solid recrystallized from methanol. The product, 5.4 g (47%), mp 156–158°, crystallized from methanol as colorless needles (analytical sample, mp 158–159°).

Anal. Calcd for $C_{13}H_{11}NO_3S$: C, 59.75; H, 4.24; N, 5.36. Found: C, 59.67; H, 4.33; N, 5.39.

3-Carboxylthiazolo[3,2-*a*]pyridinium Bromide (XVIII).—Keto sulfide (I, R = H, R′ = 3,4-$(OH)_2C_6H_3$) (1 g) was heated on a steam bath for 9 hr with 10 g of polyphosphoric acid. The mixture which contained XV was diluted with ice water, 20 ml of 8 *M* nitric acid was added, and the solution was heated for 12 hr on a steam bath. After the mixture was cooled, the product was precipitated as the tribromide salt by addition of a solution of bromine in 48% hydrobromic acid. The orange-brown precipitate was collected and dissolved in dry acetone. After 15 min, the bromide precipitated as a cream powder, mp 285° dec, yield 0.55 g (55%). The analytical sample was crystallized from methanol–ethyl acetate: mp 287° dec; λ_{max}, mμ (log ϵ), 311 (4.17), 304 (4.06), and 229 (4.16).

Anal. Calcd for $C_8H_6NSO_2Br$: C, 36.94; H, 2.33; N, 5.39. Found: C, 36.94; H, 2.39; N, 5.46.

2-Carboxylthiazolo[3,2-*a*]pyridinium Bromide (XVII).—The reaction of 5.58 g of 3′,4′-dihydroxyphenacyl chloride with an excess of 2-bromopyridine in 10 ml of tetramethylene sulfone afforded 12.0 g of a light gray powder which was allowed to react in water solution with 2.2 g of potassium hydrogen sulfide. The gummy precipitate solidified when triturated with acetone affording a tan powder, mp 188° dec, yield 4.0 g (40% based on the phenacyl halide). The tan powder (0.5 g) was heated on a steam bath for 13 hr with 10 ml of polyphosphoric acid and, after dilution of the polyphosphoric acid with ice water, the crude XV present was oxidized with 8 *M* nitric acid and the bromide salt of the acid XVII was isolated as in the case of the isomer XVIII. The product was obtained from methanol–ethyl acetate as a buff powder: mp 270–274° (darkens at 200°); yield 0.05 g (4% over-all from the dihydroxyphenacyl chloride); λ_{max}, mμ (log ϵ), 310 (3.86), 277 sh (3.62), 260 sh (3.60), 228 (3.93), and 201 (4.08).

Anal. Calcd for $C_8H_6NSO_2Br$: C, 36.94; H, 2.33; N, 5.39. Found: C, 36.95; H, 2.40; N, 5.63.

pK_a Determinations on Acids XVII and XVIII.—The determination of the pK_a for the 2- and 3-carboxylic acids (XVII and XVIII) was carried out by titrating aqueous solutions of the bromides with standard sodium hydroxide solution and measuring the hydrogen ion concentration with a pH meter. Since only relative pK_a values were required for our purpose, it was assumed that the pK_a was approximately equal to the pH when one-half of the volume of hydroxide needed for complete neutralization had been added. By this method both acids XVII and XVIII were shown to have pK_a values of 2.3 ± 0.2.

Registry No.—I [R = H, R′ = 3,4-$(OH)_2C_6H_3$] 13134-60-6; I (R = H, R′ = *t*-Bu) hydrobromide, 13134-61-7; II (R = H, R′ = *t*-Bu) perchlorate, 13169-24-9: VIIb bromide, 13134-62-8; VIIb perchlorate, 13134-63-9; VIIc bromide, 13127-29-2; VIIc perchlorate, 13134-64-0; VIId bromide, 13134-65-1; VIId perchlorate, 13134-662-; VIIe perchlorate, 13134-67-3; VIIf bromide, 13134-68-4; VIIf perchlorate, 13434-69-5; VIIg bromide, 13221-14-2; VIIg perchlorate, 13434-70-8; IXb, 13134-71-9; IXc, 13134-80-0; IXd, 13134-81-1; IXe, 13134-82-2; IXf, 13134-83-3; IXg, 13134-84-4; XIa, 13134-85-5; XIb, 13134-86-6; XIc, 13127-33-8; XId, 13127-34-9; XIe, 13134-87-7; XIf, 13134-88-8; XIg, 13134-89-9; XVII, 13169-29-4; VXIII, 13134-90-2.

Pyrazines. V. The Amination of Chloropyrazines and Chloropyrazine N-Oxides[1a]

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Marked activation of the chloro group to nucleophilic replacement by ammonia and amines by the N-oxide function was demonstrated when the reactivities of chloropyrazine and 3-chloropyrazine-1-oxide were compared. Similarly enhanced activation by the $N^+ \rightarrow O^-$ was observed when 2-chloro-3,6-dimethylpyrazine and 3-chloro-2,5-dimethylpyrazine 1-oxide were compared, although dialkyl substitution further retarded over-all aminolysis. 3-Chloropyrazine 1-oxide heated 2.5 hr (120°) with aqueous ammonia gave a good yield of the 3-amino derivative. However, when the reactants were heated 16 hr at 140°, aminopyrazine and 2,3-diaminopyrazine were formed also. A reaction sequence accounting for these products is suggested. Heating chloropyrazine with benzylamine produced benzaldehyde and aminopyrazine in addition to the expected benzylamino derivative. 2-Benzylamino-3,6-dimethylpyrazine underwent similar cleavage and benzaldehyde and 2-amino-3,6-dimethylpyrazine were isolated.

In connection with another investigation, information was required on the reactivity of chloropyrazine, the alkyl chloropyrazines, and their N-oxides toward ammonia and amines. Aminolysis of chloropyrazine and alkylchloropyrazines has usually been conducted under fairly severe conditions, *e.g.*, heating in a sealed vessel for 16–24 hr or longer at elevated temperatures.[2–7] Arylaminopyrazines have been prepared by boiling the chloro compound with excess amine at temperatures over 200°.[8]

In the previous paper in this series,[9] N-oxide activation was demonstrated in nucleophilic displacement of the chloro group by hydroxyl, although this effect was not as apparent when alkoxide was the reagent. Recent descriptions of the preparation of 3-aminopyrazine 1-oxide[10] and the amination of 3-chloro-2-methylpyrazine 1-oxide[11] suggested similar halogen activation by the N → O since milder conditions were used to effect the amination. This report presents the results of an extended examination of the comparative N-oxide activation and the influence of alkyl heterocyclic ring substitution on the nucleophilic reaction.

(1) (a) Presented in part in Abstracts, 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1964, p 54S. (b) To whom correspondence should be addressed: Research Division, Hoffmann-LaRoche, Inc., Nutley, N. J. 07110.

(2) A. E. Erickson and P. E. Spoerri, *J. Am. Chem. Soc.*, **68**, 400 (1946).

(3) G. W. H. Cheeseman, *J. Chem. Soc.*, 242 (1960).

(4) A. E. Hirschberg and P. E. Spoerri, *J. Org. Chem.*, **26**, 2356 (1961).

(5) H. Gainer, M. Kokorudz, and W. K. Langdon, *ibid.*, **26**, 2360 (1961).

(6) W. B. Lutz, S. Lazarus, S. Kutchko, and R. I. Meltzer, *ibid.*, **29**, 415 (1964).

(7) (a) B. Camerino and G. Palamidessi, *Gazz. Chim. Ital.*, **90**, 1807 (1980); (b) L. Bernardi, G. Palamidessi, A. Leone, and G. Larini, *ibid.*, **91**, 1431 (1961); (c) F. Chillemi and G. Palamidessi, *Farmaco* (Pavia), *Ed. Sci.*, **18**, 566 (1963).

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(9) B. Klein, E. O'Donnell, and J. M. Gordon, *ibid.*, **29**, 2623 (1964).

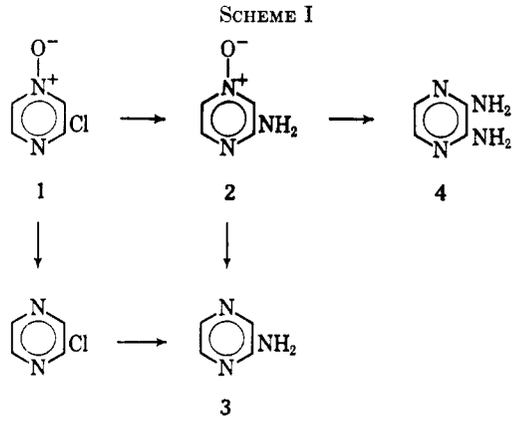
(10) G. Palamidessi and L. Bernardi, *Gazz. Chim. Ital.*, **93**, 339 (1963).

(11) W. B. Lutz, S. Lazarus, S. Klutchko, and R. I. Meltzer, *J. Org. Chem.*, **29**, 1645 (1964).

The preparation of aminopyrazine in 87% yield from chloropyrazine required at least 16 hr at 140°. By contrast, when 3-chloropyrazine 1-oxide (1) was heated with excess aqueous ammonia at 115–120° for 2.5 hr,[10] 3-aminopyrazine 1-oxide (2) was formed in good yield, but, when 1 and ammonia were subjected to the more usual amination conditions (140° for 16 hr), a mixture was obtained from which aminopyrazine (3) and 2,3-diaminopyrazine (4) were isolated. At temperatures and heating times between those cited above, mixtures of differing composition were obtained, containing two or all three products in varying proportions, depending on the experimental conditions applied. The products, after chromatographic separation, were identified by elemental analysis, conversion to known derivatives, comparison by thin layer chromatography, and identity of their infrared and ultraviolet absorption spectra with authentic specimens.

To account for these products, 3-aminopyrazine 1-oxide (2) was assumed to be the pivotal intermediate (Scheme I). On one hand, deoxygenation of 2 would

SCHEME I



yield 3. On the other hand, by an as yet undetermined mechanism, 2 was converted to another intermediate which subsequently formed 4. Support for the latter transformation was obtained when 3-aminopyrazine 1-oxide was heated with aqueous ammonia at 140–145° for 16 hr and only 2,3-diaminopyrazine was isolated. On the other hand, the absence of aminopyrazine under these conditions suggested that 3 was formed following removal of oxygen from 3-chloropyrazine 1-oxide and the resulting chloropyrazine underwent ammonolysis. The intermediates leading from 2 to 4 are still speculative, although several hypothetical structures can be written.[12] The unexpected formation of 4 was of considerable interest. 2,3-Diaminopyrazine had been prepared by heating the difficultly accessible 2-amino-3-chloropyrazine with ammonia[13,14] or by dehalogenation of 2,3-diamino-5-bromopyrazine.[7a] Now this useful intermediate can be prepared in a two-step synthesis from 2-chloropyrazine.[15]

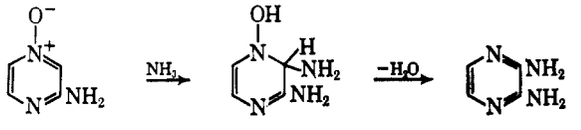
Attempts to prepare *n*-butylaminopyrazine (III) in reasonable yield by heating chloropyrazine with *n*-butylamine under reflux for periods up to 16 hr were unsuccessful. Formation of *n*-butylaminopyrazine in spectrophotometrically detectable quantities first appeared at 5 hr, as indicated by the development of absorptions at 246 and 334 mμ without any absorption or shoulders at 275 mμ.[15] *n*-Butylaminopyrazine was best prepared in 74.5% yield by heating the reactants in a sealed vessel for 8 hr at 120°. By contrast *n*-butylaminopyrazine 1-oxide (XIV) was readily formed in 60% yield when 1 was refluxed with excess *n*-butylamine for 30 min.

Comparative N-oxide activation was similarly observed when other amine types such as hexylamine, aniline, benzylamine, piperidine, and dimethylamine were used. In general, the ease of amination of 3-chloropyrazine 1-oxide increased with increasing boiling point of the amine, *e.g.*, increasing chain length in aliphatic amines, and with increasing amine basicity. It was also noted, in every example studied, when amination of the chloropyrazine or alkylchloropyrazine N-oxide was attempted at elevated temperatures in a sealed vessel, mixtures were obtained containing greater or lesser amounts of deoxygenated pyrazyl halide or amine which could be demonstrated by thin layer chromatography but were difficult to isolate and purify. This was particularly true in the preparation of 3-dimethylaminopyrazine 1-oxide. A good yield of the compound was finally obtained by heating 1 and aqueous dimethylamine briefly (1 hr) at 120°. Similarly enhanced reactivity of 3-chloro-2-methylpyrazine 1-oxide during the preparation of 3-dimethylamino-3-methylpyrazine 1-oxide, with liquid dimethylamine, had been reported without comment by Lutz, *et al.*[11]

The synthesis of benzylaminopyrazine by heating chloropyrazine and benzylamine without solvent at atmospheric pressure was accompanied by another, unexpected by-product. During the work-up, the odor of benzaldehyde was detected. This was isolated and its identity confirmed as the 2,4-dinitrophenylhydrazone. Although aminopyrazine was not isolated, its presence was demonstrated by thin layer chromatography. Presumably, partial cleavage of benzylaminopyrazine had occurred. Similar cleavage was observed during the synthesis of 2-benzylamino-3,6-dimethylpyrazine. In this reaction, the other cleavage product, 2-amino-3,6-dimethylpyrazine, was also isolated and identified. Mechanistically, this development is obscure. The reaction is being examined in greater detail and these studies will be reported later.

To determine the influence of ring alkyl substitution, 2-chloro-3,6-dimethylpyrazine and its N-oxide[15,16] were used as model substrates. The results indicated that, although ring alkylation in each series further retarded amination, N-oxidation did enhance the relative reactivity of the halogen. The results are summarized in Tables I and II.

(12) A referee suggested an addition–elimination reaction, shown below,



which seems pertinent and may also have some bearing on the deoxygenation observed in this and other experiments. Experiments to test this hypothesis are in progress.

(13) R. C. Ellingson and R. L. Henry, *J. Am. Chem. Soc.*, **70**, 1257 (1948).

(14) F. C. Muehlmann and A. R. Day, *ibid.*, **78**, 242 (1956).

(15) B. Klein, N. E. Hetman, and M. E. O'Donnell, *J. Org. Chem.*, **28**, 1682 (1963).

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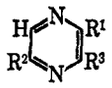
TABLE I

AMINOPYRAZINES

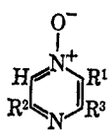


No.	R¹	R²	R³	Reaction time, hr	T, °C	Yield, %	Bp (mm) or mp, °C	$n^{25}D$	Formula	Analyses, % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
I	H	H	NH_2	16	140	87	117–118[a]								
II	NH_2	H	NH_2	16	140	42	205–206		$C_4H_6N_4$	43.63	5.49	50.88	43.81	5.51	51.10
III	H	H	NHC_4H_9	12	120	74.5	148–151 (17)	1.5476	$C_8H_{13}N_3$	63.54	8.66	27.79	62.92	9.13	27.70
IV	H	H	NHC_6H_{13}	18	140–145	75	134 (2.0); 32	1.5335	$C_{10}H_{17}N_3$	66.99	9.57	22.44	66.96	9.86	22.63
V	H	H	NHC_6H_5	1.25	Reflux	81	135–136[b]		$C_{10}H_9N_3$	70.14	5.30	24.55	69.66	5.40	24.76
VI	H	H	Piperidino	3	Reflux	64	36–37[c]		$C_9H_{13}N_3$	66.23	8.03	25.79	66.23	8.07	25.82
VII	H	H	$N(CH_3)_2$	16	140	76	88–90 (8)[d]	1.5680							
VIII	H	H	$NHCH_2C_6H_5$	1	Reflux	49	68–69		$C_{11}H_{11}N_3$	71.33	5.99	22.68	71.55	6.15	22.65
IX	CH_3	CH_3	NH_2	29	160–165	65	112–114[e]								
X	CH_3	CH_3	NHC_4H_9	46	140	81	127–128 (5)	1.5360	$C_{10}H_{17}N_3$	67.38	9.05	23.57	67.02	9.53	23.92
XI	CH_3	CH_3	Piperidino	30	Reflux	72	136–137[f]		$C_{11}H_{17}N_3$	58.01	7.97	18.45	58.09	8.09	18.57
XII	CH_3	CH_3	$NHCH_2C_6H_5$	2	Reflux	35.9	96–96.5		$C_{13}H_{15}N_3$	73.21	7.09	19.70	73.28	7.53	19.60
XIII	CH_3	CH_3	$N(CH_3)_2$	8	200	37	100 (20)[g]	1.5338	$C_8H_{13}N_3$	63.54	8.67	27.79	63.89	8.74	27.52

[a] Reference 3 gives mp 121–122°; ref 2 gives mp 118–120°. [b] Reference 21 gives mp 135.5–136.2°. [c] Reference 6 gives melting point of the HCl salt. [d] Reference 3 gives bp 64° (1.2 mm). [e] Reference 4 gives mp 111–113°. [f] See footnote 28 of this paper. [g] Reference 5.

TABLE II

AMINOPYRAZINE 1-OXIDES



No.	R¹	R²	R³	Reaction time, hr	T, °C	Yield, %	Mp, °C	Formula	Analyses, % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
XIV	H	H	NH_2	2.5	115–120	75.3	175–176[a]	$C_4H_6N_3O$	43.20	4.54		42.96	4.33	
XV	H	H	NHC_4H_9	0.5	Reflux	60	64.5–66	$C_8H_{13}N_3O$	57.80	7.29	25.29	57.66	7.17	24.86
XVI	H	H	NHC_6H_{13}	0.25 (3.25)	Reflux (ethanol)	93	83.5–84	$C_{10}H_{17}N_3O$	61.49	8.78	21.54	61.76	8.78	21.25
XVII	H	H	$NHCH_2C_6H_5$	3.75	Reflux (ethanol)	92	124–126	$C_{11}H_{11}N_3O$	65.65	5.51	20.88	65.71	5.66	20.81
XVIII	H	H	NHC_6H_5	3.75	Reflux (*i*-AmOH)	38	165–166	$C_{10}H_9N_3O$	64.10	4.81	22.44	64.16	4.95	22.24
XIX	H	H	Piperidino	2	Reflux	73	124–125	$C_9H_{13}N_3O$	60.30	7.31	23.50	60.55	7.56	23.60
XX	H	H	$N(CH_3)_2$	1	120	93	149–150	$C_6H_9N_3O$	51.70	6.52	30.20	51.82	6.66	29.95
XXI	CH_3	CH_3	NH_2	6	120	79	239–240	$C_6H_9N_3O$	51.70	6.52	30.20	51.71	6.74	30.08
XXII	CH_3	CH_3	NHC_4H_9	6	Reflux	76	104–105	$C_{10}H_{17}N_3O$	61.53	8.78	21.53	61.57	9.05	21.51
XXIII	CH_3	CH_3	NHC_6H_{13}	1	Reflux	37	82.5–83.5	$C_{12}H_{21}N_3O$	64.54	9.48	18.82	64.88	9.70	18.47
XXIV	CH_3	CH_3	$NHCH_2C_6H_5$	6	Reflux (BuOH)	40	195–196	$C_{13}H_{15}N_3O$	68.10	6.59	18.33	68.34	6.84	18.16
XXV	CH_3	CH_3	Piperidino	1	Reflux	73	73–75	$C_{11}H_{17}N_3O$	63.72	8.27	20.28	63.98	8.24	20.02
XXVI	CH_3	CH_3	$N(CH_3)_2$	24	Room temp		72–74	$C_8H_{13}N_3O$	57.46	7.83	25.13	57.54	8.00	25.18

[a] Reference 10 gives mp 175°. [b] See footnote 30 of this paper.

Cheeseman[3] concluded, on the basis of the comparatively similar ultraviolet absorption spectra of 2-amino-, 2-methylamino-, and 2-dimethylaminopyrazine, that aminopyrazine in aqueous solution existed mainly in the amino form. A comparison of the ultraviolet absorption spectra of 3-aminopyrazine 1-oxide and 3-dimethylaminopyrazine 1-oxide showed similar spectral differences and bathochromic shifts on protonation and suggested that 3-aminopyrazine 1-oxide also existed predominantly in the amino form. This was also true of the 2,5-dimethyl homolog. The infrared spectra of both 3-aminopyrazine 1-oxide and 3-amino-2,5-dimethylpyrazine 1-oxide exhibited the twin absorptions at 3400 and 3350 cm^{-1} (symmetric and asymmetric N–H vibrations) characteristic of the primary amino group and an absorption at 3180 cm^{-1} (H bonding?). The 1655-cm^{-1} (NH_2 bonding) vibration observed further supported an amino structure.

Experimental Section[17,18]

Preparation of Aminopyrazines.—Following is a general description of the procedure used for the preparation of compounds I, III, IV, VII, IX, X. Chloropyrazine[19] and excess amine were heated in a stainless-steel bomb (Table I gives heating times and temperature). The cooled product was made alkaline and extracted continuously with ether. The dried extract was concentrated, excess amine was removed under reduced pressure, and the residue was recrystallized or distilled.

2-Anilinopyrazine.—A solution of chloropyrazine (2.9 g, 0.025 mole) and aniline (4.7 g, 0.050 mole) in 10 ml of octanol was refluxed for 75 min during which time a new absorption peak at 340 mμ developed. The reaction mixture was added to 100 ml of chloroform, the precipitated aniline hydrochloride was removed by filtration, and the filtrate was extracted with four 50-ml portions of 10% hydrochloric acid. The acid extract was extracted once with ether which was discarded, made alkaline with 50% sodium hydroxide, and chilled. The precipitated solid,

(17) Boiling points are uncorrected. Melting points were determined in a Mel-Temp block in capillary tubes and are uncorrected. Reagents were purified by recrystallization or redistillation before use. Solvents were evaporated and extracts were concentrated in a rotary evaporator at 50–80° (bath temperature) under reduced pressure. Thin layer chromatography was done on either 2 in. × 8 in. glass plates layered with silica gel containing a fluorescing agent or on 2-in. strips of Eastman K 301 R chromatographic film. The developing solutions were either ether–methanol (9:1) (A) or acetonitrile (B). The separated components were visualized by ultraviolet light (254 or 360 mμ). Most reactions were monitored by semiquantitative ultraviolet spectrophotometery. Probe samples (0.01 ml) of reaction mixture were withdrawn at 15-min intervals (first 2 hr) and at 30-min intervals thereafter, diluted with water or 95% ethanol, and scanned. The development and subsequent stabilization of an absorption between 320 and 360 mμ marked the formation of the aminated product and then completion of the reaction.

(18) Analyses were by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. 11377.

(19) Obtained from American Cyanamid Co., Bound Brook, N. J., through the courtesy of Dr. Allen G. Potter.

collected and air dried, weighed 3.5 g (81.4%), mp 125–130°. Several recrystallizations from benzene and once from chloroform–hexane raised the melting point of the colorless crystals to 135–136°.[20]

2-(1-Piperidino)pyrazine.—A mixture of 5.7 g (0.05 mole) of chloropyrazine 12.8 g (0.15 mole) of piperidine was heated under reflux with magnetic stirring a total of 3 hr. Samples taken for spectrophotometric analysis showed the beginning of new absorption at 345 mμ after 20 min, with full development of this peak at 1 hr. The reaction mixture was made alkaline and extracted with chloroform. The organic extract was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure, leaving a 9.2 g of residue which partly solidified. Most of the material melted at 37–40°. Crystallization from benzene after filtration from some insoluble matter afforded 5.2 g (63.7%) of yellow crystals, mp 35–36°. For analysis, a portion was sublimed at 120° (10 mm), mp 36.5–37°.[21]

2-Benzylaminopyrazine.—A mixture of 11.6 g (0.1 mole) of chloropyrazine and 20.1 g (0.2 mole) of redistilled benzylamine was heated under reflux for 1 hr. In 30 min, the original peak at 270 mμ had disappeared and new peaks at 245 and 333 mμ had developed. On cooling, a solid precipitated which was slurried in benzene and taken to dryness. The dark green crystalline residue which had a pronounced odor of benzaldehyde weighed 9.0 g (48.6%) and melted at 63–65°. A small amount of the residue dissolved in alcohol gave a positive carbonyl reaction with acidic 2,4-dinitrophenylhydrazine reagent. The crude material was dissolved in chloroform and chromatographed on basic alumina. The column was developed first with two 150-ml portions of petroleum ether (bp 30–60°), which eluted about 1.0 g of brown oil which had a strong odor of benzaldehyde. This was converted into the 2,4-dinitrophenylhydrazone, mp 237–238° (lit.[22] mp 237°). Chloroform (200 ml) eluted about 5.0 g of yellowish solid, mp 63–65°, which after repeated recrystallization from chloroform–hexane with charcoaling raised the melting point of the colorless crystals to 66–66.5°. This material still gave an unsatisfactory elemental analysis.

Analytically pure material was finally obtained by distillation at 205° (bath temperature) (1.9 mm) and recrystallization of the distillate from chloroform–hexane: mp 68–69° (lit.[23] mp 67–68°), picrate mp 139–140° (lit.[23] mp 139.5–140°).

2-(*n*-Hexylamino)-3,6-dimethylpyrazine.—The preparation of this compound in 46.1% yield, bp 90–91° (0.02 mm), $n^{25}D$ 1.5273, by heating 2-chloro-3,6-dimethylpyrazine and *n*-hexylamine at 195° for 12.5 hr was reported by Kan, *et al.*[24]

3-(1-Piperidino)-2,5-dimethylpyrazine.—This compound was isolated by Lutz, *et al.*,[25] as the hydrochloride, mp 136–137°, in 72% yield, after heating the reactants 30 hr under reflux.

2-Benzylamino-3,6-dimethylpyrazine.—A mixture of 14.3 g (0.1 mole) of 2-chloro-3,6-dimethylpyrazine and 20.1 g (0.2 mole) of benzylamine were heated with magnetic bar mixing for a total of 2 hr, during which time the temperature of the gradually darkening solution rose from 184 to 250°. The solution was cooled and the crystalline mass was extracted continuously with ether for a total of 6 hr. The ether extract, after removal of the solvent, left a 18-g residue which slowly crystallized on refrigeration and gave a strong odor of benzaldehyde. The residue was slurried in petroleum ether and filtered (filtrate A), to give 7.0 g of yellow crystals, mp 83–92°. This was purified by several recrystallizations from benzene–petroleum ether (bp 30–60°) which raised the melting point to 94.5–96°. Thin layer silica gel chromatography (solvent A) showed only a single spot, R_f 0.75. For analysis, the compound was recrystallized from hexane, mp 96–96.5°.

The filtrate A was percolated through a 110-g column of neutral alumina. The column was developed first with benzene. The first 350 ml eluted 3.5 g (33%) of yellow oil identified as benzaldehyde by preparation of its 2,4-dinitrophenylhydrazone. Continued elution with 150 ml of benzene gave 0.65 g of yellow oil which slowly crystallized, mp 93–96°. Further elution with 250 ml of 10% ether in chloroform produced about 1.5 g of solid material which was recrystallized from benzene–petroleum ether, mp 109–111°. On thin layer chromatography (solvent A), the 93–96° material was homogeneous, R_f 0.75. The 109–111° material contained two substances, R_f 0.75 (identical with the 93–96° material) and 0.69. Authentic 2-amino-3,6-dimethylpyrazine was used as standard, R_f 0.69. Attempts to separate and purify the two components on a larger scale by repeated column chromatography were not completely successful since apparently homogeneous material, mp 112–113° (lit.[5] mp 111–112°), still gave an unsatisfactory elemental analysis.[26] Total crude yield of 2-benzylamino-3,6-dimethylpyrazine was 7.65 g (35.9%).

3-Aminopyrazine 1-Oxide. A.—A mixture of 10.0 g (0.074 mole) of 3-chloropyrazine 1-oxide[15] and 48 ml of concentrated ammonium hydroxide was heated in a 100-ml stainless-steel bomb at 115–120° for 2.5 hr. The cooled mixture was evaporated to dryness and the air-dried residue, mixed with activated charcoal, was extracted in a Soxhlet with chloroform for 10 hr.[27]

The extract, on removal of the solvent and crystallization of the crude residue from absolute ethanol, afforded 6.1 g (75.3%) of product, mp 173–176°. Recrystallization from absolute ethanol gave 5.1 g of compound, mp 175–176° (lit.[10] mp 175°).

B.—Identical quantities of reactants as in A were heated at 120° for 4–6 hr and taken to dryness. The residue was extracted (Soxhlet) with chloroform overnight. The extract, taken to dryness, gave 3.0 g of yellow solid, mp 158–170°. The residue, as demonstrated by silica gel thin layer chromatography and development in solvent A,[17] contained two substances, R_f 0.19,[28] 0.37 (fluorescent at 254 mμ). Aminopyrazine, 3-aminopyrazine 1-oxide, and 2,3-diaminopyrazine[14] used as comparison standards had R_f values 0.50,[28] 0.19,[28] and 0.37 (fluorescent at 254 mμ), respectively. The residue, extracted with three 50-ml portions of boiling benzene, left a brown solid, mp 137–163°, which, following repeated recrystallization from 95% ethanol (charcoal), gave 0.5 g of yellow crystals, mp 177–179°, identical with the compound obtained by method A.

The fluorescent benzene extract was chromatographed on 50 g of basic alumina and eluted with ether. The first 120 ml eluted a small amount of oily material which was not identified. The next 80 ml eluted 0.3 g of material, mp 199–203°, then followed a 1.4-g intermediate portion, mp 192–199°, and the final 150 ml eluted 0.5 g of material, mp 177–180°, identical with the 3-aminopyrazine 1-oxide described above. The higher melting fractions were recrystallized from water, mp 204–206°, and identified as 2,3-diaminopyrazine. Both compounds A and B, mp 177–180°, were homogeneous on thin layer silica gel chromatography with identical R_f values (0.16).

2,3-Diaminopyrazine. A.—A mixture of 6.5 g (0.05 mole) of 3-chloropyrazine 1-oxide and 15.2 ml of concentrated ammonium hydroxide was heated in a stainless-steel bomb at 140° for 16 hr. The dark solution was taken to dryness and the dried residue mixed with activated charcoal was transferred to a Soxhlet apparatus and extracted overnight with chloroform. The extract, after removal of solvent, left 3.5 g of yellow solid, mp 120–200°, with about 80% melting at 190–200°.

The solid was chromatographed on 125 g of basic alumina and eluted with ether–methanol (90:10). The first 200 ml eluted a small amount of oil which did not crystallize; the next 200 ml eluted 0.8 g (17%) of yellow solid, mp 108.5–110°. This was followed by 2.3 g of yellow solid (41.8%), mp 192–204°. The low-melting fraction was recrystallized from benzene to give 0.5 g of aminopyrazine, mp 115–116°, identified by mixture melt-

(20) H. Rutner and P. E. Spoerri (private communication) prepared 2-anilinopyrazine, mp 135.5–136.2°, from 2-fluoropyrazine in 24% yield by heating the latter with aniline at 130–135° for 9 hr in a sealed tube. The present authors are indebted to P. E. Spoerri for permitting us to review their manuscript prior to publication.

(21) W. B. Lutz (private communication) and associates of the Warner-Lambert Research Institute, Morris Plains, N. J., obtained this compound as the hydrochloride, mp 153–155°, in 92% yield by heating chloropyrazine with piperidine under reflux for 18 hr.

(22) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," 2nd ed, Interscience Publishers, Inc., New York, N. Y., 1960, p 582.

(23) H. Rutner and P. E. Spoerri, *J. Heterocyclic Chem.*, **2**, 492 (1965).

(24) P. T. Kan, J. D. Behun, S. M. Naqvi, M. A. Jorgensen, and P. A. Gibson, Technical Document Report WADD TR 60-838, Part II, 1962, p 128. The present authors are grateful to P. T. Kan, Wyandotte Chemicals Corp., Wyandotte, Mich., for a generous gift of this compound.

(25) W. B. Lutz, S. Lazarus, S. Klutchko, and R. I. Meltzer, unpublished observations. The authors are grateful to R. I. Meltzer and his associates at the Warner-Lambert Research Institute, Morris Plains, N. J., for making this information available in advance of publication.[6]

(26) *Anal.* Calcd for $C_6H_8N_2$: C, 54.6; H, 7.6; N, 31.8. Found: C, 57.86; H, 8.31; N, 32.67.

(27) Extraction with dioxane[10] gave gummy material which was difficult to handle and purify.

(28) This substance appeared as dark purple spots against a pale green background when the plates were exposed to 254-mμ radiation.

ing point with authentic material, conversion to the picrate, mp 234° dec,[2] and comparison of the ultraviolet and infrared absorption spectra with the spectra given by authentic material (I). Silica gel, thin layer chromatography developed in solvent A showed a single component, R_f 0.60 (pure aminopyrazine, R_f 0.60). The high-melting material was recrystallized from water to give 1.1 g of 2,3-diaminopyrazine, colorless crystals, mp 205–206° (lit.[14] mp 203°). The 2,3-diaminopyrazine was converted to 2,3-imidazoylpyrazine, mp 254.5–256° (lit.[14] mp 257°).

B.—3-Aminopyrazine 1-oxide (2 g, 0.018 mole) and 11.5 ml of concentrated ammonium hydroxide were heated in a bomb at 140° for 16 hr. The bomb contents were taken to dryness under reduced pressure. The dried residue, mixed with activated charcoal, was Soxhlet extracted with chloroform for 8 hr. Removal of solvent left a solid, mp 158–180°. Silica gel thin layer chromatography (solvent A) showed a single component, R_f 0.38 (authentic 2,3-diaminopyrazine, R_f 0.38). The solid was chromatographed on basic alumina and eluted with 10% methanol in ether; 0.59 g of colorless crystals, mp 190–206°, were collected. Recrystallization from water raised the melting point to 204–206° which did not depress the melting point of the 2,3-diaminopyrazine prepared by method A.

3-Amino-2,5-dimethylpyrazine 1-Oxide.—A mixture of 3-chloro-2,5-dimethylpyrazine 1-oxide[15] (7.42 g, 0.05 mole) and 32.5 ml of concentrated ammonium hydroxide was heated in a stainless-steel bomb at 120° for 6 hr.[29] The cooled mixture was taken to dryness and the residue was mixed with activated charcoal and Soxhlet extracted with chloroform for 12 hr. The extract yielded 5.5 g (78.5%) of crude product, mp 234–238°. Several crystallizations from 95% ethanol raised the melting point to 239–240°.

Preparation of Substituted Aminopyrazine N-Oxides.—Following is a general description of the procedure used for the preparation of compounds XV–XIX and XXII–XXV. 3-Chloropyrazine 1-oxide[15] and excess amine were heated under reflux, either neat or in 20 ml of solvent (Table II gives reaction conditions). The cooled mixture was made alkaline and extracted with chloroform. The dried organic extract was concentrated, excess amine was removed, and the residue was recrystallized. The solvents used follow: XV, benzene–hexane; XVI–XVIII, chloroform–hexane; XIX, benzene; XXII, chloroform–hexane; XXIII, ether–petroleum ether (bp 30–60°), following chromatography on alumina and elution with 10% methanol in ether; XXIV, chloroform–hexane; XXV, hexane.

3-Dimethylaminopyrazine 1-Oxide.—3-Chloropyrazine 1-oxide (5.23 g, 0.04 mole) and 96 ml of 25% aqueous dimethylamine were heated in a bomb for 1 hr at 120°. The bomb contents were made alkaline (pH 10) and taken to dryness. The residue, mixed with charcoal, was extracted for 10 hr with chloroform. The dried extract was taken to dryness leaving 6.2 g of material, mp 144–146°, which gave a faint Beilstein test. This was recrystallized from chloroform–hexane (charcoal) to give 5.1 g of compound, mp 148–150°, but which still was not homogeneous on thin layer chromatography (solvent B). A sample for analysis was obtained by chromatographing 300 mg of compound on 25 g of alumina, eluting with 5% chloroform in ether, and recrystallizing the combined homogeneous fractions with chloroform–hexane.

3-Dimethylamino-2,5-dimethylpyrazine 1-Oxide.—This compound was prepared by Lutz and co-workers[11] by allowing 3-chloro-2,5-dimethylpyrazine 1-oxide and liquid dimethylamine to stand in a sealed vessel at room temperature for 2 days.[30]

Absorption Spectra.—Ultraviolet absorption spectra were determined on a Bausch and Lomb 505 recording spectrophotometer. These are given in Table III. Infrared spectra were obtained with a Perkin-Elmer Model 21 recording spectrophotometer as chloroform solutions or potassium bromide disks. The instrument was calibrated with a polystyrene film.

TABLE III

ULTRAVIOLET ABSORPTION SPECTRA

No.	Solvent	λ_{max}	Log ϵ	λ_{max}	Log ϵ	λ_{max}	Log ϵ
I	EtOH	230	4.03	285	sh[a]	316	3.70[b]
II	H_2O	239	4.02			324	3.91
III	EtOH	246	4.20	290	sh	338	3.16
IV	MeOH	246	4.22	285	sh	335	3.73
V	EtOH			274	4.43	344	3.92
VI	MeOH	216	3.54	256	4.26	345	3.71
VII	MeOH	252	4.22	293	sh	345	3.72[c]
VIII	EtOH	248	3.92			332	3.52
IX	EtOH	234	3.92			320	3.85[d]
X	MeOH	247	4.17	285	sh	329	3.91
XI	H_2O	250	3.76			318	3.68[e]
XII	EtOH	247	4.34			325	4.09
XIII	EtOH	251	3.77			315	3.69[e]
XIV	H_2O	237	4.35	268	3.93	339	3.59
XV	H_2O	245	4.40			357	3.51
XVI	H_2O	247	4.40			357	3.66
XVII	EtOH	249	4.43	280	3.83	348	3.66
XVIII	EtOH	216	3.62	277	4.41	360	3.38
XIX	H_2O	<210		257	4.56	364	3.52
XX	EtOH	254	4.39	280	sh	360–365[f]	3.62
XXI	EtOH	236	4.37	266	3.99	335	3.86
XXII	MeOH	243	4.57			343	3.89
XXIII	H_2O	243	4.49			345	3.89
XXIV	EtOH	245	4.45			340	3.78
XXV	MeOH	215	4.20	252	4.38	335	3.78
XXVI	EtOH	213	4.05	253	4.36	338	3.75[e]
2,3-Imidazoylpyrazine	H_2O			290	4.01		

[a] sh, shoulder. [b] Reference 3 gives $\lambda_{max}^{pH\ 6.3}$ 230 mμ (log ϵ 4.00), 285 (sh), 318 (3.69). [c] Reference 3 gives $\lambda_{max}^{pH\ 7.2}$ 252 mμ (4.13), 287 (2.75), 346 (3.64). [d] Reference 16 gives λ_{max}^{EtOH} 234 (4.08), 319 (3.88). [e] W. B. Lutz, *et al.*[11] [f] Broad.

Registry No.—I, 5049-61-6; II, 13134-31-1; III, 13134-32-2; IV, 13134-33-3; V, 13134-34-4; VI, 6705-23-3; VII, 5214-29-9; VIII, 7375-45-3; IX, 13134-38-8; X, 13134-39-9; XI, 13134-40-2; XII, 13134-41-3; benzaldehyde 2,4-dinitrophenylhydrazone, 1157-84-2; XIII, 13134-42-4; XIV, 6863-77-0; XV, 13134-44-6; XVI, 13134-45-7; XVII, 13134-46-8; XVIII, 13134-47-9; XIX, 13134-48-0; XX, 13134-49-1; XXI, 13134-50-4; XXII, 13134-51-5; XXIII, 13192-28-4; XXIV, 13134-52-6; XXV, 13134-53-7; XXVI, 13134-54-8; 2-(*n*-hexylamino)-3,6-dimethylpyrazine, 13134-55-9.

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(29) Heating for a shorter period at this temperature gave incomplete conversion. Heating at a higher temperature (140–145°) for periods of 3–16 hr gave mixtures of varying composition containing the desired product and 2-amino-3,6-dimethylpyrazine. Examples of similar deoxygenation during the attempted amination of chloro N-oxides of other azaheterocyclic compounds have been reported: A. R. Katritsky, *J. Chem. Soc.*, 2404 (1956) (pyridine); I. J. Pachter and M. C. Kloetzel, *J. Am. Chem. Soc.*, **74**, 971 (1952) (phenazine).

(30) R. I. Meltzer, private communication. The melting point and other data given in their paper for this compound (ref 11, footnote 13) is incorrect and is actually that of 3-dimethylamino-2-methylpyrazine 1-oxide, mp 89–91°. The correct melting point is 72–74°. *Anal.* Calcd for $C_8H_{13}N_3O$: C, 57.46, H, 7.81; N, 25.13. Found: C, 57.54, H, 8.00; N, 25.18. Ultraviolet spectrum showed λ_{max}^{EtOH} 213 mμ (log ϵ 4.05), 253 (4.36), 338 (3.75).