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Pyrazines. I. Pyrazine-N-oxides. Preparation and Spectral Characteristics[1]

BY BERNARD KLEIN AND JUDITH BERKOWITZ

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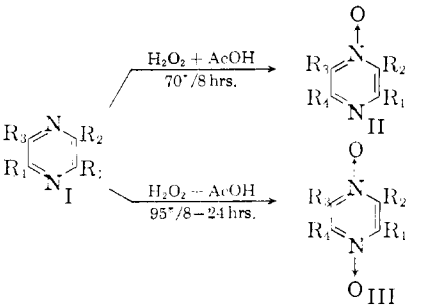
The preparation of pyrazine and substituted pyrazine mono- and di-N-oxides has been improved and simplified. The N-oxides, prepared by the method of Ochiai are: pyrazine-1-oxide, a 45° and 80–82° form of 3-methylpyrazine-1-oxide, 2,5-dimethylpyrazine-1-oxide, 2,6-dimethylpyrazine-1-oxide and -4-oxide and 2,3,5,6-tetramethylpyrazine-1-oxide. The mono-N-oxides have two characteristic absorptions in the ultraviolet, one at 216 mμ and the other at 260 mμ. With increasing substitution, a third absorption appears at 295 mμ. In the infrared, the compounds exhibit characteristic absorptions of N → O at 7.4–7.8 and 11.4–11.8 μ. The 1,4-dioxides of the pyrazine compounds above as well as several trisubstituted pyrazine compounds have been prepared and characterized. The 1,4-dioxides also have two characteristics absorptions in the ultraviolet, at about 230 and 300 mμ. Characteristic absorptions are also seen in the infrared region at about 7.7 and 11.6 μ.

Recent publications have described the preparation and reactions of heterocyclic N-oxides. The pyridine - N - oxides,[2a] pyrimidine - N - oxides,[2b,3,4] quinoline-N-oxides,[2] isoquinoline N-oxides[5,6] and most recently purine-N-oxides[7–11] have now been characterized.

The possibility of utilizing pyrazine-N-oxides in substitution and rearrangement reactions similar to those developed for pyridine-N-oxides, in connection with a study on the utilization of pyrazine derivatives in biological systems, warranted additional study. A number of pyrazine-N-oxides have been described. Newbold and Spring[12] prepared the mono- and di-N-oxides of 2,5-dimethylpyrazine and later reported the preparation of 2,5-dimethyl-6-chloropyrazine-4-oxide and its conversion to the corresponding 6-hydroxy and 6-ethoxy derivatives.[13] They could not prepare the 1-oxide; Kushner, *et al.*,[14] reported the preparation of pyrazinamide - 4 - oxide. Later Karmas and Spoerri[15] prepared 2-methoxy-3-phenylpyrazine-4-oxide. Other N-oxides reported include tetramethylpyrazine - 1,4 - dioxide[16] and tetraphenylpyrazine-1,4-dioxide.[17] Most recently Gumprecht[18] described the preparation of pyrazine N-oxide, 2-methylpyrazine-1-oxide, 3-methylpyrazine-1-oxide and the corresponding di-N-oxides.

The present authors have been able to improve and simplify the preparation of pyrazine and substituted pyrazine mono- and di-N-oxides. Several hitherto unreported N-oxide compounds in this heterocyclic series are included. The ultraviolet and infrared absorption spectra of these compounds have been obtained and compared with pyridine and alkylpyridine-N-oxides. Unfortunately, the ultraviolet spectra of the analogous methylpyrimidine-N-oxide compounds are not yet available for comparison.

The pyrazine-N-oxides were prepared by the procedure of Ochiai[1]



Pyrazine-mono-N-oxides.—The pyrazine mono-N-oxides have been obtained in good (60–90%) yield (Table I). Pyrazine-1-oxide and the substituted pyrazine - mono - N - oxides are low melting, somewhat deliquescent or hygroscopic solids, which sublime readily. These characteristics have been noted among other heterocyclic-N-oxides.[4] The ease of sublimation is advantageous in purification.

Gumprecht[18] has claimed the isolation of a low melting (45°) 2-methylpyrazine-1-oxide and a higher melting (92°) 2-methylpyrazine-4-oxide (3-methylpyrazine-1-oxide). Both a low melting (45°) and a higher melting (80–82°) form have been isolated in this Laboratory. A mixture of equal parts of lower and higher melting forms melted from 40–60° in agreement with Gumprecht. It is believed, however, that both forms are the identical 3-methylpyrazine-1-oxide. Higher and lower melting forms of N-oxides are described.[5] Both forms of 3-methylpyrazine-N-oxide isolated in this Laboratory give identical ultraviolet and infrared absorption spectra, as well as identical *picrates*, which do not give depressed mixed melting points. Both forms give, on treatment with phosphorus oxychloride, the known 2-chloro-3-methylpyrazine,[19]

(1) Presented at the 135th Meeting of the American Chemical Society, Boston, Mass., April, 1959.

(2) (a) E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953); (b) E. Ochiai, M. Ishikawa and S. Zai-Ren, *J. Pharm. Soc. Japan*, **67**, 34 (1947).

(3) E. Ochiai and H. Yamanaka, *Pharm. Bull. (Japan)*, **3**, 175 (1955).

(4) R. H. Wiley and S. C. Slaymaker, THIS JOURNAL, **79**, 2233 (1957).

(5) M. M. Robison and B. L. Robison, *J. Org. Chem.*, **21**, 1337 (1956).

(6) M. M. Robison and B. L. Robison, THIS JOURNAL, **80**, 3443 (1958).

(7) G. M. Timmis, I. Cooke and R. G. W. Spickett, in "Ciba Foundation Symposium on the Chemistry and Biology of Purines," Little, Brown and Co., Boston, Mass., 1957, p. 139.

(8) E. C. Taylor, T. S. Osdene, E. Richter and O. Vogt, *ibid.*, p. 23.

(9) G. B. Brown, *ibid.*, p. 143.

(10) M. A. Stevens, D. I. Magrath, H. W. Smith and G. B. Brown, THIS JOURNAL, **80**, 2755 (1958).

(11) M. A. Stevens and G. B. Brown, *ibid.*, **80**, 2759 (1958).

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

(13) R. A. Baxter, G. T. Newbold and F. S. Spring, *ibid.*, 1859 (1948).

(14) S. Kushner, *et al.*, THIS JOURNAL, **74**, 3617 (1952).

(15) G. Karmas and P. E. Spoerri, *ibid.*, **78**, 4076 (1956).

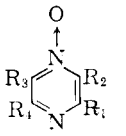
(16) E. Durio and M. Bissi, *Gazz. chim. ital.*, **60**, 899 (1930).

(17) T. Takabashi and J. Shibaschi, *J. Pharm. Soc. Japan*, **72**, 1188 (1952); *C. A.*, **47**, 7500 (1953).

(18) C. F. Koelsch and W. H. Gumprecht, *J. Org. Chem.*, **23**, 1602 (1958).

TABLE I

PYRAZINE-MONO-N-OXIDES

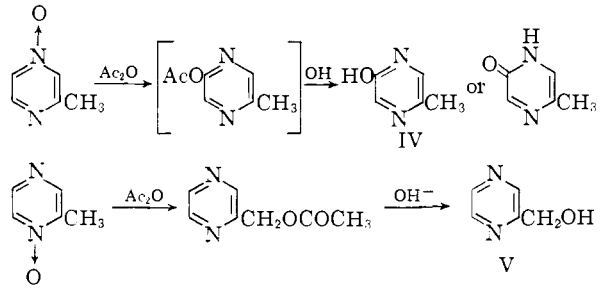


Compd.	R_1	R_2	R_3	R_4	Yield, %	M.p., °C.	B.p. °C.	Mm.	Empirical formula	Analyses, % Calcd.	Found	Calcd.	Found
I	H	H	H	H	60[a]	104[b]	126–127	14	$C_4H_4N_2O$	C 49.99	50.48	H 4.20	4.43
II	CH_3	H	H	H	57[c]	45[d]	128–132	15	$C_5H_6N_2O$	C 54.54	54.36	H 5.49	5.71
III	CH_3	H	H	H		80–82[e]			$C_5H_6N_2O$	N 25.44	25.26		
IV	CH_3	H	CH_3	H	84	108[f]			$C_6H_8N_2O$				
V	H	CH_3	CH_3	H	29[g]	55	134–135	17	$C_6H_8N_2O$	C 58.04	58.64	H 6.49	6.60
VI	CH_3	H	H	CH_3	33[g]	108–110			$C_6H_8N_2O$				
VII	CH_3	CH_3	CH_3	CH_3	90	83			$C_8H_{12}N_2O$	C 63.14	63.25	H 8.21	8.07

[a] Prepared by heating 8 hr. at 95°; heating at 70° for 8 hr. gave only a 45% yield. [b] Reference 18 gives the m.p. of pyrazine-mono-N-oxide as 113–114°. [c] Total yield of both high and low melting isomers. [d] Reference 18 gives m.p. 43–45°, b.p. 109–111° (5 mm.); picrate, m.p. 128–130°. [e] Reference 18 gives m.p. 91–92°, b.p. 111–116° (7 mm.); picrate, m.p. 128–130°; mixed m.p. with picrate II, 128–130°. [f] Reference 12 gives m.p. 107–108°. [g] Yield of individual isomer, total yield 62%; picrate V, m.p. 199–203°; picrate VI, m.p. 214–215°, mixed m.p. 155–160°.

confirming the position of the N-oxide as the 1-oxide.

In his proof of structure of the 1- and 4-oxide, Gumprecht presented experiments involving rearrangements of the N-oxides with boiling acetic anhydride

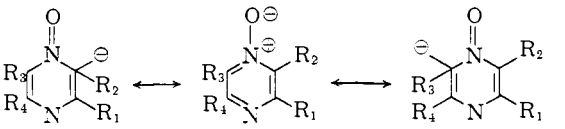


Hydrolysis of the "acetoxy" derivatives in each case gave low melting substances, one (IV) melted at 68–69°, the other (V) was described as a low melting solid (b.p. 64–65° (0.3 mm)). These exhibited absorption maxima (ethanol) at 220 and 270 mμ (IV) and 222 and 265 mμ (V). Elemental analysis supported the empirical formula $C_5H_6N_2O$. This is also the empirical formula of α-methylpyrazine-N-oxide. As will be described later, the ultraviolet absorption spectrum of 3-methylpyrazine-1-oxide (water) exhibits maxima at 216 and 260 mμ. In ethanol, this shifts to 220 and 270 mμ. Such bathochromic shifts of the ultraviolet absorption spectral maxima produced by changing the solvent from water to alcohol are well known.[4,19] Furthermore, the ultraviolet absorption spectrum of hydroxypyrazine derivatives show maxima around 228 and 325 mμ[20] while pyrazinemethanol derivatives have ultraviolet spectra resembling the parent heterocycle.[21] It is difficult, on the basis of these observations, to accept the existence of both a 2-methylpyrazine-1-oxide and 3-methylpyrazine-1-oxide. Experiments in this Laboratory on the reaction of pyrazine-N-oxides with acetic anhydride will be the subject of another report.

(19) E. Shaw, THIS JOURNAL, 71, 67 (1949).
(20) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 373 (1947).
(21) B. Klein and J. Berkowitz, unpublished observations.

By contrast, a low melting (55°) and a higher melting (108–110°) mono-N-oxide have been isolated following the reaction of 2,6-dimethylpyrazine with 30% hydrogen peroxide in glacial acetic acid. As expected, the ultraviolet absorption spectra are similar, but the infrared absorption spectra are different (see below). The two compounds form dissimilar *picrates* and the mixed melting point of equal parts of higher and lower melting N-oxide is depressed to 48°. Both compounds behave differently on treatment with boiling acetic anhydride.[21] Thus the low melting compound has been assigned the structure of 2,6-dimethylpyrazine-1-oxide and the higher melting compound 2,6-dimethylpyrazine-4-oxide.

A number of resonance forms presumably contribute to the structure of the substituted pyrazine-mono-N-oxides. Since attempts to nitrate 3-methylpyrazine-1-oxide (R_1 = Me, R_2, R_3, R_4 = H) by Gumprecht[18] and in this Laboratory were unsuccessful, it is believed that forms VI and VIII do not make large contributions.



VI VII VIII

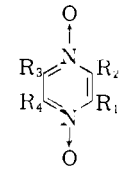
Pyrazine-di-N-oxides (Table II).—The pyrazine-1,4-dioxides have been prepared by heating the reactants for a longer period at a slightly higher temperature usually in good yield (50–90%).

Most of the pyrazine-dioxides are high melting solids, attesting to their relatively polar character. Their ease of sublimation here, too, is an asset in purification. The trisubstituted pyrazine dioxides melt surprisingly lower and at first were thought to be mono-N-oxides. Elemental analysis and comparison of their ultraviolet absorption spectra with the spectra of other dioxides established their identity. All attempts to prepare mono-N-oxides of these trisubstituted pyrazines were unsuccessful.

Ultraviolet Absorption Spectra.—There are few definitive studies in the literature of the ultraviolet

TABLE II

PYRAZINE-1,4-DIOXIDES



Compd.	R_1	R_2	R_3	R_4	Yield, %	M.p., °C.	Empirical formula	Analyses, % Calcd.	Found	Calcd.	Found
VIII	H	H	H	H	90	300 d.[a]	$C_4H_4N_2O_2$	C 42.86	42.42	H 3.60	3.84
IX	CH_3	H	H	H	57	242–244[b]	$C_5H_6N_2O_2$	C 47.61	47.93	H 4.80	4.92
X	CH_3	H	CH_3	H	60	>300[c]					
XI	CH_3	H	H	CH_3	86	227	$C_6H_8N_2O_2$	C 51.42	51.84	H 5.75	5.72
XII	CH_3	CH_3	CH_3	CH_3	89	224[d]	$C_8H_{12}N_2O_2$	C 57.12	57.38	H 7.12	7.24
XIII	CH_3	H	CH_3	C_4H_9	72[e]	105–106	$C_{10}H_{16}N_2O_2$	N 14.31	14.07		
XIV	CH_3	H	CH_3	C_5H_{11}	50[e]	123	$C_{11}H_{18}N_2O_2$	N 13.33	13.07		
XV	CH_3	H	CH_3	C_6H_{13}	69[e]	111	$C_{12}H_{20}N_2O_2$	C 64.25	64.55	H 8.99	9.26
XVI	CH_3	H	CH_3	C_6H_5	50[e]	165	$C_{12}H_{12}N_2O_2$	N 12.96	13.33		

[a] Darkens but does not melt at 300°; ref. 18 gives decomposition temp. at 285–295°. [b] Ref. 18 gives m.p. 230–231°. [c] Ref. 12 gives m.p. 360°. [d] Ref. 17 gives m.p. 220° (prepared by a different method). [e] Heating 8 hours at 70°.

absorption spectra of pyrazine compounds in relation to structure. A comprehensive study is under way in this Laboratory and will be reported later. At this time, the authors wish to confine themselves to observations and remarks on the ultraviolet absorption spectra of the parent heterocycle, alkyl and otherwise substituted pyrazines, together with their mono- and di-N-oxide derivatives.

Pyrazine itself, in water, exhibits an absorption maximum at 261 mμ and a second broad absorption at 300–310 mμ. Halverson and Hirt,[22] in their study of the ultraviolet spectra of diazines, found a diffuse absorbing system common to all at 250 mμ, and a particular sharp system for pyrazine at 323.8 mμ; pyridazine, 375 mμ; pyrimidine, 321.7 mμ. At this time, the apparent discrepancy cannot be reconciled. The spectrum of 2-methylpyrazine shows a single peak at 275 mμ. On the other hand, 2,5-dimethylpyrazine is characterized by a broad absorption between 265–271 mμ. By contrast, the unsymmetrical 2,6-dimethylpyrazine again shows a single peak at 275 mμ. Trisubstituted pyrazines absorb strongly at 278–279 mμ. The 6-phenyl substituent produces a bathochromic shift to 284 mμ, with broad absorption at 220–230 mμ, indicating continued conjugation or resonance. Tetramethylpyrazine absorbs at 295 mμ, with a shoulder at 280–285 mμ. This is shown in Table III.

TABLE III

ULTRAVIOLET ABSORPTION SPECTRA

Compound	Solvent	λ_{max}, mμ	log ε
Pyrazine	H_2O	261[a]	3.40
2-Methylpyrazine	H_2O	275	3.86
2,5-Dimethylpyrazine	H_2O	265–271	3.73
2,6-Dimethylpyrazine	H_2O	275	3.95
Tetramethylpyrazine	H_2O	295	3.71
2,5-Dimethyl-6-butylpyrazine[b]	Ethanol	279	3.88
2,5-Dimethyl-6-amylpyrazine[b]	Ethanol	278	3.76
2,5-Dimethyl-6-hexylpyrazine[b]	Ethanol	280	3.88
2,5-Dimethyl-6-phenylpyrazine[b,c]	Ethanol	284	3.74

[a] Broad absorption from 300–310 mμ. [b] B. Klein and P. E. Spoerri, THIS JOURNAL, **73**, 2950 (1951). [c] Broad absorption from 220–230 mμ.

(22) F. Halverson and R. C. Hirt, *J. Chem. Phys.*, **17**, 1165 (1949).

By comparison, pyridine absorbs at 256 mμ (water)[23,24] or 257 mμ (ethanol) with fine structure at 250 and 265 mμ. A symmetrically substituted pyridine compound[25] such as 2-methyl-5-ethylpyridine absorbs at 268 and 275 mμ (ethanol), while the asymmetrical 2,6-dimethylpyridine absorbs at 268 mμ, with a very strong absorption below 210 mμ, and is transparent above 290 mμ.

The ultraviolet absorption spectra of pyrazine-1-oxide and the substituted pyrazine-mono-N-oxides are characterized by the appearance of two peaks, one about 216 mμ, the other about 260 mμ (Table IV). Pyrazine-1-oxide absorbs at 214

TABLE IV

ULTRAVIOLET ABSORPTION SPECTRA OF PYRAZINE-MONO-N-OXIDES

Compound	λ_{max}, mμ	log ε	λ_{max}, mμ	log ε	λ_{max}, mμ	log ε
I	214	4.15	263	3.95		
II	216	4.18	260	4.10	285(sh)[a]	
III	216	4.18	260	4.10	285(sh)	
IV	216	4.13	261	3.88	293-296(sh)	
V	215	4.19	262	4.03	294	3.60
VI	215	4.19	262	4.03	294	3.60
VII	212	4.16	259	3.74	297	3.78

[a] sh = shoulder.

and 263 mμ. 3-Methylpyrazine-1-oxide (both forms) also absorbs at 216 and 263 mμ and, in addition, displays a shoulder at 285 mμ. 2,5-Dimethylpyrazine-1-oxide absorbs at 216.5 and 260.5 mμ but now shows a low broad absorption with a peak at 295 mμ. In the case of the asymmetrical 2,6-dimethylpyrazine-1-oxide and 2,6-dimethylpyrazine-4-oxide, in addition to the characteristic peaks at 215 and 262 mμ, a well defined absorption peak is seen at 294 mμ. Finally in tetramethylpyrazine-1-oxide, the third peak at 297 mμ has a greater extinction than the peak at 259 mμ. Evidently with increasing substitution, either additional electronic transitions become operative or, less likely, a new chromophore group is introduced.

(23) E. B. Hughes, H. H. G. Jellinek and B. A. Ambrose, *J. Phys. Colloid Chem.*, **53**, 410 (1949).

(24) M. L. Swain, A. Eisner, C. F. Woodward and B. A. Brice, THIS JOURNAL, **71**, 1342 (1949).

(25) O. H. Bullit, Jr., and J. T. Maynard, *ibid.*, **76**, 1370 (1954).

TABLE V

ULTRAVIOLET ABSORPTION SPECTRA PYRAZINE-1,4-DIOXIDES

Compound	λ_{max}, mμ	log ε	λ_{max}, mμ	log ε
VIII	222	3.78	302	4.34
IX	228	4.18	301	4.20
X	231	3.56	296	4.32
XI	231	3.77	300	4.31
XII	234.5	4.14	295	4.34
XIII	235	4.00	299	4.25
XIV	234	3.95	299	4.32
XV	235	4.37	298	4.40
XVI	234	4.03	299	4.21

lished figure[19]). Interestingly, both the 2-benzyloxypyridine-N-oxide and 3-hydroxypyridine-N-oxide also exhibit peaks at about 305 mμ (estimated from the published figure[14]). Jaffé[26] in his study of the characteristics of the ultraviolet absorption spectrum of pyridine-N-oxides, demonstrated that the lower wave length band is susceptible to the effects of substituents. This has not been seen in the corresponding pyrazine-N-oxide series, since on increasing substitution, there is no shift in the lower wave length, nor marked alteration in the intensity of the band. Further studies on the

TABLE VI

PRINCIPAL ABSORPTIONS IN THE INFRARED[d]

Compound	3 μ	6 μ	7 μ	8 μ
Pyrazine[a]	3.25(s)	6.20(vs), 6.60(m), 6.85(s)	7.27(m), 7.40(vs), 7.10(vs)[c]	8.15(w), 8.45(vs)
2-Methyl-[b]	3.25–3.30(vs)	6.30(s), 6.55(vs), 6.75–7.15(vs)	7.40(vs)	8.0(s), 8.55(vs), 7.70(vs)
2,5-dimethyl-[b]	3.30–3.40(vs)	6.75–6.90(vs)	7.25(vs), 7.55(vs), 7.95(s)	8.15(m), 8.55–8.65(vs)
2,6-dimethyl-[a]	3.40(vs)		7.05, 7.25	8.00(m), 8.65(s)
2,3,5,6-tetramethyl-[a]	3.40(s)		7.10(vs), 7.40(m)	8.20(vs), 8.35(m), 8.50(s)
2,5-dimethyl-6-butyl-[b]	3.40(vs)	5.85(s), 6.30(s), 6.45(s), 6.75–6.95(vs)	7.25(vs), 7.50(s), 7.70(w), 7.80-(vs), 7.95(s)	8.20(w), 8.55(vs), 8.75(s)
2,5-dimethyl-6-amyl-[b]	3.40–3.50(vs)	5.95(s), 6.50(s), 6.85–6.95(vs)	7.30(vs), 7.80(vs)	8.00(m), 8.55(vs), 8.75(s)
2,5-dimethyl-6-hexyl-[b]	3.45(vs)	5.95(m), 6.35(m), 6.50(s), 6.85–6.95(vs)	7.30(vs), 7.80(m)	8.00(s), 8.25(w), 8.55(s), 8.75(m)
2,5-dimethyl-6-phenyl-[b]	3.00(s), 3.45-(vs)	5.80(m), 6.25(vs), 6.35(s), 6.50(s), 6.85(vs), 6.95-(vs)	7.30(s), 7.75(vs)	8.35(s), 8.65(s)

9 μ	10 μ	11 μ	12 μ	13 μ	14 μ
9.65(w), 9.90(s)	10.35–10.45(m)	11.50(s)	12.25(s)		14.05(s)
9.45(vs), 9.85(vs)	10.30(s)		12.15(vs)	13.20–13.40(vs)	
9.60–9.70(vs)	10.40(s)	11.40(s)		13.55(vs)	14.70(s)
9.60(s), 9.80(s)	10.75(m)	11.65(m)		13.5(m)	
9.60(m)	10.10(vs)	11.45(w)	12.55(s)		14.75(m)
9.35(vs), 9.65(s), 9.90(s)	10.65(s)	11.20(s)	12.45–12.55(w)	13.65–13.75(m)	
9.30(s), 9.65(m), 9.95(m)	10.65(s)	11.20(s)		13.30–13.35	
9.30(m), 9.65(m), 9.95(m)	10.65(m)	11.20(s)		13.20–13.40(vs)	
9.40(s), 9.60, 9.9.70(s)	10.35(s), 10.80(w)	11.05(m), 11.15(m)	12.30–12.40(m), 12.70(vs)	13.10–13.40(m), 13.45–13.55(vs)	14.30–14.40(vs)

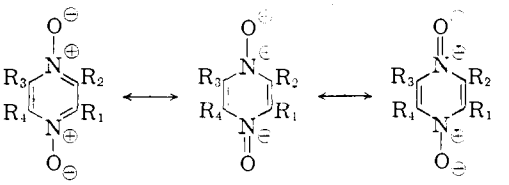
[a] KBr disk preparation. [b] Liquid (0.05-cm. cell). [c] $CHCl_3$ soln. (0.05-cm. cell). [d] (w) = weak; (m) = medium; (s) = strong; (vs) = very strong.

The distinctive absorption maxima at about 215 and 260 mμ is evidently characteristic of the N→O function. For example, pyridine-N-oxide absorbs at 213 and 265 mμ (ethanol); 4-methylpyridine-N-oxide absorbs at 212 and 266 mμ.[26] Shaw[19] assigned the 260 mμ absorption to the N→O function as found in 2-benzyloxypyridine-N-oxide. Similarly 3-hydroxypyridine-1-oxide has a peak absorption at 263 mμ, but the peak at lower wave lengths has shifted to about 227 mμ (estimated from the published figure[19]). Interestingly, both the 2-benzyloxypyridine-N-oxide and 3-hydroxypyridine-N-oxide also exhibit peaks at about 305 mμ (estimated from the published figure[14]). Jaffé[26] in his study of the characteristics of the ultraviolet absorption spectrum of pyridine-N-oxides, demonstrated that the lower wave length band is susceptible to the effects of substituents. This has not been seen in the corresponding pyrazine-N-oxide series, since on increasing substitution, there is no shift in the lower wave length, nor marked alteration in the intensity of the band. Further studies on the effect of functional substituents on the ultraviolet absorption spectrum of pyrazine-N-oxides are in progress.

Pyrazine-1,4-dioxides also exhibit characteristic and distinctive ultraviolet absorption spectra (Table V). Nearly all 1,4-dioxides show a peak at about 230 mμ and another at about 300 mμ. In the parent pyrazine-1,4-dioxide, the lower wave length maximum is found at 222 mμ. Addition of substituents to the ring causes a shift of this absorption maximum to 230–235 mμ. With

(26) H. H. Jaffé, THIS JOURNAL, 77, 4451 (1955).

increased loading of substituents, the intensity of the band shows a moderate increase, indicating perhaps some increased resonance transition



Unfortunately, 2,5-dimethyl-6-substituted pyrazine-mono-N-oxides are unavailable for comparison of ultraviolet spectra.

Infrared Absorption Spectra.—The N → O stretching frequency in pyridine and pyrimidine-N-oxides has been assigned to the 1255–1300 cm.$^{-1}$ (7.65–7.85 μ) band.[4] A second characteristic band for N-oxides is also found by Wiley and Slaymaker[4] to exist at 847–872 cm.$^{-1}$ (11.45–11.80 μ). In infrared absorption studies of pyrazine-N-oxides and -di-N-oxides, Gumprecht[18] found typical absorptions at 1300–1305 cm.$^{-1}$ (7.7 μ) for the mono-N-oxides and 1260–1270 cm.$^{-1}$ (7.95 μ) for the di-N-oxides.

Pyrazine and Substituted Pyrazines.—The infrared absorption spectra of the parent heterocyclic pyrazine and substituted pyrazine compounds were determined in this Laboratory to serve as a background against which the spectra of the corresponding mono- and di-N-oxides could be compared. These are listed in Table VI.

Pyrazine-mono-N-oxides.—The principal absorptions in the infrared spectra of the mono-N-oxides are given in Table VII. It will be seen that another and distinctive absorption is present at 7.60 μ for pyrazine-1-oxide. Among the methyl substituted compounds, the new and characteristic wave length occurs at 7.75 μ in the case of both forms of 3-methylpyrazine-1-oxide. The symmetrical 2,5-dimethylpyrazine-1-oxide is characterized by the appearance of two peaks which absorb weakly at 7.65 and 7.77 μ in chloroform solution but are markedly in evidence in potassium bromide disk preparations. The low melting asymmetrical 2,6-dimethylpyrazine-1-oxide in chloroform solution shows a distinct peak at 7.72 μ with weak absorption at 7.40 μ. The high melting 4-oxide exhibits its strong N→O absorption (in chloroform solution) at 7.42 μ and weak absorption at 7.75 μ. Tetramethylpyrazine-1-oxide exhibits two strongly absorbing peaks at 7.57 and 7.65 μ.

The pyrazine-mono-N-oxides also exhibit the absorptions at 11.4–11.8 μ ascribed to the N→O function by Wiley and Slaymaker.[4] Thus, pyrazine-1-oxide shows strongest absorptions at 11.6 and 11.95 μ. Both the low and high melting 3-methylpyrazine-1-oxide show strong absorption at 11.5 and 11.75 μ. 2,5-Dimethylpyrazine-1-oxide absorbs at 11.70 μ (KBr) and 11.80 μ (chloroform solution). These absorptions were apparently overlooked by Gumprecht[18] in his study of the infrared spectra of the above three compounds. Both 2,6-dimethylpyrazine-1-oxide and 4-oxide in chloroform solution exhibit a weak absorption at 11.45 μ and a fairly strong absorption at 11.77 μ for the former and at 11.80 μ for the

TABLE VII

PRINCIPAL ABSORPTIONS IN THE INFRARED

Compound	6 μ	7 μ	8 μ	9 μ	10 μ	11 μ	12 μ	13 μ	14 μ
I[a]	6.25(s), 6.70(s), 6.95(s)	7.60(vs)	8.25(s)	9.30(m), 9.95(vs)		11.60(vs), 11.80(m)			
						11.95(vs)			
II[a]	6.30(s), 6.80(s)	7.15(m), 7.75(vs)	8.20, 8.45		10.10	11.50(m), 11.75(m)	12.85(s)		
		7.20(m)							
III[b]	6.25(s), 6.50, 6.80(s)	7.15(s), 7.20(s)	8.20, 8.45		10.05	11.50(m), 11.75(m)			
		7.75(vs)							
IV[b]	6.20(m), 6.60(vs), 6.75(vs)	7.20(s), 7.40(s)	8.25(s), 8.75	9.60(w), 9.90(vs)	10.55(s)	11.0(w), 11.45(s)	12.70(m)	13.45(vs)	
		7.65(vs), 7.77(vs)							
V[a]	6.20(vs), 6.55(s), 6.75(vs)	7.20(s), 7.40(s)	8.45	9.90–10.0(s)		11.45(w), 11.75(vs)		13.50(s)	
		7.72(vs)							
VI[a]	6.20, 6.55, 6.75(vs)	7.42(vs), 7.75(w)	8.55	9.60(s), 9.90(s)	10.0(w), 10.80(s)	11.45(w), 11.80(vs)		13.45(s)	
VII[b]	6.30(m), 6.75(s), 6.90(s)	7.20(m), 7.40(m)	8.00(w), 8.50(w)	9.00(m), 9.85–9.90(m)	10.15(m)	11.0(w), 11.65(w)	12.50(w)	13.50(s)	14.65(s)
		7.57(vs), 7.65(s)	8.80(s)						

[a] $CHCl_3$ solution, 0.05-cm. cell. [b] KBr disk preparation.

TABLE VIII

PRINCIPAL ABSORPTIONS IN THE INFRARED

Compound[a]	6 μ	7 μ	8 μ
VIII	6.75(m), 6.90(vs)	7.22(s), 7.65(m), 7.95(vs)	
IX	3.30(s), 6.55(m), 6.90(vs)	7.15(s), 7.25(s), 7.55(s), 7.85(vs)	8.45(m), 8.55(vs)
X	3.25(m), 6.50(s), 6.90(vs)	7.10(m), 7.35(vs), 7.85(vs)	8.40(s), 8.60(vs), 8.75(vs)
XI	3.50(m), 6.10(w), 6.50(s), 6.85(vs)	7.20–7.30(s), 7.80(vs)	8.45(vs)
XII	6.55(s), 6.85–7.00(s)	7.20(s), 7.45(s), 7.65(vs)	8.95(vs)
XIII	3.40(s), 6.15(m), 6.60(s), 6.95(vs)	7.45(vs), 7.75(vs)	8.30(vs), 8.80(s), 8.90(vs)
XIV	3.40(m), 6.15(w), 6.60(m), 6.95(s)	7.40(vs), 7.65–7.75(s)	8.20(s), 8.90(vs)
XV	3.40–3.50(m), 6.55(m), 6.90(s)	7.70(vs), 7.85(m), 7.10(w), 7.40(vs)	8.10(vs), 8.40(s), 8.95(vs)
XVI	6.70(w), 6.95(s)	7.40(vs), 7.70(s)	8.20(vs), 8.80(s)

9 μ	10 μ	11 μ	12 μ	13 μ	14 μ
9.70(vs)		11.15(w), 11.50(vs)	12.45(vs)		
9.0(m), 9.65(w), 9.95(vs)	10.25(s)	11.0(s), 11.60(vs)	12.30(vs)	13.20(vs)	
9.90(vs)		11.05(s), 11.50(vs)		13.50(w)	14.20(vs)
9.50(s)	10.10(vs)	11.20(vs)	12.20–12.30(vs)		14.30(s)
9.65(m)		11.55(vs)			
9.0(vs), 9.65(vs)	10.10(s), 10.50(s)	11.56(m), 11.65(vs)	12.40(w), 12.75(w)	13.15(w), 13.75(vs)	
9.45(m), 9.60(s)	10.25(m), 10.60(w)	11.20(m), 11.60(s)		13.65(s), 13.85(s)	
9.50(m), 9.60(m)	10.05(w), 10.15(w), 10.60(m)	11.10(m), 11.60(m)		13.60(s), 13.90(vs)	
9.65(vs), 9.85(vs)		11.05(s), 11.40(m)		13.20(s), 13.70(vs)	14.40(vs)

[a] All spectra were prepared from KBr disks.

latter compound. In a potassium bromide disk preparation, a weakly absorbing peak at 11.65 μ characterizes the spectrum of tetramethylpyrazine-1-oxide.

Pyrazine-1,4-dioxides (Table VIII).—The pyrazine-1,4-dioxides exhibit the characteristic absorptions assigned to the N→O function. Pyrazine-1,4-dioxide shows its N→O absorption at 7.95 and 11.50 μ. 2-Methylpyrazine-1,4-dioxide absorbs very strongly at 7.85 and 11.60 μ. 2,5-Dimethylpyrazine-1,4-dioxide exhibits its absorption at 7.85 and 11.50 μ. 2,6-Dimethylpyrazine-1,4-dioxide absorbs very strongly at 7.80 μ and surprisingly at 11.20 μ. Finally, in tetramethylpyrazine-1,4-dioxide, the characteristic absorption is at 7.65 and 11.55 μ.

Among the trisubstituted pyrazine-1,4-dioxides, the appearance of characteristic absorptions again holds true. 2,5-Dimethylpyrazine-3-butylpyrazine-1,4-dioxide absorbs strongly at 7.75 and 11.65 μ. The corresponding 3-amyl derivative shows a somewhat broadened absorption at 7.65–7.75 μ and again at 11.60 μ. Characteristically, the 3-hexyl analog shows absorption at 7.70 and 11.60 μ. Finally, 2,5-dimethyl-3-phenylpyrazine-1,4-dioxide shows the distinct sharp absorption at 7.70 μ and a broadened absorption at 11.40 μ.

Experimental[27,28]

Materials.—Pyrazine, 2-methylpyrazine, 2,5-dimethylpyrazine, 2,6-dmethylpyrazine and tetramethylpyrazine were obtained from the Wyandotte Chemicals Corp., Wyandotte, Mich.[29] The preparation of the trisubstituted pyrazines were reported in an earlier publication from this Laboratory.[30]

Preparation of Pyrazine-mono-N-oxides.—The general procedure used in the preparation of the mono-N-oxides was similar to that published by Ochiai.[2]

Pyrazine or the substituted pyrazine compound was heated with 2 molar equivalents of 30% hydrogen peroxide in 5 molar equivalents of glacial acetic acid for a total of 8 hours at 70°. One-half the quantity of hydrogen peroxide was added initially, the remainder about midway during the heating period. The solution was concentrated under reduced pressure (45°) to about one-third the volume and diluted with an equal quantity of cold water. The solution was made alkaline with 20% sodium hydroxide and extracted with chloroform. The combined extracts were dried, the solvent stripped under reduced pressure and the residues chilled. The crystalline residue was usually recrystallized from benzene or purified for analysis by sublimation *in vacuo* (125–180° (10 mm.)).

The residues in the reactions with 2-methylpyrazine and 2,6-dimethylpyrazine were semi-solid oils. The solid was separated from the oil by decantation and filtration, washed with small amounts of cold petroleum ether and either recrystallized from benzene or purified for analysis by vacuum sublimation.

The oil was combined with the petroleum ether washings and concentrated under reduced pressure and distilled.

Preparation of Pyrazine-1,4-dioxides.—The pyrazine compounds were heated in 10 molar equivalents of glacial acetic acid with 4 molar equivalents of 30% hydrogen peroxide, added in 2 portions, on a steam-bath (95°) for 16 to 24 hours. The solutions were worked up as described above. After removal of the solvent, the residues usually crystallized. Portions of the crystalline materials were purified for analysis by sublimation *in vacuo* (150° (10 mm.)).

Preparation of 2-Chloro-3-methylpyrazine.—(A) To 50 ml. of cold redistilled phosphorus oxychloride, 11.0 g. (0.1 mole) of 3-methylpyrazine-1-oxide (m.p. 45°) was added in several portions. The mixture was warmed and after a vigorous reaction had subsided, refluxed for an additional hour. The excess phosphorus oxychloride was removed *in vacuo* and the residual black oil poured cautiously onto 200 g. of chopped ice. The solution was neutralized with cold 20% sodium hydroxde and extracted with chloroform. The combined extracts were dried over anhydrous sodium sulfate and the solvent removed. The residual oil was dis-

(27) Melting points were taken either on a Fisher–Johns melting point block or a Kofler hot-stage and are uncorrected.

(28) Microanalyses by Schwarzkopf Microanalytical Laboratories, Woodside, L. I., N. Y.

(29) The authors wish to acknowledge with thanks, their gratitude to Dr. Phelps Trix of the Wyandotte Chemicals Corp. for making these compounds available to us, and for his continued interest throughout the course of this study.

(30) B. Klein and P. E. Spoerri, THIS JOURNAL, 73, 2950 (1951).

tilled to give 2.2 g. (18%) of product, b.p. 78° (25 mm.), $n^{27}D$ 1.5283. Karmas and Spoerri[31] give the b.p. of this compound as 94–96° (65 mm.), $n^{25}D$ 1.5302.

(B) A similar experiment with 11.0 g. (0.10 mole) of the 3-methylpyrazine-1-oxide (m.p. 80–82°) gave a 4.0-g. residue which, on distillation, gave 1.2 g. (10.4%) of product, b.p. 80° (27 mm.).

Both compounds gave identical ultraviolet and infrared absorption spectra ($CHCl_3$ solution), which in turn, were identical with the spectra of an authentic sample of 2-chloro-3-methylpyrazine.[32]

(31) G. Karmas and P. E. Spoerri, THIS JOURNAL, **74**, 1582 (1952).

Absorption Spectra.—Ultraviolet absorption spectra were obtained on a Beckman DU spectrophotometer, with 1-cm. quartz cuvets. Infrared absorption spectra were obtained on a Perkin–Elmer model 21 recording spectrophotometer either as chloroform solutions, carbon disulfide solutions or potassium bromide disk preparations.[33]

(32) Obtained from the Wyandotte Chemicals Corp. by the courtesy of Dr. Phelps Trix.

(33) The authors are indebted to Dr. Oscar Auerbach, Assistant Director, Professional Services for Research, V. A. Hospital, East Orange, N. J., for loan of the infrared spectrophotometer.

BRONX 68, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE COLLEGE OF LIBERAL ARTS OF TEMPLE UNIVERSITY]

The Synthesis of 2-Amino-5-pyrimidinesulfonamide and Some of its Derivatives

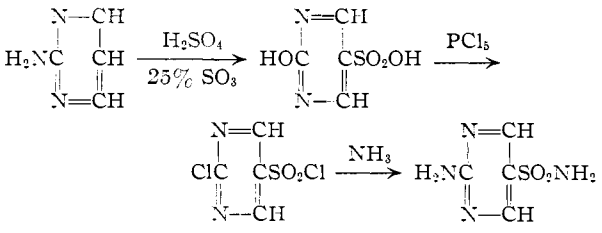
BY WILLIAM T. CALDWELL AND GERALD E. JAFFE

RECEIVED MARCH 23, 1959

2-Amino-5-pyrimidinesulfonamide and a number of its N^1,N^4-substituted derivatives have been prepared from 2-chloro-5-pyrimidinesulfonyl chloride, readily obtainable from 2-aminopyrimidine in two steps.

The therapeutic value of sulfanilamide led naturally to the preparation of many of its derivatives and analogs such as sulfadiazine[1] on the one hand and 2-amino-5-pyridinesulfonamide,[2] 3-amino-6-pyridinesulfonamide[3] and 2-amino-5-thiazolesulfonamide[4] on the other. Because of the efficacy of sulfadiazine, the preparation of 2-amino-5-pyrimidinesulfonamide and its derivatives has seemed intriguing, particularly in view of the fact that such a comparatively simple compound has not yet been described in the literature. The reason for this is, doubtless, that the obviously requisite intermediates such as 2-acetamido-5-pyrimidinesulfonyl chloride or 2-nitro-5-pyrimidinesulfonyl chloride are not readily accessible.

After many abortive experiments, we have found a simple sequence of reactions by which we have prepared the primary objective of our work, 2-amino-5-pyrimidinesulfonamide, as well as a number of its derivatives; this sequence is illustrated by the transitions



These reactions, some of which are described below, involve first the conversion of 2-aminopyrimidine into an unanticipated, deaminated product, 2-hydroxy-5-pyrimidinesulfonic acid, which is readily convertible into 2 - chloro - 5 - pyrimidinesulfonyl chloride. The latter, in turn, serves as an intermediate for preparing 2-amino-5-pyrimidinesulfonamide and N^1,N^4-disubstituted derivatives thereof; unfortunately, it is not suited to the preparation of N^1-monosubstituted sulfonamides. Attempts to prepare 2-acetamido-5-pyrimidinesulfonyl chloride have so far been unsuccessful in our hands; both 2-aminopyrimidine and 2-acetamidopyrimidine, when treated with chlorosulfonic acid, yielded 2-amino-5-pyrimidinesulfonic acid. The latter was obtained unchanged after attempts to acetylate it, and when treated with phosphorus pentachloride formed only refractory products.

We wish to thank Eli Lilly and Co. for carrying out pharmacological tests and the Temple University Committee on Research and Publications for a grant-in-aid.

The tests so far reported on these compounds indicate that they have no significant value pharmacologically.

(1) R. O. Roblin, J. H. Williams, P. S. Winnek and J. P. English, THIS JOURNAL, **62**, 2002 (1940).

(2) C. Naegeli, W. Kündig and H. Bradenburger, *Helv. Chim. Acta*, **21**, 1746 (1938).

(3) W. T. Caldwell and E. C. Kornfeld, THIS JOURNAL, **64**, 1695 (1942).

(4) H. J. Backer and J. A. K. Buisman, *Rec. trav. chim.*, **63**, 228 (1944).

Experimental

2-Hydroxy-5-pyrimidinesulfonic Acid.—To 400 ml. of fuming sulfuric acid (25% SO_3) was added cautiously 95 g. (1 mole) of 2-aminopyrimidine. The temperature was then raised to 180° and kept there for five hours. After cooling, the contents of the flask were poured upon 4 kg. of crushed ice and the white solid filtered off; yield, after recrystallization from water, 42 g. (23.8%), m.p. above 300°.

Anal. Calcd. for $C_4H_4N_2O_4S$: C, 27.27; H, 2.29; N, 15.90. Found: C, 27.45; H, 2.47; N, 15.95.

2-Chloro-5-pyrimidinesulfonyl Chloride.—A mixture of 104.3 g. (0.5 mole) of phosphorus pentachloride and 35.2 g. (0.2 mole) of 2-hydroxy-5-pyrimidinesulfonic acid was heated in an oil-bath at 180° under reflux. After two hours, the material formed a tan-colored liquid which was refluxed for an additional two hours. To the cooled liquid, 400 ml. of benzene was added and the solution filtered. Upon concentration under diminished pressure, a light tan-colored solid remained which was placed in a Soxhlet apparatus and continuously extracted with 500 ml. of petroleum ether (b.p. 30–60°) for 16 hours. This solution was concentrated to one-half of its original volume and then cooled. After filtering and drying, the yield of white, crystalline product was 37 g. (87%), m.p. 66–67°.

Anal. Calcd. for $C_4H_2Cl_2N_2O_2S$: C, 22.55; H, 0.95; N, 13.15; Cl, 33.28. Found: C, 22.79; H, 0.97; N, 12.94; Cl, 33.18.

2-Amino-5-pyrimidinesulfonamide.—A mixture of 2.13 g. (0.01 mole) of 2-chloro-5-pyrimidinesulfonyl chloride and