47. *The Synthesis and Tautomerism of Some 2-Substituted Pyrazines.*

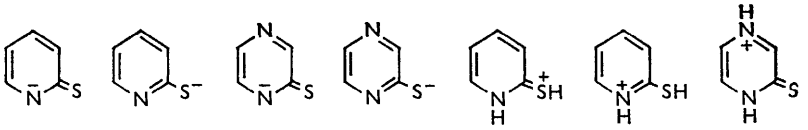
By G. W. H. Cheeseman.

Various replacement reactions with 2-chloropyrazine have been carried out, and the ionisation and ultraviolet absorption properties of 2-hydroxy-, 2-mercapto-, and 2-amino-pyrazine have been compared with those of their " fixed " methylated tautomers.

The pyrazine syntheses described in this paper were based on 2-hydroxypyrazine. This was converted in excellent yield into 2-chloropyrazine which underwent replacement reactions with ammonia,[1] methylamine, dimethylamine, sodium hydrogen sulphide, and sodium methoxide [2] to give the required 2-substituted pyrazines. 2-Chloropyrazine failed to react with thiourea in conditions in which 2-chloroquinoxaline reacted.[3]

Although 2-mercaptopyrazine was purified satisfactorily by vacuum-sublimation, at atmospheric pressure it melted with decomposition and evolution of hydrogen sulphide. Di-2-pyrazinyl sulphide was identified as a product of decomposition; this compound was also obtained, together with 2-mercaptopyrazine, from the reaction of approximately equimolecular quantities of 2-chloropyrazine and potassium hydrogen sulphide in water at 100°. Oxidation of 2-mercaptopyrazine with iodine and alkali gave di-2-pyrazinyl disulphide, and methylation with methyl iodide and alkali gave 2-methylthiopyrazine. 1,2-Dihydro-1-methyl-2-oxopyrazine, obtained by treatment of 2-hydroxypyrazine with methyl sulphate and alkali, was converted into the corresponding sulphur derivative by phosphorus pentasulphide in pyridine.* The reaction of both 2-amino- and 2-dimethylamino-pyrazine with methyl iodide in methanol, probably gave mixtures of methiodides. The major components of these mixtures were readily separated by crystallisation and thus pure monomethiodides of 2-amino- and 2-dimethylamino-pyrazine were obtained.

Comparison of the ionisation [2] and spectral properties [4] of 2-hydroxypyrazine and its *O*- and *N*-methyl derivatives (Table) indicated that in aqueous solution the amide form was the predominant tautomer. Similarly the basic strengths and ultraviolet absorption properties of the neutral molecule and cation of 2-mercaptopyrazine and its *N*-methyl derivative differed from those of 2-methylthiopyrazine (Table and Fig. 1). This indicated that in aqueous solution 2-mercaptopyrazine existed mainly in the thioamide form. Neutral solutions of 2-mercaptopyrazine decolorised slowly on standing; in strongly acidic media the decomposition of 2-mercaptopyrazine was comparatively rapid.



(IA) (IB) (IIA) (IIB) (IIIA) (IIIB) (IV)

2-Mercaptopyridine shows marked hypsochromic shifts on passing from neutral to either basic or acidic solution.[5] In the case of 2-mercaptopyrazine anion formation is accompanied by hypsochromic shifts, and cation formation by bathochromic shifts. Analogous canonical structures may be written for the anions of 2-mercaptopyridine (IA) and (IB) and 2-mercaptopyrazine (IIA) and (IIB). Protonation of 2-mercaptopyridine gives the

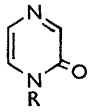
* During the course of this investigation Professor A. Albert and Dr. G. B. Barlin kindly informed the author that they had prepared 2-mercaptopyrazine and its *N*- and *S*-methyl derivatives.

[1] Erickson and Spoerri, *J. Amer. Chem. Soc.*, 1946, **68**, 400.
[2] Albert and Phillips, *J.*, 1956, 1294.
[3] Wolfe, Wilson, and Tishler, *J. Amer. Chem. Soc.*, 1954, **76**, 2266.
[4] Mason, *J.*, 1959, 1253.
[5] Jones and Katritzky, *J.*, 1958, 3610.

mesomeric cation (IIIA) and (IIIB). The basic centre of 2-mercaptopyrazine is presumably position 4, giving the cation (IV).

The wavelengths of the first and the second absorption maxima of the different species of 2-mercaptopyrazine (neglecting the effect of methyl substitution) follow the sequence, cation > thioamide > anion > thiol. This sequence is also observed for the long-wavelength maxima of the corresponding species of 2-hydroxypyrazine and is in accord with a molecular-orbital theory developed by Mason.[4] The sequence for the second absorption maxima, also predicted by this theory, is anion > cation > amide > enol.

2-Mercaptopyrazine has some anti-thyroid activity;[6] it has also been tested for anti-tumour activity, and the results will be published elsewhere.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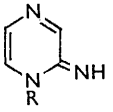
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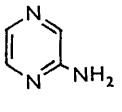
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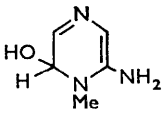
(VIII)

A similarity has been observed[7] between the spectra in alcohol of 2-hydroxypyrazine (V; R = H), 1,2-dihydro-1-methyl-2-oxopyrazine (V; R = Me), and 2-aminopyrazine, and the conclusion drawn that the amino-compound exists in the imino-form (VI; R = H).

It is now shown (Table and Fig. 2) that there is the expected relation between the

	Ionisation [a] (in H_2O)				Spectroscopy (in H_2O)		
		Spread	Concn.	Analyt.		$\varepsilon_{max.}$ ($m\mu$)	log ε
Pyrazine	pK_a	(±)	(10^{-5}M)	($m\mu$) [b]	pH	(values in italics refer to shoulders or inflexions)	
2-Hydroxy-	—				5·1	316; 221 [c]	3·74; 3·96 [c]
anion	8·23 [d]				12·0	316; 227 [c]	3·75; 3·94 [c]
cation	−0·1 [d]				−3·1	342; 223 [c]	3·795; 4·01 [c]
2-Methoxy-	—				5·1	292; <210 [c]	3·71 [c]
cation	0·75 [d]				−2·25	305; 217 [c]	3·84; 3·96 [c]
1,2-Dihydro-1-methyl-2-oxo-	—				5·2	319; 223 [c]	3·75; 3·94 [c]
cation	−0·04 [d]				−3·1	344; 226 [c]	3·835; 3·99 [c]
2-Mercapto-	—				3·8	390—380; 278	3·80—3·82; 4·11
anion	6·72 [e]	0·02	1000		9·6	339; 266	3·65; 3·98
cation	−0·24	0·10	5	450	−3·1	455—445; 291	3·655; 4·25
2-Methylthio-	—				3·8	322; 250	3·725; 3·93
cation	0·55	0·09	5	360	−2·2	360; 266; 237	3·69; 4·02; 3·80
1,2-Dihydro-1-methyl-2-thiono-	—				3·8	379—376; 278	3·84; 4·11
cation	−0·18	0·13	5	440	−3·1	441—436; 290	3·66; 4·20
2-Amino-	—				6·3	318; *285*; 230 [f]	3·69; *3·33*; 4·00
cation	2·96 [g]	0·01	1000		0·1	325; 230 [f]	3·77; 4·05 [f]
2-Methylamino-	—				7·2	332; *285*; 242	3·64; *2·91*; 4·10
cation	3·42	0·02	1000		0·4	331; 237	3·71; 4·04
2-Dimethylamino-	—				7·2	346; 287; 252	3·64; 2·75; 4·13
cation	3·27	0·02	1000		0·3	352; 244	3·65; 4·00
Methiodide of 2-amino-	—				6·9	353; 244 [i]	3·70; 4·155 [i]
Methiodide of 2-dimethylamino-	—				4·9 [h]	392; 262; 234 [i]	3·575; 4·22; 3·84

[a] Potentiometric determinations of pK were carried out at 25°, and spectroscopic determinations at room temperature. [b] An entry in this column indicates that the ionisation constant was determined spectroscopically. [c] These values agree closely with those of Mason (*J.*, 1959, 1253). [d] Values from Albert and Phillips (*J.*, 1956, 1294). [e] In 50% ethanol. [f] These values agree closely with those of Brown and Mason (*J.*, 1956, 3443). [g] Albert, Goldacre, and Phillips (*J.*, 1948, 2240) obtained 3·14 potentiometrically at 0·05M and 20°. [h] Spectrum unchanged at pH 0·1 [i] Corrected for iodide ion absorption.

spectra of the neutral molecules and cations of 2-amino-, 2-methylamino-, and 2-dimethylamino-pyrazine. These compounds have closely similar basic strength, supporting the conclusion that in aqueous solution 2-aminopyrazine exists mainly in the amino-form

[6] Cheeseman, Heikel, Knight, and Rimington, *Lancet*, 1959, I, 1182.
[7] Pratt in Elderfield's " Heterocyclic Compounds," Wiley, New York, 1957, Vol. 6, p. 472.

(VII). The spectrum of the cation of 2-aminopyrazine (Table) differs from that of the neutral molecule of pyrazine.[8] This indicates that protonation does not take place at the extranuclear nitrogen atom, as in the case of aniline and benzene where the spectrum of the anilinium ion is similar to that of benzene.[9] The spectrum of the cation of 2-aminopyrazine also differs from that of the methiodide (Table). If protonation and quaternisation occur at the same ring-nitrogen atom, the resulting cations should show closely similar ultraviolet absorption (cf. Brown, Hoerger, and Mason's measurements on the cation and methiodide of 2-aminopyrimidine [9]). The methiodide of 2-aminopyrazine is rapidly decomposed by aqueous alkali to give a solution which shows no absorption maximum above 230 mμ. The alkaline decomposition of a methiodide formed by quaternisation at position 1 would be expected to yield 1,2-dihydro-2-imino-1-methylpyrazine (VI; R = Me), the corresponding oxo-compound (V; R = Me), or 2-methylaminopyrazine (by rearrangement of the imine [9]). No spectroscopic evidence for the formation of these compounds was obtained, since the spectrum in 0·1N-sodium hydroxide of 1,2-dihydro-1-methyl-2-oxopyrazine (V; R = Me) showed maxima at 316 and 223 mμ and that of

FIG. 1. FIG. 2.

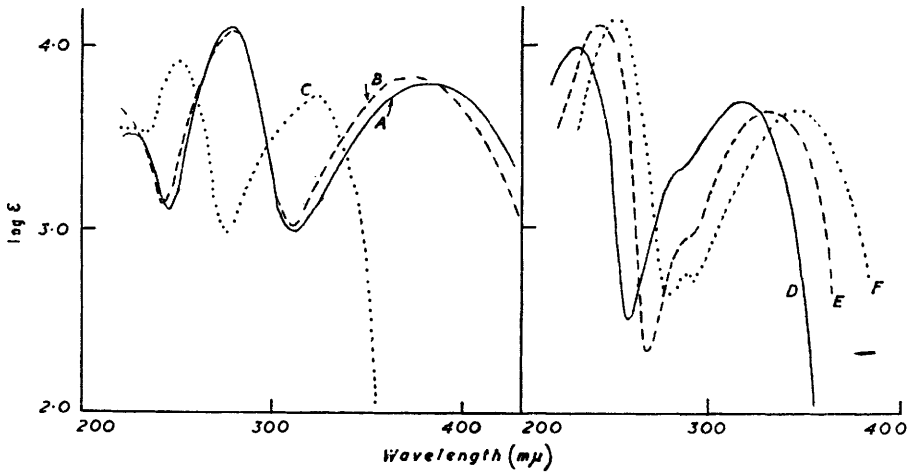

FIG. 1. *Ultraviolet absorption spectra of neutral molecules of* (*A*) 2-*mercapto-*, (*B*) 1,2-*dihydro*-1-*methyl*-2-*thiono-*, *and* (*C*) 2-*methylthio-pyrazine.*

FIG. 2. *Ultraviolet absorption spectra of neutral molecules of* (*D*) 2-*amino-*, (*E*) 2-*methylamino-*, *and* (*F*) 2-*dimethylamino-pyrazine.*

2-methylaminopyrazine showed maxima at 332 and 242 mμ. The spectrum of the imine (VI; R = Me) should be of similar form to that of (V; R = Me). This evidence does not preclude the formation of (VIII), but these observations are consistent with the assumption that protonation of 2-aminopyrazine occurs mainly at position 1 and quaternisation at position 4. The spectra of the cation and methiodide of 2-dimethylaminopyrazine were also dissimilar (Table).

EXPERIMENTAL

Measurements of ionisation and ultraviolet absorption properties were carried out as described previously.[10]

Aminomalonamide.—A solution of ethyl hydroxyiminomalonate [11] (94·5 g., 0·5 mole) in ethanol (50 ml.) was shaken in hydrogen in the presence of 5% palladium–charcoal (10 g.) until 2·0 mol. of gas had been absorbed at room temperature and pressure. Catalyst and solvent

[8] Mason, *J.*, 1959, 1247.
[9] Brown, Hoerger, and Mason, *J.*, 1955, 4035.
[10] Cheeseman, *J.*, 1958, 108.
[11] Schipper and Day, *J. Amer. Chem. Soc.*, 1952, **74**, 350.

were removed and distillation of the residue gave ethyl aminomalonate (69·9—75·6 g., 80—87%), b. p. 83°/0·7 mm., n_D^{19} 1·434. Acetone was added to the non-volatile oil and after cooling, the precipitate of *diethyl-2,5-dioxopiperazine-3,6-dicarboxylate*, m. p. 180—182°, was filtered off. The m. p. was raised to 185—186° by two crystallisations from ethanol (20 parts) (Found: C, 46·7; H, 5·4; N, 10·8. $C_{10}H_{14}O_6N_2$ requires C, 46·5; H, 5·5; N, 10·85%). Ammonia gas was bubbled through an ice-cooled mixture of ethyl aminomalonate (76·8 g.) and aqueous ammonia (*d* 0·88; 100 ml.) for 2 hr., and the mixture then refrigerated overnight. The crystalline precipitate of aminomalonamide (43·2 g., 84%), m. p. 198° (decomp.), was filtered off and washed with a little ice-cold water. Cerchez [12] gives m. p. 197°.

2-Hydroxypyrazine.—Aminomalonamide was converted into 2-hydroxypyrazine-3-carboxyamide by Meuhlmann and Day's method,[13] and 2-hydroxypyrazine-3-carboxylic acid prepared by Jones's method.[14] A suspension of the acid (7·0 g.) in diethylene glycol monoethyl ether (20 ml.) was heated under reflux until carbon dioxide was no longer evolved, then for a further 2 min. (total time, *ca.* 10 min.). The hot mixture was allowed to cool to *ca.* 100°, then filtered, and the black insoluble material washed with a little hot 96% ethanol. The combined filtrate and washings were cooled to 0° and the crystalline precipitate of 2-hydroxypyrazine, m. p. 187—189°, was filtered off (3·6—4·1 g., 75—85%). Vacuum-concentration of the mother-liquor yielded further 2-hydroxypyrazine, m. p. 183—185°. The analytical sample was sublimed at 160°/20 mm. and had m. p. 188—189°; it crystallised from 96% ethanol (20 parts) in colourless needles of unchanged m. p. (Found: C, 50·2; H, 4·4; N, 29·2. Calc. for $C_4H_4ON_2$: C, 50·0; H, 4·2; N, 29·2%). Weijlard, Tishler, and Erickson [15] give m. p. 187—188°.

2-Chloropyrazine.—This was prepared by the following modification of Albert and Phillips's method.[2] 2-Hydroxypyrazine (30 g.) and freshly distilled phosphoryl chloride (90 ml.) were heated at 105° for 1 hr. The cooled mixture was slowly poured into stirred ice-water, insoluble material was removed, and the filtrate extracted with ether. The combined ethereal extracts were washed with excess of sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated at atmospheric pressure. Distillation at 20 mm. gave 2-chloropyrazine (26 g., 92%), b. p. 52°, n_D^{20} 1·538. Albert and Phillips [2] give b. p. 60—61°/28 mm.

2-Aminopyrazine.—This was prepared by Erickson and Spoerri's method.[1] The product was isolated by continuous extraction with ether (18 hr.). A sample crystallised from benzene (40 parts) had m. p. 121—122° (Found: C, 50·5; H, 5·1; N, 44·35. Calc. for $C_4H_5N_3$: C, 50·5; H, 5·3; N, 44·2%). The *picrate*, prepared in ethanol, had m. p. 243° (decomp.) (Found: C, 37·4; H, 2·25; N, 25·5. $C_{10}H_8O_7N_6$ requires C, 37·0; H, 2·5; N, 25·9%).

Quaternisation. A solution of 2-aminopyrazine (1·9 g.) in methanol (10 ml.) and methyl iodide (4 ml.) was set aside at room temperature for 3 days. The crystalline precipitate (3·35 g.) was then filtered off. Crystallisation from 96% ethanol (10 parts) gave the *methiodide*, m. p. 176—178° (decomp.) (Found: C, 25·1, 25·9, 25·2; H, 2·9, 3·5, 4·0; N, 18·0; I, 54·3. $C_5H_8N_3I$ requires C, 25·3; H, 3·4; N, 17·7; I, 53·5%).

2-Methylaminopyrazine.—2-Chloropyrazine (6·7 g.) was heated with ethanolic methylamine (33% w/w; 30 g.) at 150° for 7 hr. Solvent and excess of methylamine were then removed in a vacuum. The residue was extracted with benzene, and the extract evaporated. Distillation gave *2-methylaminopyrazine* (4·7 g., 67%) as a hygroscopic oil, which crystallised. The analytical specimen had b. p. 76°/1 mm., m. p. (mainly) 49—50° (Found: C, 54·8; H, 6·9. $C_5H_7N_3$ requires C, 55·05; H, 6·5%). The *picrate*, prepared in ethanol, had m. p. 181—182° (decomp.) (Found: C, 39·1; H, 3·3; N, 25·0. $C_{11}H_{10}O_7N_6$ requires C, 39·05; H, 3·0; N, 24·85%).

2-Dimethylaminopyrazine.—Dimethylamine (11 g.) and 2-chloropyrazine (5 g.) in ethanol (30 ml.) were heated at 150° for 7 hr., then cooled and poured into *ca.* 8N-sodium hydroxide (20 ml.). The product was isolated by continuous extraction with ether (18 hr.). Distillation of the dried (Na_2SO_4) and evaporated extract gave *2-dimethylaminopyrazine* (4·0 g., 74%). The analytical sample had b. p. 64°/1·2 mm., m. p. 25·7° (Found: C, 58·8; H, 7·7. $C_6H_9N_3$ requires C, 58·5; H, 7·4%). The *picrate*, prepared in ethanol, had m. p. 158—160° (decomp.) (Found: C, 40·8; H, 3·7; N, 23·7. $C_{12}H_{12}O_7N_6$ requires C, 40·9; H, 3·4; N, 23·9%).

Quaternisation. A solution of 2-dimethylaminopyrazine (1·23 g.) in methanol (5 ml.) and

[12] Cerchez, *Bull. Soc. chim. France*, 1930, **47**, 1287.
[13] Meuhlmann and Day, *J. Amer. Chem. Soc.*, 1956, **78**, 242.
[14] Jones, *ibid.*, 1949, **71**, 78.
[15] Weijlard, Tishler, and Erickson, *ibid.*, 1945, **67**, 802.

methyl iodide (2 ml.) was set aside at room temperature for 3 days. Solvent and excess of methyl iodide were then removed and the residue crystallised from ethanol (5 ml.). Mixed crystals, m. p. (mainly) 134—135°, were obtained which gave the *methiodide*, m. p. 136—137°, after two further crystallisations from ethanol (5 parts) (Found: C, 31·8; H, 4·5; N, 16·0; I, 47·7. $C_7H_{12}N_3I$ requires C, 31·7; H, 4·6; N, 15·85; I, 47·9%).

2-*Mercaptopyrazine*.—(*a*) Dimethylformamide (100 ml.) was added to a solution of sodium ethoxide, prepared from sodium (4·6 g., 0·2 g.-atom) and ethanol (100 ml.). Most of the ethanol was removed by distillation and the residual solution then saturated with dry hydrogen sulphide. The resulting deep green solution of sodium hydrogen sulphide was heated with 2-chloropyrazine (11·5 g., 0·1 mole) at 100° for 3 hr., and solvent was then removed at 100°/20 mm. The residue was dissolved in water, then acidification with acetic acid gave a yellow precipitate which was extracted with 2N-sodium hydroxide (50 ml.). After removal of insoluble material, acidification of the filtrate gave 2-*mercaptopyrazine* (10·0 g., 89%), m. p. *ca.* 210—215° (decomp.). The m. p. of this compound was not a reliable criterion of purity. The analytical specimen was sublimed at 180°/1·5 mm. and rapidly crystallised from butan-1-ol (40 parts) (Found: C, 42·6, 42·9; H, 3·9, 3·8; N, 24·9, 24·85; S, 28·5, 28·3. $C_4H_4N_2S$ requires C, 42·8; H, 3·6; N, 25·0; S, 28·6%).

(*b*) A mixture of 2-hydroxypyrazine (0·96 g., 0·01 mole) and phosphorus pentasulphide (2·45 g., 0·011 mole) in pyridine (40 ml.) was heated at 120° for 2 hr. Pyridine was removed under reduced pressure, and the residue dissolved in 2N-sodium hydroxide. Acidification with dilute sulphuric acid gave black insoluble material which on sublimation at 174°/2 mm. yielded 2-mercaptopyrazine. A further crop was obtained by chloroform extraction of the filtrate (total yield, 0·37 g., 33%).

(*c*) A mixture of 2-chloropyrazine (13·4 g., 0·117 mole) and aqueous potassium hydrogen sulphide [prepared by saturating a solution of potassium hydroxide (6·2 g., 0·11 mole) in water (45 ml.) with hydrogen sulphide at 0°] was heated in a sealed tube at 100° for 6 hr. After cooling, the solid (9·4 g.) was filtered off and then extracted with 0·5N-potassium hydroxide (200 ml.). Insoluble material (2·1 g.), m. p. (mainly) 102—106°, was collected. Acidification of the filtrate gave 2-mercaptopyrazine, 5·65 g. (43%). The alkali-insoluble fraction gave *di-2-pyrazinyl sulphide*, m. p. 106—107° after two crystallisations from 96% ethanol (12 parts) (Found: C, 50·4; H, 3·3; N, 29·6; S, 17·2. $C_8H_6N_4S$ requires C, 50·5; H, 3·2; N, 29·45; S, 16·9%).

Decomposition of 2-Mercaptopyrazine.—2-Mercaptopyrazine was heated at 220° until hydrogen sulphide was no longer evolved. The non-volatile residue was separated from the yellow sublimate of the unchanged mercapto-compound. Extraction with 0·5N-potassium hydroxide, and crystallisation of the alkali-insoluble material from ethanol, gave di-2-pyrazinyl sulphide, m. p. 104—106° (undepressed when mixed with a specimen prepared as described above).

Oxidation of 2-Mercaptopyrazine.—A solution of iodine (2·6 g.) in potassium iodide (5 g.) and water (20 ml.) was added dropwise to a solution of 2-mercaptopyrazine (1·1 g.) in 2N-sodium hydroxide (10 ml.). After refrigeration, the crystalline precipitate (0·71 g.) was filtered off. Successive crystallisation from methanol (10 parts) and light petroleum (b. p. 60—80°; 50 parts) gave *di-2-pyrazinyl disulphide*, m. p. 107—109° (Found: C, 43·5; H, 2·6; N, 24·7; S, 28·7. $C_8H_6N_4S_2$ requires C, 43·2; H, 2·7; N, 25·2; S, 28·8%).

Oxidation of Di-2-pyrazinyl Sulphide.—A solution of the sulphide (0·95 g.) in glacial acetic acid (30 ml.) and 30% w/w hydrogen peroxide (2·5 ml.) was set aside at room temperature for 7 days, then concentrated in a vacuum. Water (50 ml.) was added to the residue, and the crystalline precipitate (0·33 g.) filtered off in two crops. Crystallisation from benzene–light petroleum (b. p. 80—100°) (1 : 3; 500 parts) and 96% ethanol (50 parts) gave *di-2-pyrazinyl sulphone*, m. p. 160—161° (Found: C, 42·8; H, 2·6; N, 25·4; S, 14·6. $C_8H_6O_2N_4S$ requires C, 43·2; H, 2·7; N, 25·2; S, 14·4%).

2-*Methylthiopyrazine*.—A solution of 2-mercaptopyrazine (4·5 g., 0·04 mole) in 0·5N-potassium hydroxide (100 ml.) was shaken with methyl iodide (7·1 g., 0·05 mole) for 1½ hr. at room temperature. After cooling, the precipitate (2·2 g.) was filtered off and dried over potassium hydroxide. A further 1·25 g. was obtained by continuous ether-extraction (18 hr.) of the filtrate. Sublimation at 40°/20 mm. gave colourless 2-*methylthiopyrazine*, m. p. 45—47·5°. The m. p. was unchanged by crystallisation from light petroleum (b. p. 40—60°; 10 parts) (Found: C, 47·4; H, 5·1; N, 21·8; S, 25·1. $C_5H_6N_2S$ requires C, 47·6; H, 4·8; N, 22·2; S, 25·4%).

1,2-*Dihydro*-1-*methyl*-2-*oxopyrazine*.—Methyl sulphate (6·3 g., 0·05 mole) was added to a stirred suspension of 2-hydroxypyrazine (4·8 g., 0·05 mole) and anhydrous potassium carbonate (10 g.) in acetone (50 ml.). After 18 hr., acetone was removed by distillation, and the residue dissolved in water and chloroform. The aqueous layer was separated and repeatedly extracted with chloroform. The combined extracts were dried (Na_2SO_4) and evaporated, and distillation of the residue (3·5 g.) at 1 mm. gave 1,2-dihydro-1-methyl-2-oxopyrazine (1·6 g., 27%), b. p. (mainly) 96°. The analytical sample, crystallised from light petroleum (b. p. 60—80°; 300 parts) and sublimed at 70°/0·5 mm., had m. p. 84—85° (Found: C, 54·9; H, 5·3; N, 25·3. Calc. for $C_5H_6ON_2$: C, 54·55; H, 5·5; N, 25·45%). Dutcher [16] gives m. p. 83—84°.

1,2-*Dihydro*-1-*methyl*-2-*thionopyrazine*.—A mixture of 1,2-dihydro-1-methyl-2-oxopyrazine (1·6 g., 0·0145 mole) and phosphorus pentasulphide (3·5 g., 0·0160 mole) in pyridine (50 ml.) was heated at 120° for 2 hr. Pyridine was removed under reduced pressure, and the residue dissolved in water (10 ml.) and 2N-sodium hydroxide (25 ml.). Extraction with chloroform, and evaporation of the dried (Na_2SO_4) extracts, gave a residue (1·15 g.) which furnished yellow 1,2-*dihydro*-1-*methyl*-2-*thionopyrazine* (1·0 g., 55%), m. p. 133—134°, on sublimation at 100°/0·04 mm. The analytical sample, crystallised from benzene (10 parts), had m. p. 134—135° (Found: C, 48·0; H, 4·5; N, 21·9; S, 25·0. $C_5H_6N_2S$ requires C, 47·6; H, 4·8; N, 22·2; S, 25·4%).

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[16] Dutcher, *J. Biol. Chem.*, 1947, **171**, 321.