371. *Pyrazine Derivatives. Part VI. The Oxidation of 2-Ethoxy- and 2-Chloro-pyrazine Derivatives with Hydrogen Peroxide.*

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In a preliminary study of possible methods for the synthesis of aspergillic acid, a cyclic hydroxamic acid related to pyrazine, the oxidation of some pyrazine derivatives has been investigated. Oxidation of 2-chloro-3 : 6-dimethylpyrazine (VII) with hydrogen peroxide gives the corresponding 4-oxide (VIII) and similar oxidation of 2-ethoxy-3 : 6-dimethylpyrazine (X) gives the 4-oxide (IX). Oxidation at the 1-position does not occur and the 4-oxides resist oxidation at the 1-position. An interesting case of side-chain halogenation was observed, treatment of 2-ethoxy-3 : 6-dimethylpyrazine 4-oxide (IX) with phosphoryl chloride yielding 2-ethoxy-6-methyl-3-chloromethylpyrazine (XI).

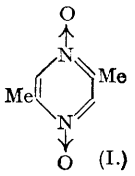
In Part IV (*J.*, 1947, 1183), we described the preparation of 2 : 5-dimethylpyrazine 1-oxide (VI) and 2 : 5-dimethylpyrazine 1 : 4-dioxide (I) and we showed that, when treated with phosphoryl chloride, they are converted into 2-chloro- (VII) and 2 : 5-dichloro-3 : 6-dimethylpyrazine (II), respectively. In Part III (*J.*, 1947, 1179) we showed that the mono- and di-chloro-3 : 6-dimethylpyrazines can be obtained by treatment of alanine anhydride with phosphoryl chloride.

An examination of the oxidation of 2-chloro- and 2-ethoxy-3 : 6-dimethylpyrazine was undertaken in the hope that a method might thereby be developed for the synthesis of a cyclic hydroxamic acid related to aspergillic acid (Newbold and Spring, *J.*, 1947, 373). Treatment of 2-chloro-3 : 6-dimethylpyrazine (VII) with hydrogen peroxide gives 2-*chloro*-3 : 6-*dimethylpyrazine* 4-*oxide* (VIII) and not the 1-oxide. Treatment of the 4-oxide with phosphoryl chloride yields 2 : 5-dichloro-3 : 6-dimethylpyrazine (II). The 4-oxide (VIII) is smoothly converted into 2-*ethoxy*-3 : 6-*dimethylpyrazine* 4-*oxide* (IX) when treated with sodium ethoxide. The 2-ethoxy-4-oxide (IX) is also obtained by oxidation of 2-ethoxy-3 : 6-dimethylpyrazine (X) with hydrogen peroxide; when treated with mineral acid it readily gave 2-*hydroxy*-3 : 6-*dimethylpyrazine* 4-*oxide* (XIII) which did not show the properties of a hydroxamic acid. Thus oxidation of a 2-chloro- or a 2-ethoxy-pyrazine derivative with hydrogen peroxide yields a 4-monoxide only, and the latter appears to resist further oxidation at the 1-position. The synthesis of a pyrazine cyclic hydroxamic acid by a direct oxidation of a 2-substituted pyrazine appears to be impracticable.

Reaction of 2-ethoxy-3 : 6-dimethylpyrazine 4-oxide (IX) with phosphoryl chloride yields a mixture of two products, easily separable by virtue of their different basicities. The non-basic component was identified as the expected 2-*chloro*-5-*ethoxy*-3 : 6-*dimethylpyrazine* (III). This compound is also obtained by treatment of 2 : 5-dichloro-3 : 6-dimethylpyrazine with sodium ethoxide using relatively mild reaction conditions, and on hydrolysis with dilute sulphuric acid it yields 2-chloro-5-hydroxy-3 : 6-dimethylpyrazine (IV).

The second product of the reaction between 2-ethoxy-3 : 6-dimethylpyrazine 4-oxide and phosphoryl chloride is 2-*ethoxy*-6-*methyl*-3-*chloromethylpyrazine* (XI), characterised by the

formation of a crystalline *hydrochloride*. When treated with sodium ethoxide it gives 2-*ethoxy*-6-*methyl*-3-*ethoxymethylpyrazine* (XII) and on hydrolysis with potassium hydroxide solution 2-*ethoxy*-6-*methyl*-3-*hydroxymethylpyrazine* is obtained. Attempted acid hydrolysis of 2-ethoxy-6-methyl-3-chloromethylpyrazine (XI) and of 2-ethoxy-6-methyl-3-ethoxymethylpyrazine (XII) was unsuccessful. The ultra-violet absorption spectra of (XI), (XII), and 2-ethoxy-6-methyl-3-hydroxymethylpyrazine are very similar to that of 2-ethoxy-3 : 6-dimethylpyrazine (see table). The substitution of hydrogen by halogen in a side chain of a heterocyclic compound *via* a *N*-oxide has previously been observed in the case of a quinoxaline *N*-oxide derivative (Newbold and Spring, this vol., p. 519), and we intend to determine whether this reaction is of general applicability.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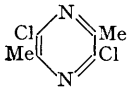
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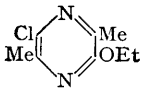
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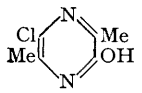
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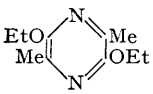
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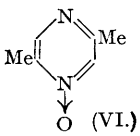
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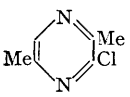
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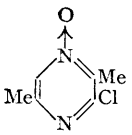
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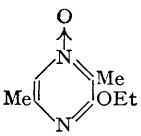
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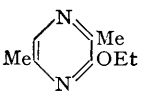
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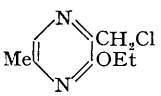
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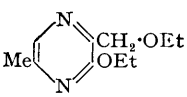
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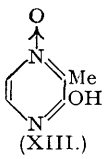
(XIII.)

The experiments described below were undertaken with the object of preparing a 2 : 5-dihydroxypyrazine derivative which was required in connection with an examination of a substance, $C_{12}H_{20}O_3N_2$, obtained together with aspergillic acid from culture filtrates of *Aspergillus flavus* (Menzel, Wintersteiner, and Rake, *J. Bact.*, 1943, **46**, 109). Such a 2 : 5-dihydroxypyrazine derivative would be of interest in that it is the simplest oxidation product of a diketopiperazine. Treatment of either 2-chloro-5-ethoxy-3 : 6-dimethylpyrazine (III) or 2 : 5-dichloro-3 : 6-dimethylpyrazine (II) with sodium ethoxide yields 2 : 5-*diethoxy*-3 : 6-*dimethylpyrazine* (V), which was recovered unchanged after prolonged heating with mineral acids. We have previously reported that drastic alkaline hydrolysis of 2 : 5-dichloro-3 : 6-dimethylpyrazine gives 2-chloro-5-hydroxy-3 : 6-dimethylpyrazine and not the 2 : 5-dihydroxy-derivative, and that fusion of 2-chloro-5-hydroxy-3 : 6-dimethylpyrazine with alkali gives 2-hydroxy-3 : 6-dimethylpyrazine.

In an alternative attempt to prepare 2 : 5-dihydroxy-3 : 6-dimethylpyrazine, we were

Absorption spectra.

(All determinations in ethanol solution.)

	Maxima A.	ε.
2-Chloro-5-ethoxy-3 : 6-dimethylpyrazine (III)	3040	9,200
2 : 5-Diethoxy-3 : 6-dimethylpyrazine (V)	3180	10,600
2-Ethoxy-3 : 6-dimethylpyrazine (X)	2980	8,400
2-Ethoxy-6-methyl-3-chloromethylpyrazine (XI)	2980	8,800
2-Ethoxy-6-methyl-3-ethoxymethylpyrazine (XII)	2970	8,400
2-Ethoxy-6-methyl-3-hydroxymethylpyrazine	2950	7,100
2-Hydroxy-3 : 6-dimethylpyrazine 4-oxide (XIII)	2250	15,200
	2720	6,200
	3270	4,800

unable to convert 2-chloro-5-hydroxy-3 : 6-dimethylpyrazine into 2-hydroxy-5-ethoxy-3 : 6-dimethylpyrazine. Whilst treatment of 2-chloro-5-ethoxy-3 : 6-dimethylpyrazine with dilute sulphuric acid yields 2-chloro-5-hydroxy-3 : 6-dimethylpyrazine, hydrolysis with concentrated

hydrochloric acid leads to rupture of the pyrazine ring and formation of DL-alanine. 2-Hydroxy-3 : 6-dimethylpyrazine couples with benzenediazonium chloride in alkaline solution to give 2-hydroxy-5-phenylazo-3 : 6-dimethylpyrazine (Gastaldi and Princevalle, *Gazzetta*, 1928, **58**, 679). When treated with sodium hydrosulphite (dithionite), this gives 2-*amino*-5-*hydroxy*-3 : 6-*dimethylpyrazine*, but attempts to convert this into 2 : 5-dihydroxy-3 : 6-dimethylpyrazine with nitrous acid were unsuccessful.

EXPERIMENTAL.

2-*Chloro*-3 : 6-*dimethylpyrazine* 4-*Oxide*.—A solution of 2-chloro-3 : 6-dimethylpyrazine (2·25 g.) in glacial acetic acid (10 c.c.) was treated with hydrogen peroxide (100-vol., 20 c.c.) and kept at 56° for 16 hours. The reaction mixture was concentrated (reduced pressure) and made alkaline by the addition of 20% potassium hydroxide solution. The solid was isolated by means of chloroform and crystallised from benzene–light petroleum (b. p. 60—80°), from which 2-*chloro*-3 : 6-*dimethylpyrazine* 4-*oxide* separated as needles, m. p. 113—115° (yield 65%). For analysis, it was sublimed at 100°/0·5 mm. (Found : C, 45·7; H, 4·2. $C_6H_7ON_2Cl$ requires C, 45·4; H, 4·4%).

2 : 5-*Dichloro*-3 : 6-*dimethylpyrazine*.—2-Chloro-3 : 6-dimethylpyrazine 4-oxide (0·6 g.) was added to phosphoryl chloride (6 c.c.), and the mixture heated under reflux for 15 minutes, then concentrated to one-third bulk and poured on crushed ice. After standing, the solid was collected and purified by sublimation at 70°/0·5 mm., 2 : 5-dichloro-3 : 6-dimethylpyrazine (0·2 g.) being obtained as needles, m. p. 70° either alone or when mixed with an authentic specimen.

2-*Ethoxy*-3 : 6-*dimethylpyrazine* 4-*Oxide*.—(*a*) A solution of 2-chloro-3 : 6-dimethylpyrazine 4-oxide (0·3 g.) in dry ethanol was added to one of sodium ethoxide in ethanol (from 0·25 g. of sodium and 10 c.c. of ethanol), and the mixture heated under reflux for 5 hours. The product isolated in the usual manner was purified by sublimation at 90°/0·5 mm., 2-*ethoxy*-3 : 6-*dimethylpyrazine* 4-*oxide* being obtained as needles, m. p. 92—94° (Found : C, 56·9; H, 6·8; N, 16·5. $C_8H_{12}O_2N_2$ requires C, 57·1; H, 7·1; N, 16·7%).

(*b*) A solution of 2-ethoxy-3 : 6-dimethylpyrazine (2·5 g.) in acetic acid (10 c.c.) was oxidised with hydrogen peroxide, the method described above being used. The oxide (2·55 g.) was obtained as needles, m. p. 92—94° either alone or when mixed with a specimen obtained by method (*a*).

2-*Hydroxy*-3 : 6-*dimethylpyrazine* 4-*Oxide*.—2-Ethoxy-3 : 6-dimethylpyrazine-4-oxide (0·5 g.) in hydrochloric acid (10 c.c.; 3N) was heated under reflux for 3 hours. The solution was concentrated (reduced pressure), and the solid (210 mg.) collected. Crystallisation from ethanol (charcoal) gave 2-*hydroxy*-3 : 6-*dimethylpyrazine* 4-*oxide* as prismatic needles which decomposed above 250°; for analysis it was sublimed at 190°/0·001 mm. It does not give a colour with ferric chloride and does not exhibit acidic properties (Found : C, 51·7; H, 6·0. $C_6H_8O_2N_2$ requires C, 51·4; H, 5·7%).

2-*Chloro*-5-*ethoxy*-3 : 6-*dimethylpyrazine*.—(*a*) A solution of 2 : 5-dichloro-3 : 6-dimethylpyrazine (2 g.) in ethanolic sodium ethoxide (from 1 g. of sodium and 25 c.c. of ethanol) was refluxed for 8 hours. The excess of alcohol was removed by distillation, and the residue diluted with water (50 c.c.) and extracted with ether. The dried (Na_2SO_4) extract was evaporated, the oily product (1·6 g.) solidifying on standing. 2-*Chloro*-5-*ethoxy*-3 : 6-*dimethylpyrazine*, b. p. 65°/1 mm., was purified by sublimation, being obtained as needles, m. p. 30° (Found : C, 51·7; H, 5·9. $C_8H_{11}ON_2Cl$ requires C, 51·5; H, 5·9%).

(*b*) 2-Ethoxy-3 : 6-dimethylpyrazine 4-oxide (2·5 g.) was added to phosphoryl chloride (15 c.c.), and the mixture gradually heated and finally refluxed for 10 minutes. The cooled reaction mixture was poured on ice (100 g.) and stirred, the temperature being kept below 5°. The solid was filtered off (filtrate A), and after drying was purified by sublimation at 30°/10^{-4} mm., 2-chloro-5-ethoxy-3 : 6-dimethylpyrazine being obtained as needles (0·93 g.), m. p. 30° either alone or when mixed with the specimen obtained by method (*a*).

2-*Chloro*-5-*hydroxy*-3 : 6-*dimethylpyrazine*.—2-Chloro-5-ethoxy-3 : 6-dimethylpyrazine (0·25 g.) was heated for 16 hours with 6N-sulphuric acid (10 c.c.). The cold solution was extracted with ether, and the dried extract evaporated, 2-chloro-5-hydroxy-3 : 6-dimethylpyrazine being obtained; after crystallisation from ethanol, it formed needles, m. p. 222—224° not depressed by an authentic specimen (Part III, *loc. cit.*).

DL-*Alanine*.—A solution of 2-chloro-5-ethoxy-3 : 6-dimethylpyrazine (1 g.) in ethanol (5 c.c.) and concentrated hydrochloric acid (15 c.c.) was refluxed for 16 hours. The solution was evaporated to dryness, and a crystalline solid was obtained which was very soluble in water, the solution giving an acid reaction. An excess of an ammoniacal solution of silver nitrate was added to an aqueous solution of the solid, and the precipitated silver chloride and oxide removed by filtration. The filtrate was treated with hydrogen sulphide and the precipitated silver sulphide removed by filtration. Evaporation of the solution yielded a crystalline solid which, after recrystallisation from water, yielded DL-alanine as needles, m. p. 274—276° either alone or when mixed with an authentic specimen (Found: C, 40·8; H, 7·75. Calc. for $C_3H_7O_2N$: C, 40·45; H, 7·9%).

2-*Ethoxy*-6-*methyl*-3-*chloromethylpyrazine*.—The filtrate A (above) was neutralised by addition of solid sodium carbonate and extracted with ether. The dried (Na_2SO_4) extract was evaporated, and the residual oil distilled to give a colourless mobile oil (1·2 g.), b. p. 65°/0·5 mm. Redistillation gave 2-*ethoxy*-6-*methyl*-3-*chloromethylpyrazine* as a colourless oil, b. p. 106°/10 mm., $n_D^{18°}$ 1·5235 (Found : C, 51·7; H, 6·1. $C_8H_{11}ON_2Cl$ requires C, 51·5; H, 5·9%). The *hydrochloride*, obtained by passing dry hydrogen chloride into a dry ethereal solution of the base, separated as colourless needles, which, after sublimation at 100°/0·5 mm., had m. p. 115°. It is decomposed by water with regeneration of the base (Found : C, 43·3; H, 5·3. $C_8H_{11}ON_2Cl,HCl$ requires C, 43·05; H, 5·4%).

2-*Ethoxy*-6-*methyl*-3-*ethoxymethylpyrazine*.—2-Ethoxy-6-methyl-3-chloromethylpyrazine (0·6 g.) was treated with ethanolic sodium ethoxide (from 0·4 g. of sodium and 15 c.c. of ethanol), and the mixture heated in a sealed tube for 6 hours at 130—135°. The reaction product was isolated by means of ether,

and after distillation gave 2-*ethoxy*-6-*methyl*-3-*ethoxymethylpyrazine* as a colourless oil (0·5 g.), b. p. 112°/10 mm., $n_D^{18°}$ 1·4950 (Found: C, 61·6; H, 8·1. $C_{10}H_{16}O_2N_2$ requires C, 61·2; H, 8·2%). The *chloroplatinate* separated from methanol as orange-coloured prismatic needles, m. p. 170° (decomp.) [Found: Pt, 24·5, 24·35. $(C_{10}H_{16}O_2N_2)_2,H_2PtCl_6$ requires Pt, 24·3%].

2 : 5-*Diethoxy*-3 : 6-*dimethylpyrazine*.—A solution of 2-chloro-5-ethoxy-3 : 6-dimethylpyrazine (0·45 g.) in ethanolic sodium ethoxide (from 0·5 g. of sodium and 10 c.c. of ethanol) was heated in a sealed tube at 140° for 12 hours. The ethanol was removed by distillation, and the residue treated with water. The solid (0·3 g.) which separated as blades, m. p. 75—78°, was purified by sublimation at 70°/0·01 mm., 2 : 5-*diethoxy*-3 : 6-*dimethylpyrazine* being obtained as a crystalline mass, m. p. 79—80°. This base was also obtained in 60% yield by heating 2 : 5-dichloro-3 : 6-dimethylpyrazine with ethanolic sodium ethoxide for 8 hours at 150° (Found: C, 61·3; H, 8·3. $C_{10}H_{16}O_2N_2$ requires C, 61·2; H, 8·2%).

2-*Ethoxy*-6-*methyl*-3-*hydroxymethylpyrazine*.—2-Ethoxy-6-methyl-3-chloromethylpyrazine (1·0 g.) in dioxan (2 c.c.) was heated under reflux with potassium hydroxide solution (20%; 5 c.c.) for 14 hours. The cooled mixture was extracted with ether, and the dried (Na_2SO_4) extract evaporated. The residue was distilled at 0·001 mm.; the fraction distilling at a bath temperature of 100° (200 mg.) solidified on standing. Crystallisation from light petroleum (b. p. 60—80°) at −20°, followed by sublimation at 40°/0·0001 mm., gave 2-*ethoxy*-6-*methyl*-3-*hydroxymethylpyrazine* as needles, m. p. 45—46°. It is very soluble in water and the common organic solvents (Found: C, 57·45; H, 7·4. $C_8H_{12}O_2N_2$ requires C, 57·1; H, 7·1%).

2-*Amino*-5-*hydroxy*-3 : 6-*dimethylpyrazine*.—A suspension of 2-hydroxy-5-phenylazo-3 : 6-dimethylpyrazine (0·15 g.) in sodium hydroxide solution (2N; 10 c.c.) was treated with sodium hydrosulphite (dithionite) (0·6 g.), and the mixture boiled. When solution was complete, the mixture was evaporated to half bulk under reduced pressure, acidified with acetic acid, and evaporated to dryness. The residue was dried in a vacuum over phosphoric oxide and then extracted with benzene (Soxhlet). Concentration of the benzene extract gave 2-*amino*-5-*hydroxy*-3 : 6-*dimethylpyrazine* which, after two recrystallisations from ethanol–benzene, separated as small yellow needles, m. p. 225—230° (decomp.) (Found: C, 51·9; H, 6·6; N, 29·7. $C_6H_9ON_3$ requires C, 51·8; H, 6·5; N, 30·2%).

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