-dibenzyloxypyrazine (XIII) into 2,6-dihydroxypyrazine using a variety of acidic and alkaline reagents and also by treatment with hydrogen and a

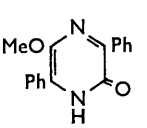
[3] M. S. Habib and C. W. Rees, *J.*, 1960, 3371.
[4] W. E. Taft, U.S.P. 2,797,219/1957 (*Chem. Abs.*, 1958, **52**, 460).
[5] B. Klein, N. E. Hetman, and M. E. O'Donnell, *J. Org. Chem.*, 1963, **28**, 1682.

palladium–charcoal catalyst were unsuccessful. 2-Benzyloxy-6-hydroxypyrazine (XIV) was obtained from reaction of 2,6-dibenzyloxypyrazine with 0·67 molar proportions of hydrogen and 2,6-dioxopiperazine was isolated from a reaction in which 2·0 molar proportions of hydrogen were consumed. 2-Hydroxy-6-methoxypyrazine (XI) was, however, obtained in good yield by debenzylation of 2-benzyloxy-6-methoxypyrazine (XV) with 1·0 molar proportion of hydrogen in the presence of a palladium–charcoal catalyst. The overall conversion of 2,6-dichloropyrazine into the known 2,6-dioxopiperazine [6] represents an independent proof of the structure of the dichloro-compound. This is valuable because the two methods used for its preparation do not give a product of unambiguous structure.

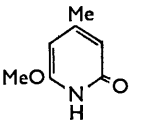
The methylation of 2-hydroxy-6-methoxypyrazine (XI) with ethereal diazomethane gave a mixture of *O*- and *N*-methyl derivatives in which the *O*-methyl derivative (X) predominated. The corresponding reaction with 2-hydroxy-6-benzyloxypyrazine gave almost exclusively the *O*-methyl derivative (XV). The results of our methylation reactions are summarised in the Table, where, following a recent review by Gompper,[7] the incidence of *O*- and *N*-methylation is correlated with carbonyl stretching frequency in the parent lactam. Gompper has shown that, with a wide variety of substrates, *O*-methyl-

Pyrazine	Methylation products	ν(CO) (cm.$^{-1}$)
2-Hydroxy-5-methoxy-3,6-diphenyl-	60%*O*; *ca.* 1·7%*N*	1640
2,5-Dihydroxy-3,6-diphenyl-	*ca.* 2·5%*O*; 22%*OO*; 7·5%*ON*	1640
2-Amino-3-hydroxy-	12%*O*; 44%*N*	1700
2,3-Dihydroxy-	*ca.* 2·5%*OO*; 24%*ON*; 9·5%*NN*	1700, 1650
2-Hydroxy-6-methoxy-	13·5%*O*; 6%*N*	1750, 1620
2-Hydroxy-6-benzyloxy-	95%*O*; *ca.* 2·5%*N*	1750, 1620

ation is favoured in lactams which exhibit carbonyl absorption in the region 1620—1680 cm.$^{-1}$; both *O*- and *N*-methylation is observed when the carbonyl absorption is in the region 1680—1720 cm.$^{-1}$, and *N*-methylation is preferred when the carbonyl absorption falls in the range 1730—1800 cm.$^{-1}$. The results of the first four methylation experiments are in accord with these generalisations, though with the 3,6-diphenyl compounds steric effects may also be important. The solid-state infrared spectra of 2-hydroxy-6-methoxypyrazine (XI) and 2-benzyloxy-6-hydroxypyrazine (XIV), like that of 2-hydroxypyrazine itself,[8] show two maxima in the amide-carbonyl region. Compounds (XI) and (XIV) exhibit a sharp band at 1620 cm.$^{-1}$ and a broad band centred near 1750 cm.$^{-1}$; this latter band is also prominent in the spectrum of 2-chloro-6-hydroxypyrazine (IX). As a single sharp



(XVII)



(XVIII)

amide-carbonyl band in the region of 1650 cm.$^{-1}$ is present in the spectra of 2-hydroxy-5-methoxy-3,6-diphenylpyrazine (XVII), the pyridine (XVIII),[9] and the *N*-methyl derivatives of compounds (XI), (XVII), and (XVIII), the assignment of the bands centred at 1750 cm.$^{-1}$ remains uncertain.

Experimental

Infrared spectra were measured on a Perkin-Elmer model 137 instrument, for liquid films, Nujol mulls, or potassium bromide discs. The identity of samples was confirmed by comparison of their infrared absorption.

Methylation of 2-Amino-3-hydroxypyrazine (I).—(a) *With methyl iodide.* Methyl iodide (6 ml., 0·096 mole) was added to a solution of 2-amino-3-hydroxypyrazine [10] (3·3 g., 0·03 mole) in methanolic sodium methoxide (prepared from 0·8 g. of sodium and 200 ml. of methanol),

[6] W. J. A. Jongkees, *Rec. Trav. chim.*, 1908, **27**, 287.
[7] R. Gompper, *Adv. Heterocyclic Chem.*, 1963, **2**, 245.
[8] S. F. Mason, *J.*, 1957, 4874.
[9] D. E. Ames, R. E. Bowman, and T. F. Grey, *J.*, 1953, 3008.
[10] F. L. Muehlmann and A. R. Day, *J. Amer. Chem. Soc.*, 1956, **78**, 242.

and the mixture was heated under reflux for 2 hr. After cooling, further methyl iodide (2 ml., 0·032 mole) was added, and the heating continued for 1 hr. Concentration of the resulting solution to *ca.* 25 ml. gave a product (4·5 g.), m. p. *ca.* 255—260°, which on fractional crystallisation from ethanol yielded the *methiodide* of 3-amino-1,2-dihydro-1-methyl-2-oxopyrazine (III) (2·7 g., 33%), m. p. 281—282°, and the parent *base* (II) (0·55 g., 11%), m. p. 167—169°. The m. p. of the methiodide was raised to 286—287° by two recrystallisations from methanol (Found: C, 27·1; H, 3·7; I, 48·5; N, 15·7. $C_6H_{10}IN_3O$ requires C, 27·0; H, 3·8; I, 47·5; N, 15·7%). A sample of 3-amino-1,2-dihydro-1-methyl-2-oxopyrazine (II), m. p. 172°, was obtained by two recrystallisations from ethanol (Found: C, 48·2; H, 5·5; N, 33·5. $C_5H_7N_3O$ requires C, 48·1; H, 5·6; N, 33·6%). Compound (II) was isolated in 35% yield from a similar experiment in which methyl iodide was used in only slight excess.

(b) *With methyl sulphate.* Freshly distilled methyl sulphate (10·1 g., 0·08 mole) was added slowly and with occasional shaking to an ice-cooled solution of 2-amino-3-hydroxypyrazine (3·3 g., 0·03 mole) in 10% sodium hydroxide (75 ml.). The reaction mixture was kept at room temperature overnight and then extracted continuously with chloroform. Evaporation of the dried (Na_2SO_4) extract gave a solid (1·4 g.) which furnished 1,2,3,4-*tetrahydro*-1,4-*dimethyl*-2,3-*dioxopyrazine* (V) (0·7 g., 17%), m. p. 250—253°, and 3-amino-1,2-dihydro-1-methyl-2-oxopyrazine (0·4 g., 11%), m. p. 158—160°, on fractional crystallisation from methanol. The m. p. of the dioxo-compound was raised to 257—259° by two recrystallisations from methanol (33 parts) (Found: C, 51·5; H, 5·7; N, 20·4. $C_6H_8N_2O_2$ requires C, 51·4; H, 5·75; N, 20·6%).

(c) *With diazomethane.* Diazomethane (from methylnitrosourea, 20·6 g.) in dry ether (100 ml.) was added dropwise at 0° to a stirred suspension of 2-amino-3-hydroxypyrazine (4·4 g., 0·04 mole) in dry methanol (75 ml.). The reaction mixture was stirred at 0° for 24 hr., then filtered, and insoluble material rejected. Evaporation of the filtrate gave a residue (4·5 g.) which on sublimation at 80—82°/0·4 mm. yielded 2-*amino*-3-*methoxypyrazine* (IV) (0·95 g.), m. p. 79—85°. Recrystallisation of the residue from the sublimation from benzene gave 3-amino-1,2-dihydro-1-methyl-2-oxopyrazine (2·2 g., 44%), m. p. 166—168°. The m. p. of the amino-methoxy-compound was raised to 85—86° by two recrystallisations from light petroleum (b. p. 40—60°) (42 parts) (Found: C, 48·0; H, 5·7; N, 33·2. $C_5H_7N_3O$ requires C, 48·1; H, 5·6; N, 33·6%).

Alkaline Decomposition of the Methiodide of 3-*Amino*-1,2-*dihydro*-1-*methyl*-2-*oxopyrazine* (III).—A mixture of the methiodide (1·35 g.) and 2N-sodium hydroxide (10 ml.) was kept at room temperature for 3 days. Repeated extraction with chloroform and evaporation of the combined and dried (Na_2SO_4) extracts gave 1,2,3,4-tetrahydro-1,4-dimethyl-2,3-dioxopyrazine (0·4 g., 57%), m. p. 248—256°.

Reaction of 2-*Amino*-3-*hydroxypyrazine and Methyl Toluene*-p-*sulphonate.*—A mixture of 2-amino-3-hydroxypyrazine (3·3 g., 0·03 mole) and methyl toluene-*p*-sulphonate (13·1 g., 0·072 mole) was heated at 150° for 15 min., then cooled, and extracted with benzene to remove excess of ester. Recrystallisation of the residue from ethanol (100 ml.) gave a fraction (1·6 g.) of m. p. *ca.* 180—240°, and concentration of the filtrate produced a fraction (6·4 g.) of m. p. *ca.* 180—195°. Repeated recrystallisation of the lower-melting fraction from ethanol yielded the *toluene*-p-*sulphonate* (VI) as crystals, m. p. 218—219° (Found: C, 48·4; H, 5·0; N, 14·1. $C_{12}H_{15}N_3O_4S$ requires C, 48·5; H, 5·1; N, 14·1%).

1,2-*Dihydro*-3-*hydroxy*-1-*methyl*-2-*oxopyrazine* (VII).—A mixture of the crude toluene-*p*-sulphonate (VI) (6·0 g.), m. p. *ca.* 180—195°, and 10% sodium hydroxide (15 ml.) was heated at 95° for 5 hr. The resulting solution was cooled, the pH adjusted to 4 with 2N-hydrochloric acid, and evaporated to dryness in a vacuum. The residue was extracted continuously (Soxhlet) with chloroform. Evaporation of the dried (Na_2SO_4) extract gave 1,2-*dihydro*-3-*hydroxy*-1-*methyl*-2-*oxopyrazine* (1·2 g., 48%), m. p. 230—232°. An analytical specimen, m. p. 233—234°, was prepared by recrystallisation from ethanol (33 parts) (Found: C, 47·5; H, 5·0; N, 22·1. $C_5H_6N_2O_2$ requires C, 47·6; H, 4·8; N, 22·2%). This compound was also prepared, in poor yield, by the action of nitrous acid on 3-amino-1,2-dihydro-1-methyl-2-oxopyrazine, similarly to 2,3-dihydroxypyrazine, below.

2,3-*Dihydroxypyrazine.*—The method of Habib and Rees [3] was modified as follows. A solution of sodium nitrite (6·2 g., 0·088 mole) in water (20 ml.) was added intermittently to a stirred solution of 2-amino-3-hydroxypyrazine (8·8 g., 0·08 mole) in 2N-hydrochloric acid

(120 ml.) at 0°. After the addition was complete (8 hr.), the resulting mixture was stirred at room temperature overnight and then refrigerated. The precipitate of 2,3-dihydroxypyrazine (5·5 g.) was filtered off and the filtrate treated similarly with another portion of sodium nitrite (2·1 g., 0·03 mole) in water (5 ml.). This gave an additional 0·9 g. of product (total yield 73%). Recrystallisation from water (66 parts) gave very pale yellow plates of 2,3-dihydroxypyrazine.

Methylation of 2,3-*Dihydroxypyrazine.*—(a) *With methyl sulphate.* Freshly distilled methyl sulphate (8·8 g., 0·07 mole) was added slowly to a stirred ice-cooled solution of 2,3-dihydroxypyrazine (2·2 g., 0·02 mole) in 10% sodium hydroxide (26 ml.). The reaction mixture was neutralised with potassium dihydrogen phosphate and then extracted repeatedly with chloroform. Evaporation of the combined and dried (Na_2SO_4) extracts yielded 1,2,3,4-tetrahydro-1,4-dimethyl-2,3-dioxopyrazine (0·9 g., 41%), m. p. 254—258°.

(b) *With diazomethane.* Diazomethane (from methylnitrosourea, 20·6 g.) in dry ether (100 ml.) was added dropwise at 0° to a stirred suspension of 2,3-dihydroxypyrazine (3·3 g., 0·03 mole) in dry methanol (50 ml.). The reaction mixture was stirred for 5 hr. at 0° and then at room temperature for 15 hr. After cooling to 0°, a second portion of ethereal diazomethane solution (from 10·3 g. of methylnitrosourea) was added. Stirring was continued for 6 hr. at 0°, and then for 15 hr. at room temperature. Ether and excess of diazomethane were removed under reduced pressure, and, on cooling the resulting solution, a precipitate (1·4 g.) m. p. 230—255°, crystallised out. This was filtered off and the filtrate evaporated to dryness at 20°/20 mm. Sublimation of the residue (1·7 g.) at 40—45°/0·5 mm. gave a small amount of 2,3-dimethoxypyrazine, which was characterised by its infrared spectrum and by conversion into 2,3-dihydroxypyrazine.[11] The residue from the sublimation was combined with the fraction of m. p. 230—235°. Sublimation of this mixture at 95—100°/0·6 mm. yielded 1,2-*dihydro*-3-*methoxy*-1-*methyl*-2-*oxopyrazine* (1·0 g., 24%), m. p. 135—137°. An analytical sample of m. p. 136—137° was prepared by recrystallisation from light petroleum (b. p. 80—100°) (200 parts) (Found: C, 51·5; H, 5·8; N, 20·2. $C_6H_8N_2O_2$ requires C, 51·4; H, 5·8; N, 20·0%). The residue from the sublimation, recrystallised from ethanol, gave 1,2,3,4-tetrahydro-1,4-dimethyl-2,3-dioxopyrazine (0·4 g., 9·5%), m. p. 254—256°.

Methylation of 2-*Hydroxy*-5-*methoxy*-3,6-*diphenylpyrazine* (XVII).—A distilled and dried solution of diazomethane (from 2·6 g. of methylnitrosourea) in ether (15 ml.) was added dropwise with stirring at 0° to a solution of 2-hydroxy-5-methoxy-3,6-diphenylpyrazine [11] (0·56 g., 0·002 mole) in freshly distilled tetrahydrofuran (20 ml.). The resulting mixture was stirred at 0° for 8 hr., then filtered, and the insoluble material rejected. The filtrate was evaporated and the residue dissolved in benzene (40 ml.). The solution was filtered through a column of silica gel, and the chromatogram developed first with benzene. This gave 2,5-dimethoxy-3,6-diphenylpyrazine (0·35 g., 60%) which was identified by its infrared spectrum. Elution was continued with ethyl acetate–benzene mixtures of increasing ethyl acetate content. 10% Ethyl acetate–benzene produced 1,2-*dihydro*-5-*methoxy*-1-*methyl*-2-*oxo*-3,6-*diphenylpyrazine* (0·01 g.), m. p. 183—185° (from methanol) (Found: C, 73·8; H, 5·5; N, 9·5; OCH_3, 10·5. $C_{18}H_{16}N_2O_2$ requires C, 74·0; H, 5·5; N, 9·6; OCH_3, 10·6%).

Methylation of 2,5-*Dihydroxy*-3,6-*diphenylpyrazine.*—A distilled and dried solution of diazomethane (from methylnitrosourea, 5·15 g.) in ether (40 ml.) was added dropwise with stirring at 0° to a suspension of 2,5-dihydroxy-3,6-diphenylpyrazine [11] (1·2 g., 0·0045 mole) in dry ether (100 ml.). The reaction mixture was stirred at 0° for 8 hr., then a second portion of ethereal diazomethane (from methylnitrosourea, 5·15 g.) was added. Stirring was continued at 0° for another 16 hr., then unreacted 2,5-dihydroxy-3,6-diphenylpyrazine (0·6 g.) and some polymeric material were filtered off. The filtrate was evaporated and the residue dissolved in benzene (500 ml.). The solution was filtered through a column of silica gel, and the chromatogram developed first with benzene. This gave 2,5-dimethoxy-3,6-diphenylpyrazine (0·13 g.). Elution with 2% ethyl acetate–benzene gave an additional 0·015 g. (total yield 22%), then 2-hydroxy-5-methoxy-3,6-diphenylpyrazine (0·015 g.), and finally 1,2-dihydro-5-methoxy-1-methyl-2-oxo-3,6-diphenylpyrazine (0·05 g.). The identity of the products was established by their infrared spectra. Further elution with 5% ethyl acetate–benzene produced some starting material (0·015 g.), and ethyl acetate–benzene mixtures of increasing ethyl acetate content gave small amounts of unidentified materials (total 0·04 g.).

[11] G. Karmas and P. E. Spoerri, *J. Amer. Chem. Soc.*, 1957, **79**, 680.

Rearrangement of 2,5-Dimethoxy-3,6-diphenylpyrazine with Methyl Iodide.—A mixture of the dimethoxy-compound (0·82 g.) and methyl iodide (15 ml.) was heated for 62 hr. at 150° in a sealed tube. The reaction mixture was evaporated in a vacuum, and water (10 ml.) added to the residue. The product was extracted into chloroform, and evaporation of the dried (Na_2SO_4) extracts gave an oily material (0·9 g.) which was dissolved in benzene (100 ml.). The solution was filtered through a column of silica gel; elution with benzene first removed some impurities (0·01 g.), then produced 1,2-dihydro-5-methoxy-1-methyl-2-oxo-3,6-diphenylpyrazine (0·18 g., 22%).

2,6-*Dichloropyrazine* (VIII).—This was prepared by the following modification of Taft's procedure.[4] A mixture of 2-chloropyrazine (8·0 g., 0·07 mole) and sulphuryl chloride (10·4 g., 0·077 mole) was heated in a sealed tube at 120° for 3 hr., then cooled and poured into ice–water. The reaction mixture was adjusted to pH 7, then distilled in steam. The first 75 ml. of distillate was collected, and, after cooling, the precipitate of 2,6-dichloropyrazine (7·5 g., 72·5%), m. p. 55—56° (lit.,[5] 51—53°), was filtered off and washed with light petroleum (b. p. 40—60°).

2,6-*Dimethoxypyrazine* (X).—2,6-Dichloropyrazine (2·96 g., 0·02 mole) was added to a solution of sodium methoxide (prepared from 2·3 g. of sodium and 45 ml. of methanol). The mixture was heated under reflux for 8 hr., cooled, and diluted with water (120 ml.). The product was isolated by repeated extraction with ether, and the combined organic extracts were dried (Na_2SO_4) and evaporated. The residual 2,6-dimethoxypyrazine (3·0 g., 93%) solidified. The product was further purified by distillation at 90—94°/40 mm., and had m. p. 48—49° (lit.,[12] m. p. 31—31·5° and 47°). The *picrate* had m. p. 127—130° (from methanol) (Found: N, 19·0. $C_{12}H_{11}N_5O_9$ requires N, 19·0%).

2-*Hydroxy-6-methoxypyrazine* (XI).—A solution of 2,6-dimethoxypyrazine (3·0 g., 0·022 mole) in ethanol (9 ml.) was added to a solution of sodium hydroxide (1·88 g., 0·047 mole) in water (18 ml.). The mixture was heated under reflux for 24 hr., cooled, and repeatedly extracted with ether. Evaporation of the combined and dried (Na_2SO_4) ethereal extracts yielded starting material (1·55 g.). The pH of the aqueous phase was adjusted to 5, and, after cooling, the precipitate of 2-*hydroxy-6-methoxypyrazine* (0·85 g., 67%), m. p. 190—195° (decomp.) (sealed tube), was filtered off. An analytical sample of unchanged m. p. was prepared by recrystallisation from nitromethane (150 parts) (Found: C, 47·3; H, 4·7; N, 22·45. $C_5H_6N_2O_2$ requires C, 47·6; H, 4·8; N, 22·2%).

2-*Chloro-6-hydroxypyrazine* (IX).—2,6-Dichloropyrazine (0·59 g., 0·004 mole) was added to a solution of sodium hydroxide (0·36 g., 0·09 mole) in water (10 ml.), containing freshly distilled tetrahydrofuran (2 ml.). The resulting mixture was stirred and heated under reflux for 4 hr., cooled, and acidified to pH 5 with hydrochloric acid. The precipitate of 2-*chloro-6-hydroxypyrazine* (0·48 g.) was filtered off and recrystallised from benzene or 50% ethanol. An analytical sample, sublimed at 115—120°/20 mm., had m. p. 200—205° (decomp.) (sealed tube) (Found: C, 37·2; H, 2·5; Cl, 27·1; N, 21·7. $C_4H_3ClN_2O$ requires C, 36·8; H, 2·35; Cl, 27·2; N, 21·5%).

2-Chloro-6-hydroxypyrazine was converted in low yield into 2,6-dichloropyrazine (m. p. 55—56°) by heating under reflux for 6 hr. with phosphoryl chloride. The bulk of the chloro-hydroxy-compound was recovered unchanged.

2-*Benzyloxy-6-chloropyrazine* (XII).—Sodium hydride (0·51 g., 0·021 mole) was added to freshly distilled benzyl alcohol (2·26 g., 0·021 mole) in benzene (20 ml.), and the mixture heated under reflux for 1 hr. The resulting solution was cooled and a solution of 2,6-dichloropyrazine (3·2 g., 0·021 mole) in benzene (20 ml.) added. The mixture was then heated under reflux for 24 hr., cooled, and washed with water. The benzene layer was separated, dried, and evaporated. Distillation of the residue at 136—138°/1·5 mm. gave crystals of 2-*benzyloxy-6-chloropyrazine* (2·75 g., 59%), m. p. 44—45° unchanged by sublimation at 80—82°/1·5 mm. (Found: C, 60·2; H, 3·9; Cl, 15·9; N, 12·8. $C_{11}H_9ClN_2O$ requires C, 59·9; H, 4·1; Cl, 16·1; N, 12·7%).

Alkaline Hydrolysis of 2-benzyloxy-6-chloropyrazine (XII).—A mixture of 2-benzyloxy-6-chloropyrazine (1·5 g., 0·007 mole), 96% ethanol (5 ml.), and 3·5N-sodium hydroxide (5 ml.) was heated under reflux with continuous stirring for 4½ hr., then acidified to pH 5 with 2N-hydrochloric acid. After refrigeration, the precipitate was filtered off, dried, and recrystallised from toluene (15 ml.). This gave 2-chloro-6-hydroxypyrazine (0·25 g., 28%), m. p. 195—200° (decomp.), identical with a sample prepared as described above. Ether extraction of the

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aqueous phase gave an impure solid which was sublimed at 80—82°/1·5 mm. to remove starting material. The infrared absorption of the residue indicated that it contained 2-benzyloxy-6-hydroxypyrazine.

2-*Benzyloxy*-6-*methoxypyrazine* (XV).—A mixture of 2-benzyloxy-6-chloropyrazine (1·25 g., 0·006 mole) and methanolic sodium methoxide (prepared from 0·14 g. of sodium and 20 ml. of methanol) was heated under reflux for 16 hr. with continuous stirring. The reaction mixture was then cooled, diluted with water, and repeatedly extracted with ether. The combined ethereal extracts were dried (Na_2SO_4) and evaporated, and distillation of the residue at 136—140°/40 mm. gave 2-*benzyloxy*-6-*methoxypyrazine* (0·32 g.) (Found: C, 67·2; H, 5·8; N, 12·8. $C_{12}H_{12}N_2O_2$ requires C, 66·7; H, 5·6; N, 13·0%).

2,6-*Dibenzyloxypyrazine* (XIII).—Sodium hydride (3·6 g., 0·15 mole) was added to freshly distilled benzyl alcohol (15·9 g., 0·15 mole) in benzene (25 ml.), and the mixture was heated under reflux for 1 hr. The resulting solution was cooled, and a solution of 2,6-dichloropyrazine (4·5 g., 0·03 mole) in benzene (25 ml.) added. The reaction mixture was heated under reflux for 24 hr., cooled, and washed with water. The benzene layer was separated, dried, and evaporated in a vacuum. Excess of benzyl alcohol was removed by distillation at *ca.* 100°/20 mm., and, on cooling, the residual 2,6-*dibenzoyloxypyrazine* (6·19 g., 70%), m. p. 60—63°, solidified. Recrystallisation from light petroleum (b. p. 30—40°) gave plates, m. p. 62—63° unchanged by recrystallisation from light petroleum (b. p. 30—40°) (25 parts) (Found: C, 74·1; H, 5·5; N, 9·7. $C_{18}H_{16}N_2O_2$ requires C, 74·0; H, 5·5; N, 9·6%).

Hydrogenation of 2-*Benzyloxy*-6-*methoxypyrazine* (XV).—5% Palladium–charcoal catalyst (0·1 g.) was added to a solution of 2-benzyloxy-6-methoxypyrazine (0·7 g., 0·0033 mole) in ethanol (20 ml.). The mixture was stirred in an atmosphere of hydrogen until 0·0033 mole of gas had been absorbed. The catalyst was then filtered off, washed well with ethanol, and the combined filtrate and washings were evaporated in a vacuum. The residual 2-hydroxy-6-methoxypyrazine (0·3 g., 71%) was identified by means of its infrared spectrum.

Hydrogenation of 2,6-*Dibenzyloxypyrazine* (XIII).—(a) *Conversion into* 2-*benzyloxy*-6-*hydroxypyrazine* (XIV). 5% Palladium–charcoal catalyst (1·0 g.) was added to a solution of 2,6-dibenzyloxypyrazine (2·92 g., 0·01 mole) in ethanol (50 ml.). The mixture was stirred in an atmosphere of hydrogen until 0·0067 mole of gas had been absorbed. The catalyst was then filtered off, washed well with ethanol, and the combined filtrate and washings were concentrated in a vacuum to about 30 ml. On cooling, a precipitate of 2-*benzyloxy*-6-*hydroxypyrazine* (0·5 g.) separated. Recrystallisation from benzene (230 parts) gave a pure specimen, m. p. 190—191° (decomp.) (sealed tube) (Found: C, 65·6; H, 5·1; N, 14·8. $C_{11}H_{10}N_2O_2$ requires C, 65·3; H, 5·0; N, 13·9%). Impure starting material (1·2 g.), m. p. 55—58°, was recovered by evaporation of the alcohol mother liquor.

(b) *Conversion into* 2,6-*dioxopiperazine* (XVI). 5% Palladium–charcoal catalyst (0·3 g.) was added to a solution of 2,6-dibenzyloxypyrazine (1·0 g., 0·0034 mole) in ethanol (25 ml.). The mixture was stirred in an atmosphere of hydrogen until 0·0068 mole of gas had been absorbed. The catalyst was then filtered off, washed well with ethanol, and the combined filtrate and washings were evaporated to dryness in a vacuum. The residue (0·15 g.) was purified first by recrystallisation from ethanol (20 ml.) and then by sublimation at 115—120°/0·8 mm. This gave 2,6-dioxopiperazine, m. p. 165—170° (decomp.) (sealed tube) (Found: C, 42·3; H, 5·3; N, 24·2. Calc. for $C_4H_6N_2O_2$: C, 42·1; H, 5·3; N, 24·6%), identical with a sample prepared by heating the ammonium salt of iminodiacetic acid.

Hydrogenation of 2-*Benzyloxy*-6-*hydroxypyrazine*.—A mixture of 2-benzyloxy-6-hydroxypyrazine (0·2 g.), 5% palladium–charcoal catalyst (0·1 g.), and ethanol (20 ml.) was stirred in an atmosphere of hydrogen until the absorption of gas ceased. Catalyst and solvent were then removed, and the residue (0·1 g.) identified as 2,6-dioxopiperazine by its infrared spectrum.

Methylation of 2-*Hydroxy*-6-*methoxypyrazine* (XI).—Diazomethane (from methylnitrosourea, 10·3 g.) in dry ether (50 ml.) was added dropwise at 0° to a stirred suspension of 2-hydroxy-6-methoxypyrazine (2·0 g., 0·015 mole) in dry methanol (25 ml.). The addition was completed in 1 hr., and the mixture stirred at 0° for a further 12 hr. Insoluble material was then filtered off, and the filtrate evaporated to dryness at 25—30°/20 mm. The syrupy residue was sublimed at 30—35°/20 mm., to give 2,6-dimethoxypyrazine (0·3 g., 13·5%), m. p. 48—49°. Further sublimation at 80—90°/20 mm. gave 1,2-*dihydro*-6-*methoxy*-1-*methyl*-2-*oxopyrazine* (0·08 g., 6%), m. p. 112—115° (decomp.) unchanged by sublimation at 80—85°/20 mm. (Found: C, 51·4; H, 5·6; N, 19·5. $C_6H_8N_2O_2$ requires C, 51·4; H, 5·8; N, 20·0%).

Methylation of 2-Benzyloxy-6-hydroxypyrazine (XIV).—Diazomethane (from methylnitrosourea, 10·3 g.) in dry ether (60 ml.) was added dropwise at 0° to a stirred solution of 2-benzyloxy-6-hydroxypyrazine (1·88 g., 0·009 mole) in freshly distilled tetrahydrofuran (40 ml.). The reaction mixture was stirred at 0° for 15 hr., filtered, and 0·1 g. of insoluble material rejected. The filtrate was evaporated to dryness in a vacuum and the residue dissolved in benzene (20 ml.). The solution was filtered through a column of silica gel, and the chromatogram developed with a 1% ethyl acetate–benzene mixture. This produced 2-benzyloxy-6-methoxypyrazine (1·9 g., 95%), which was identified by its infrared spectrum. Elution with 20% ethyl acetate–benzene produced a small amount of solid which was recrystallised from methanol. The infrared spectrum of this material showed bands at 3090 (*N*-Me), 1750 and 1660 (CO), 1215 (C–O–C, aromatic ether), and 730 and 700 cm.$^{-1}$ (monosubstituted phenyl group), which suggest that it is 6-benzyloxy-1,2-dihydro-1-methyl-2-oxopyrazine.

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